THERAPY UPDATE

Recurrent *Clostridium difficile* diarrhoea

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Clostridium difficile diarrhoea is a common iatrogenic nosocomial disease. Fortunately, most affected patients respