

Review

Alternative treatments for *Clostridium difficile* disease: what really works?

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Vancomycin and metronidazole have been used for treating *Clostridium difficile*-associated disease (CDAD) for the past 25 years, but approximately 20% of patients develop recurrent disease. The increasing incidence of nosocomial outbreaks, cases of recurrent CDAD and other complications (toxic megacolon, ileus, sepsis) has fuelled the search for different types of treatments. As the understanding of the pathogenesis of this disease has matured, newer treatment strategies that take advantage of these mechanisms have been developed. This review will describe such treatments and examine the evidence for each strategy.

Introduction

Clostridium difficile-associated disease (CDAD) has been described in the literature since the early 1980s (Burdon, 1982; Wüst *et al.*, 1982; Riley *et al.*, 1983). Although important work has been accomplished on the epidemiology, clinical diagnosis and control of hospital outbreaks, CDAD continues to persist as a costly leading cause of nosocomial gastrointestinal illness (McFarland *et al.*, 1989; Shek *et al.*, 2000; Kyne *et al.*, 2002; Berrington *et al.*, 2004). In addition, other complications of CDAD have become recognized, including toxic megacolon, *C. difficile*-associated arthritis and septicaemia (Feldman *et al.*, 1995; Pron *et al.*, 1995; Lowenkron *et al.*, 1996; Fekety, 1997; Gravisse *et al.*, 2003).

The pathogenesis of CDAD involves a triad of factors. The first factor is exposure to antibiotics. Antibiotics are given to destroy pathogens that are causing disease, but they also disrupt the protective microflora present in the intestinal tract. One function of the normal intestinal microflora is 'colonization resistance', or the ability to inhibit colonization and subsequent infection by opportunistic pathogens. When this protective barrier is disrupted (by antibiotics, other medications or procedures such as intestinal surgery) the host may become susceptible to pathogens like *C. difficile* (McFarland, 2000b; Donskey, 2004). After exposure to antibiotics, especially broad-spectrum agents that disrupt a wide variety of anaerobic microflora, there is a long period of susceptibility to colonization. It may take as long as 3 months for the normal microflora to fully recover after antibiotic exposure.

The second factor is exposure to *C. difficile*, which typically occurs in hospitals (McFarland *et al.*, 1989; Olson *et al.*, 1994; Shek *et al.*, 2000). Asymptomatic carriers and symptomatic

hospital patients shed *C. difficile* cells and resistant spores into the hospital environment. Outbreaks and new sporadic cases occur through patient-to-patient contact, usually by hand transmission, or indirectly through exposure to contaminated environmental fomites. The spores of *C. difficile* can lurk in the hospital environment for months, providing a reservoir for new infections. Once *C. difficile* colonizes the intestine, damage to enterocytes occurs due to three *C. difficile* toxins (CDTs), toxin A, toxin B and binary toxin, that cause cytoskeletal changes resulting in the release of fluids and inflammatory products (Rupnik *et al.*, 2003). Diarrhoea is the most common symptom, but fever and leukocytosis can also be present.

The third factor relates to host factors. The ability of the host's immune system to produce protective antibodies against the toxins of *C. difficile* plays an important role in reducing the severity of disease and preventing further recurrences. Other host factors may relate to how capable a person is of mounting an effective defence. Many studies have shown that co-morbidities and advanced age are important risk factors for CDAD (McFarland *et al.*, 1990; Shek *et al.*, 2000).

Traditional treatments have relied on the use of two antibiotics (vancomycin and metronidazole) that are bactericidal for *C. difficile*. However, these antibiotics do not restore the normal colonization resistance, reduce exposure to *C. difficile* spores in the environment or affect other host risk factors. Severe complications in patients, an increasing frequency of nosocomial outbreaks and cases of recurrent CDAD have fuelled the search for alternative treatments that may be more effective (McFarland, 2000a; Valiquette *et al.*, 2004). This review will discuss the different treatment strategies that have been used for CDAD over the years and determine efficacy for these treatments.

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Standard antibiotic treatments

The first step in treating CDAD is to discontinue the inciting antibiotic or switch to an antibiotic that has a narrower spectrum of activity. For cases of mild diarrhoea, this step is often sufficient to resolve the symptoms. However, most cases need treatment with one of the two standard antibiotics: vancomycin or metronidazole. In addition to antibiotic treatment, it is important to give supportive therapy with hydration and electrolyte replacement, especially in the case of young children or severe diarrhoea (McFarland *et al.*, 2000). Antiperistaltic drugs should be avoided, as they may precipitate toxic megacolon and slow the clearance of *C. difficile* from the intestine.

The immediate response to standard antibiotic treatment is usually good (most diarrhoea improves within 1–4 days and resolves within 2 weeks). However, 12–24% of patients experiencing their first episode of CDAD (initial CDAD) subsequently develop another episode of disease within 2 months. If the patient has recurrent CDAD (with more than two previous episodes), the frequency of further recurrences increases dramatically (50–65%). Repeated antibiotic courses may eventually cure the patient of recurrent CDAD, but this can require months or even years of antibiotic treatment (Fekety *et al.*, 1997; Kyne *et al.*, 1999; McFarland *et al.*, 1999; Barbut *et al.*, 2000).

Recurrent CDAD may be caused by a relapse of the original strain during the window of host susceptibility or by reinfection with a new strain of *C. difficile*. Most studies comparing strains from the original episode and subsequent episodes (or recurrent CDAD) have found that about half are relapses and half reinfections (Wilcox *et al.*, 1998; Johnson *et al.*, 1989; Barbut *et al.*, 2000; Tang-Feldman *et al.*, 2003). Relapses arise when vancomycin or metronidazole are discontinued and endogenous spores, which have not been destroyed by the antibiotics, germinate in the susceptible intestine. If the normal protective microflora has not had time to re-establish itself, then *C. difficile* can colonize the intestinal wall, produce toxins and cause disease. Reinfections occur when the host is still susceptible to overgrowth and is exposed to *C. difficile*, usually from the hands of hospital personnel or contaminated environmental surfaces.

Metronidazole

Oral metronidazole has been used to treat initial CDAD, usually at a dose of 250 or 500 mg four times a day for 7–14 days (Fekety, 1997; American Society of Health-System Pharmacists, 1998). Indeed, several guidelines suggest oral metronidazole should be the first choice treatment for CDAD. Randomized trials show excellent initial responses in approximately 95% of patients treated with metronidazole (Teasley *et al.*, 1983; Wenisch *et al.*, 1996). The response rate may be lower in patients who are extremely ill. One study found that 38% of patients treated with metronidazole had persistent diarrhoea 5 days after metronidazole treatment

was begun (Fernandez *et al.*, 2004). Such patients were more likely to have low albumin levels ($< 2.5 \text{ g l}^{-1}$) and be in intensive care units.

One concern with repeated use of metronidazole for recurrent CDAD cases is the development of antibiotic resistance (Johnson *et al.*, 2000). A study from Spain documented metronidazole resistance in 6.3% of *C. difficile* strains over an 8-year period (Pelaez *et al.*, 2002). Intolerance is also a problem as some patients cannot take metronidazole due to side effects including metallic taste, nausea, an antabuse effect and rare cases of neurotoxic complications (Beloosesky *et al.*, 2000).

Vancomycin

Several trials have demonstrated the efficacy of oral vancomycin therapy for initial CDAD, usually given at doses of 125 or 500 mg four times a day for 5–14 days (Table 1). No differences in initial cure or recurrence rates were seen in a randomized trial comparing 500 mg and 2 g daily doses of vancomycin (Fekety *et al.*, 1989). Vancomycin has no systemic adsorption and few reported side effects, except for rash (which is common). The concerns with vancomycin use are cost (USD300–USD500 for a standard 10 day course), the selection of vancomycin-resistant *Enterococcus faecium* strains and the need to reserve its use for MRSA (methicillin-resistant *Staphylococcus aureus*) infections (Lam *et al.*, 1995; Jarvis, 1998; Garbutt *et al.*, 1999).

Vancomycin versus metronidazole

Two randomized trials showed no difference in the efficacy of metronidazole and vancomycin (Table 1) for either initial response (94–100%) or recurrence rate (5–16%; Teasley *et al.*, 1983; Wenisch *et al.*, 1996). In addition, a 10 year surveillance study of 908 patients at the Minneapolis VA Medical Center reported initial responses to metronidazole and vancomycin (at a variety of dosage regimens) of 98% and 99%, respectively (Olson *et al.*, 1994).

Vancomycin and metronidazole thus appear to be equally effective for CDAD. However, metronidazole is the treatment of choice for patients with initial CDAD because of the comparable effectiveness of these two antibiotics and the lower cost of metronidazole. Vancomycin should be reserved for more severe cases or for pregnant patients or those who cannot tolerate metronidazole. The choice is not as clear for patients with recurrent CDAD. Treatment of children with CDAD follows similar guidelines as adult cases (McFarland *et al.*, 2000).

Most randomized trials involve patients with initial disease or patients for whom no history of CDAD has been clarified. However, a few have compared antibiotic treatment in patients with recurrent CDAD (Table 2). A randomized, placebo-controlled trial in patients with recurrent CDAD analysed the effects of antibiotic treatments in 78 patients during the placebo arm of the trial (Surawicz *et al.*, 2000). Patients were randomized to 10 days of high dose vancomy-

Table 1. Randomized prospective comparative trials of treatments for patients with initial CDAD

Reference	Antibiotic	Daily dose*	Duration (days)	No. of patients	Initial cure (%)	Recurrence (%)
Wenisch <i>et al.</i> (1996)	Teicoplanin	400 mg b.i.d.	10	28	96	7 NS
	Fusidic acid	500 mg t.i.d.	10	29	93	28 NS
	Vancomycin	500 mg t.i.d.	10	31	94	16
	Metronidazole	500 mg t.i.d.	10	31	94	16 NS
De Lalla <i>et al.</i> (1992)	Teicoplanin	100 mg b.i.d.	10	26	96	8†
	Vancomycin	500 mg q.i.d.	10	20	100	20
Fekety <i>et al.</i> (1989)	Vancomycin	125 mg q.i.d.	10	24	100	21 NS
	Vancomycin	500 mg q.i.d.	10	22	100	18
Dudley <i>et al.</i> (1986)	Bacitracin	25 000 U q.i.d.	10	15	80	33 NS
	Vancomycin	500 mg q.i.d.	10	15	93	20
Young <i>et al.</i> (1985)	Bacitracin	20 000 U q.i.d.	10	21	76	24 NS
	Vancomycin	125 mg q.i.d.	10	21	86	29
Teasley <i>et al.</i> (1983)	Vancomycin	500 mg q.i.d.	10	52	100	11
	Metronidazole	250 mg q.i.d.	10	42	95	5 NS
Mogg <i>et al.</i> (1982)	Colestipol	10 g q.i.d.	5	12	25	NR
	Placebo	0	5	14	21	NR
Keighley <i>et al.</i> (1978)	Vancomycin	125 mg q.i.d.	5	12	92	0†
	Placebo	125 mg q.i.d.	5	9	22	44

NR, Not reported; NS, not significant.

*b.i.d., Twice a day; q.i.d., four times a day; t.i.d., three times a day.

† $P < 0.05$ compared to control (vancomycin or placebo).

Table 2. Randomized trials of vancomycin or metronidazole therapy in patients with recurrent CDAD

Reference	Initial antibiotic therapy (10–12 days)*	No. of patients	No. of patients with subsequent recurrence of CDAD (%)
Surawicz <i>et al.</i> (2000)	Vancomycin 500 mg q.i.d.	14	7 (50)
	Vancomycin 125 mg q.i.d.	38	17 (45)
	Metronidazole 250 mg q.i.d.	26	13 (50)
McFarland <i>et al.</i> (1994)	Vancomycin 200 mg q.i.d.	65	28 (43)
	Metronidazole 300 mg q.i.d.	37	12 (32)
McFarland <i>et al.</i> (2002)	Vancomycin 250 mg q.i.d.	14	10 (71)
	Vancomycin 500 mg q.i.d.	21	9 (43)
	Metronidazole 500 mg t.i.d.	5	2 (40)

*q.i.d., Four times a day; t.i.d., three times a day.

cin (2 g per day), low dose vancomycin (500 mg per day) or metronidazole (1 g per day), and followed for CDAD recurrences over 2 months. No differences in recurrence rates were identified among the groups receiving the three antibiotic regimens. An earlier double-blinded, placebo-controlled trial also showed similar recurrence rates in 102 vancomycin- or metronidazole-treated patients (McFarland *et al.*, 1994). A third study showed similar recurrence rates in 163 patients, 125 of whom received vancomycin and 38 of whom received metronidazole (McFarland *et al.*, 2002). In this study, 143 stools were tested for *C. difficile* after antibiotic treatment had ceased. Vancomycin cleared both vegetative

cells and toxins in 89% of patients. Metronidazole also cleared vegetative cells, but only 59% of patients were toxin negative at the end of treatment ($P < 0.01$ compared to vancomycin treatment). Only half of the patients in the study (in either antibiotic group) displayed eradication of *C. difficile* spores.

Once antibiotic therapy ends, *C. difficile* spores can germinate, resulting in a rapid re-emergence of vegetative cells and recurrent infection (Bolton & Culsaw, 1986; Levett, 1991; McFarland *et al.*, 2002). The typical time required for spore germination, *C. difficile* overgrowth and acute toxigenic

symptoms is 3–5 days. A prospective follow-up of antibiotic-treated patients showed 97 % of recurrences occurred within 4 weeks post-treatment (median of 7 days) (McFarland *et al.*, 1999).

Delayed onset of new episodes (4–8 weeks later), reported in some studies, can be attributed to exposure to exogenous spores (reinfection) or overgrowth of indigenous *C. difficile* (asymptomatic carriage) before the normal colonic flora is re-established (Johnson *et al.*, 1989; Kato *et al.*, 1996; Nair *et al.*, 1998; Wilcox *et al.*, 1998). Previous work has shown the normal flora may be disrupted for up to 6 weeks after antibiotic use (Tedesco *et al.*, 1985).

Continuation of or restarting inciting antibiotics after successful treatment increases the risk of recurrence (Tedesco *et al.*, 1985). The treatment of recurrent CDAD must consider the possible role of residual *C. difficile* spores in the intestinal tract and the time the intestine is susceptible to *C. difficile* overgrowth. Short antibiotic treatment regimens may be effective in initially resolving the symptoms of diarrhoea, but do nothing during the 'window of susceptibility', i.e. the time required for re-establishment of the intestinal microflora that results in resistance to *C. difficile* overgrowth and subsequent recurrent disease.

Standard antibiotics with different dosing regimes

A prospective case series of 163 patients with recurrent CDAD documented the rate of CDAD recurrences over a 2 month period in patients who were treated with a variety of strategies using either vancomycin or metronidazole (McFarland *et al.*, 2002). Two strategies reduced recurrence rates: vancomycin tapering and vancomycin pulsed dosing (Fig. 1). The recurrence rates in patients treated with a standard vancomycin dosage (1 g per day for 10 days), a high vancomycin dosage (2 g per day for 10 days), a tapered dose of vancomycin (over a mean of 21 days) or a pulsed dosing of vancomycin (125–500 mg every 3 days over a mean of 27 days) were 54 %, 43 %, 31 % and 14 %, respectively. Tedesco *et al.* (1985) reported a case series of 22 patients with recurrent CDAD who appeared to be successfully treated

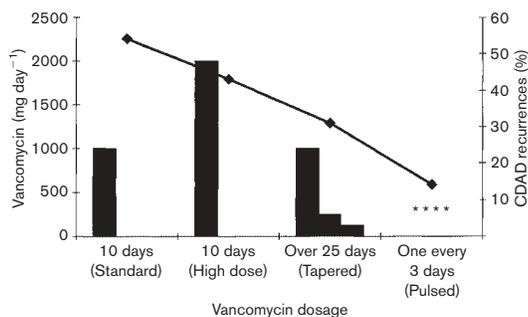


Fig. 1. Effectiveness of different treatment strategies for recurrent CDAD. Different vancomycin regimens (bars) compared to the frequency of recurrences (◆) in 200 patients followed for at least 2 months post-treatment. Asterisks indicate one dose every 3 days.

with a tapered regimen of vancomycin (500 mg per day for 1 week, 250 mg per day for 1 week, 125 mg per day for 1 week) followed by a pulsed dose regimen of vancomycin (125 mg every third day for 21 days). The results of both these observational studies suggest such strategies may be effective, and randomized clinical studies are warranted. Pulsed metronidazole regimens may also be useful, but there is a lack of published studies using metronidazole in this manner.

The reason why tapering or pulsed dosing may be more effective than a standard course is that the antibiotic eradicates vegetative cells of *C. difficile*, but is not effective against spores. Administering antibiotics over an extended time period at decreasing doses (tapered regime) or intermittent delivery (pulsed regime) gradually clears *C. difficile* by eradicating cells as spores germinate. In addition, such regimens may aid restoration of the normal microflora. One concern, particularly for pulsed dosing, is that such treatment may encourage antibiotic-resistant strains of *C. difficile* to develop (Sanchez *et al.*, 1999; Pelaez *et al.*, 2002).

Overall, metronidazole and vancomycin appear to be equally effective for treating the first episode of CDAD. Descriptive data indicate that a 10 day course of vancomycin followed by a 4–8 week tapered or pulsed dosing regime may be effective for patients with recurrent CDAD.

Other antibiotic treatments

A number of clinical trials have been published that examine a variety of antibiotics for treating CDAD. One review of nine such trials (469 patients) included six trials which compared vancomycin to other antibiotics (fusidic acid, bacitracin, teicoplanin and metronidazole), one trial which compared two doses of teicoplanin, and two placebo-controlled trials (Zimmerman, 1991). Clinical response ranged from 21 % (placebo) to 100 % (vancomycin), but no specific antibiotic demonstrated superiority compared to the others. Wenisch *et al.* (1996) performed a randomized, controlled trial of vancomycin, metronidazole, teicoplanin and fusidic acid. Patients with CDT-positive diarrhoea were randomly assigned to receive 10 days of one of the four antibiotic regimens and followed for initial resolution of symptoms ('cure') and for relapse within 30 days post-treatment. The four groups were comparable in terms of age, sex and previous antibiotic exposure. Initial cure rates were similar for all treatments, ranging between 93 % and 96 %. Patients treated with vancomycin or metronidazole had a recurrence rate of 16 %. The recurrence rate in patients receiving teicoplanin (7 %) was lower than those treated with fusidic acid (28 %, $P = 0.04$), but not significantly lower than vancomycin or metronidazole groups. No adverse reactions were reported.

Bacitracin

Bacitracin is a non-absorbable antibiotic which has an unpleasant taste and is significantly expensive. Two trials compared bacitracin to vancomycin (Young *et al.*, 1985; Dudley *et al.*, 1986). No significant difference in initial cure

rates was seen (Table 1). However, bacitracin-treated patients were reported to subsequently have higher rates of *C. difficile* carriage in their stools.

Fusidic acid

A randomized trial of 119 patients with CDAD demonstrated an initial cure rate of 93 % with fusidic acid (Wenisch *et al.*, 1996). Twenty-eight percent of fusidic acid-treated patients suffered recurrent CDAD; however, this was not significantly different from either vancomycin or metronidazole treatments. This was corroborated by Wullt & Odenholt (2004), who found similar resolution of diarrhoea in patients treated with fusidic acid (83 %) and metronidazole (93 %), with recurrence rates of 27 % and 29 %, respectively.

Rifampicin

Rifampicin has been given to a limited number of patients with CDAD in two descriptive studies, but no randomized, controlled trials have been reported. Seven patients with recurrent CDAD were treated with both vancomycin and rifampicin, with no recurrences (Buggy *et al.*, 1987). One case report of a patient with *C. difficile* colitis and non-Hodgkin's lymphoma reported success with rifampicin (600 mg twice a day) after previous treatment with vancomycin and metronidazole failed to resolve his diarrhoea (Nomura *et al.*, 2004).

Teicoplanin

The oral antibiotic teicoplanin showed initial promise in a clinical trial of 47 patients with CDAD (Swedish CDAD Study Group, 1994). High clinical responses were seen in both dose groups of teicoplanin (70 % and 96 %). De Lalla *et al.* (1992) compared teicoplanin with oral vancomycin in a randomized, controlled trial of 46 patients and showed no significant difference in initial cure rate (96 % and 100 %, respectively). A lower recurrence rate was seen with teicoplanin (7.7 %, compared to 20 % with vancomycin), though this was not statistically significant. Similar results were demonstrated by Wenisch *et al.* (1996), though teicoplanin was seen to be significantly more effective against recurrent CDAD than fusidic acid.

Non-antibiotic treatments

Meta-analysis of four randomized clinical trials comparing different antibiotics for the treatment of CDAD showed no overall superiority of any antibiotic compared to vancomycin or metronidazole (Fig. 2). Alternative treatment strategies are of great interest, particularly as most antibiotics only target vegetative *C. difficile* cells (and not spores). Furthermore, antibiotics disrupt the normal colonic flora, thereby compromising resistance to *C. difficile* colonization (McFarland, 2000b). Other strategies tested for CDAD include the use of probiotics, bacteriotherapy, adsorbents and immunotherapy.

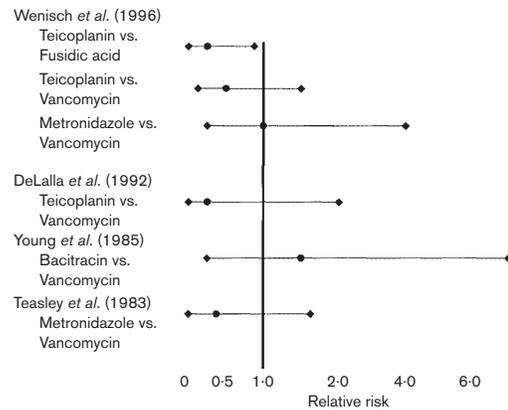


Fig. 2. Point estimates (●) and 95 % confidence limits for the risk of recurrences in patients with initial CDAD by antibiotic treatment in randomized controlled trials.

Probiotics

Probiotics are mono- or mixed-cultures of live micro-organisms which, when administered to animal or man, benefit the host by improving the properties of the indigenous microflora. Probiotics are postulated to enhance re-establishment of the normal flora following disruption (by antibiotics or other risk factors), to stimulate the immune response, to elicit production of enzymes that degrade pathogenic toxins and/or to block attachment sites in the colon (McFarland, 2000b). *Lactobacillus* species and *Saccharomyces boulardii* have been shown to reduce the occurrence of antibiotic-associated diarrhoea when given in conjunction with antibiotics (McFarland, 2000a). Several clinical trials and case reports have examined probiotics, usually in combination with vancomycin or metronidazole, for the treatment of recurrent CDAD.

***Saccharomyces boulardii*.** Two double-blind, randomized, controlled trials have investigated the use of *S. boulardii* and antibiotics for patients with recurrent CDAD (Table 3). In one, 168 patients were randomized to receive one of three standard 10 day antibiotic regimens followed by *S. boulardii* or a placebo for 28 days (Surawicz *et al.*, 2000). *S. boulardii* (2×10^{10} c.f.u. per day) or placebo administration commenced during the first 3 days of antibiotic treatment. The frequency of recurrent CDAD was monitored during a 2 month follow-up period. A significant decrease in recurrences ($P = 0.05$) was observed in patients treated with high-dose vancomycin (2 g per day) and *S. boulardii* (16.7 %) compared with patients who received high dose vancomycin and placebo (50 %). However, *S. boulardii* treatment had no impact on recurrence rates of patients treated with low dose vancomycin or metronidazole. No adverse reactions were noted.

An earlier study randomized patients to receive either *S. boulardii* (2×10^{10} c.f.u. per day) or placebo for 28 days combined with vancomycin or metronidazole in various

Table 3. Randomized trial of probiotic treatments for recurrent CDAD

Reference	Probiotic*	No. of patients	Patients with subsequent recurrence of CDAD (%)
McFarland <i>et al.</i> (1994)	<i>S. boulardii</i> (2×10^{10} c.f.u. per day for 28 days)	26	9 (35)†
	Placebo	34	22 (65)
Surawicz <i>et al.</i> (2000)	<i>S. boulardii</i> (2×10^{10} c.f.u. per day for 28 days)	18	3 (17)†
	Placebo	14	7 (50)
Pochapin (2000)	<i>Lactobacillus rhamnosus</i> GG (dose not given, 21 days)	11	4 (36) NS
	Placebo	14	5 (36)
Wullt <i>et al.</i> (2003)	<i>L. plantarum</i> 299v (5×10^{10} c.f.u. per day for 38 days)	11	4 (36) NS
	Placebo	9	6 (67)

NS, Not significant.

*Usually given with either vancomycin or metronidazole.

† $P < 0.05$ compared to control group.

doses as selected by the participating physician (McFarland *et al.*, 1994). The recurrence rate in patients with recurrent CDAD was 35 % for the *S. boulardii* group compared to 65 % for the placebo group ($P = 0.04$). Patients experiencing their first episode of CDAD had lower recurrence rates across both groups (19.3 % and 24.4 % for *S. boulardii* and placebo groups, respectively), with no statistical difference seen between the two groups.

Lactobacillus species. Several strains of lactobacilli have been tested as treatments for CDAD. Three case series, involving a total of 41 patients with recurrent CDAD, investigated treatment with *Lactobacillus rhamnosus* GG (Gorbach *et al.*, 1987; Biller *et al.*, 1995; Bennett *et al.*, 1996). No further recurrences were seen in 50–84 % of patients. A single randomized, controlled trial using *L. rhamnosus* GG with either metronidazole or vancomycin has been reported (Pochapin, 2000). The recurrence rate was similar for the probiotic (36.4 %) and placebo groups (35.7 %). A small study of 20 patients with recurrent CDAD tested metronidazole and either *Lactobacillus plantarum* 299v (5×10^{10} c.f.u. per day) or placebo given for 38 days (Wullt *et al.*, 2003). Although the recurrence frequency was lower in the *L. plantarum* group (36.4 %) compared to the placebo group (66.7 %), the difference was not significant.

Faecal enemas and bowel irrigation

Several case reports (with a total of 84 patients) describe the use of faecal enemas prepared from healthy stools, in an effort to replace the microflora disrupted by recurrent CDAD and antibiotic treatments (Bowden *et al.*, 1981; Schwan *et al.*, 1984; Tvede & Rask-Madsen, 1989; Persky & Brandt, 2000). Most of the patients (90 %) reported no further CDAD recurrence. Whole-bowel irrigation has also been used in one instance, in an effort to 'flush out' pathogenic toxins (Liacouras & Piccoli, 1996). However, no randomized, placebo-controlled trials testing such bacteriotherapies have been published to date.

Adsorbents

Another treatment strategy has been to bind the toxins of *C. difficile* in the colonic lumen before they can attach to enterocytes and induce disease. Several types of adsorbent have been tested: ion-exchange resins, oligosaccharides and various types of polymers.

Ion-exchange resins. The results of trials using ion-exchange resins to bind toxins have been varied (Pruksananonda & Powell, 1989; Ariano *et al.*, 1990). An *in vivo* study of two resins, cholestyramine and colestipol, demonstrated that binding of cytotoxin and cholestyramine delayed death in the hamster model of clindamycin-induced cecitis (Taylor & Bartlett, 1980). A placebo-controlled, randomized trial of colestipol in 38 patients with post-operative diarrhoea showed no difference in faecal excretion of CDT (Mogg *et al.*, 1982). Cholestyramine binds vancomycin and teicoplanin as well as CDT, and its use may lead to suboptimal levels of antibiotic (Pantosti *et al.*, 1985). Treatment with ion-exchange resins is not recommended when vancomycin is given, due to their antibiotic-binding property.

Polymers. Several studies have looked at the CDT-binding effectiveness of various polymers. Synsorb 90 is an oligosaccharide bound to an inert polymer matrix that acts as a 'decoy toxin receptor' and reduces fluid secretion in rat ileal loop models of CDAD (Heerze *et al.*, 1994; Castagliuolo *et al.*, 1996). However, no controlled trials testing the efficacy of Synsorb 90 on CDAD have been published to date. Another polymer (Tolvamer) was tested in patients with either initial or recurrent CDAD (Davidson *et al.*, 2004). CDAD was resolved by day 10 of treatment in 91 % of patients treated with vancomycin ($n = 80$), 67 % of patients treated with 3 g Tolvamer per day ($n = 72$) and 83 % of patients treated with 6 g Tolvamer per day ($n = 70$).

Immune products

Previous research identified the host immune response as an important predictor of recurrences of CDAD (Warny *et al.*, 1994; Kyne *et al.*, 2001). Kyne *et al.* (2001) studied 63 patients with CDAD and found serum IgG antitoxin A levels were significantly lower for patients who developed further recurrences compared to patients who only had one episode. A total of 17 patients with recurrent CDAD, from five case series reports, have been treated with intravenous human immunoglobulin and 15 responded to this treatment (Leung *et al.*, 1991; Hassett *et al.*, 1995; Salcedo *et al.*, 1997; Beales, 2002; Wilcox, 2004). Most patients given intravenous immunoglobulin treatments were adults, although one report was a series of six children aged 6–37 months (Leung *et al.*, 1991). All the patients had recurrent CDAD and had previously been treated with vancomycin, metronidazole or both. Immunoglobulin dosages ranged from 200 mg kg⁻¹ to 500 mg kg⁻¹, given every 2–3 weeks. Patients with immunodeficiency have been treated with intravenous immunoglobulin, with resultant clearing of CDAD but only modest increases in antitoxin A antibody levels (Warny *et al.*, 1994; Hassett *et al.*, 1995).

Although the immune response has been shown to be an important risk factor in CDAD, the role of immunoglobulin therapy has not been investigated with randomized, controlled clinical trials. Studies to date lack appropriate control groups, and doses, durations and timings of IgG treatment have not been standardized. In addition, different preparations of commercial pooled immunoglobulin have varying amounts of anti-CDT antibodies present (Salcedo *et al.*, 1997).

Another approach is to use an oral powder consisting of bovine immune whey powder (Thorig *et al.*, 2001; van Dissel *et al.*, 2005). The immune whey powder is polyclonal-antibody-enriched whey made from the milk of cows immunized with formaldehyde-inactivated *C. difficile* toxoid. Such a product was given to 11 patients (10 adults and a 6-year-old child), eight of whom had recurrent CDAD. All patients received a 14 day course of either metronidazole or vancomycin, after which they took whey powder three times daily for 2 weeks. No CDAD recurrence was seen during the surveillance period (median length 215 days). However, these promising immune-strengthening treatments need to be investigated more thoroughly by randomized, controlled trials.

Treatment of asymptomatic carriers

Asymptomatic carriers of *C. difficile* have been shown to be a source of new nosocomial cases of CDAD (McFarland *et al.*, 1989; Johnson *et al.*, 1990; Clabots *et al.*, 1992; Shim *et al.*, 1998). In order to control the spread of *C. difficile*, a policy of treating asymptomatic carriers has been tested by several investigators. Delmee *et al.* (1987) showed a reduction in CDAD frequency in patients on a leukaemia unit, from 16.6% to 3.6%, after all symptomatic and asymptomatic *C. difficile* carriers were treated with vancomycin.

However, treatment of asymptomatic carriers hasn't always reduced the frequency of nosocomial outbreaks (Kerr *et al.*, 1990). Bender *et al.* (1986) demonstrated that metronidazole treatment of carriers had no effect on the incidence of new CDAD cases at a chronic care facility. Johnson *et al.* (1992) treated 30 asymptomatic carriers in a randomized, placebo-controlled trial with vancomycin (1 g per day), metronidazole (1 g per day) or placebo for 10 days. The observed *C. difficile* carriage rates immediately after treatment stopped were 10% in the vancomycin group, 70% in the metronidazole group and 80% in the placebo group ($P = 0.02$). At the end of the 2 month follow-up period, significantly more of the patients who had been treated with vancomycin (67%) had reacquired *C. difficile* compared to those who had been given placebo (11%; $P < 0.05$). Overall, evidence from the limited number of studies investigating the treatment of asymptomatic carriers does not seem to warrant this policy.

Treatment of complications

Complications of CDAD are rare, but present a challenge for selecting an appropriate treatment strategy. Patients may have atypical symptoms (no diarrhoea), symptoms that mimic acute surgical abdomen, or develop ileus, toxic megacolon or even sepsis. If the patient has ileus, antibiotic treatments given orally will not reach the site of infection. If the oral route cannot be used, intracolonic or intravenous routes may be utilized. However, intravenous vancomycin is not excreted into the colon, so the use of vancomycin enemas is an alternative when the oral route is not feasible (Olson *et al.*, 1994). A review of the literature reveals a limited number of patients in whom intracolonic vancomycin has been tried. In eight out of nine patients (88.9%) this route was effective (Apisarnthanarak *et al.*, 2002). Several case reports, and an observational study in 10 patients, suggest that the intravenous route of metronidazole may be effective for patients with paralytic ileus or toxic megacolon (Friedenberg *et al.*, 2001).

Antibiotic treatment may not be sufficient for patients with toxic megacolon, perforation or severe acute abdomen. Trudel *et al.* (1995) reviewed 11 patients with toxic megacolon and found that 64% required corrective surgery. Patients who develop disease sufficiently severe to require surgery are usually extremely ill and mortality in this group of patients is high, ranging from 32% to 50% (Bradbury & Barrett, 1997; Gerding, 2000).

Control of CDAD

A more effective strategy than treating asymptomatic carriers for the control of CDAD outbreaks involves strict infection-control practices, especially handwashing, use of gloves and environmental decontamination (Gerding *et al.*, 1995; Mayfield *et al.*, 2000; Thomas *et al.*, 2002). Surveillance for new cases of CDAD and prompt treatment to limit nosocomial spread is also important. Outbreaks of CDAD may also be limited by an antibiotic-restriction policy for high-risk antibiotics (Gerding *et al.*, 1995; Berrington *et al.*, 2004).

Several studies have shown that restriction of clindamycin use was associated with a reduction in nosocomial CDAD cases (Brown *et al.*, 1990; Pear *et al.*, 1994). Other hospitals' rates of CDAD decreased, by at least 50 %, after restricting cephalosporin use (Ludlam *et al.*, 1999; Khan & Cheesbrough, 2003). The best strategy for control is a combination of all of these tactics.

Discussion

Effective treatment of CDAD needs to do three things: reduce the burden of *C. difficile* and its toxins in the intestine, restore the normal colonic microflora and assist the host's immune system. Clearing *C. difficile* and/or CDT from the intestine may be achieved using antibiotics or synthetic polymers which bind the toxins. However, treatment is complicated by the persistence of spores in the colon, which no treatment to date currently targets. In cases where the immune system does not provide protective levels of anti-CDT antibodies, passive immunoglobulin therapy is helpful. In severe cases, surgery may be the only option.

The patient's history of CDAD is an important factor in the choice of antibiotic treatment. Patients with an initial episode may be treated equally well with either vancomycin or metronidazole. A few studies also found that teicoplanin, bacitracin and fusidic acid have potential, but these antibiotics are not available in all countries. Treatment of recurrent CDAD is less clear. The standard course of antibiotic treatment for recurrent CDAD (10–14 days) is effective in 40 % of cases, although prolonged vancomycin (tapered and pulsed dose regimes) is more effective. The advantage of tapered or pulsed doses of antibiotics is that they combat the germinating *C. difficile* spores. The disadvantage is that prolonged or repeated exposure to antibiotics may increase the risk of antibiotic resistance, although current studies show a low rate of resistance to metronidazole and practically no resistance to vancomycin.

As well as reducing the level of *C. difficile* and its toxins in the intestine, treatment strategies should aim to restore the normal colonic flora. The use of probiotics in combination with antibiotic treatments has shown promise. Furthermore, some probiotics have additional mechanisms that specifically target *C. difficile* (Castagliuolo *et al.*, 1996). The use of probiotics is safe for most patients, although rare complications have occurred in immunocompromised adults and children (Hennequin *et al.*, 2000; Borrelieo *et al.*, 2003).

Recent studies have provided more antibiotic options for initial cases of CDAD and a combination of a short antibiotic course and longer probiotic treatment may be the most effective therapy for recurrent CDAD.

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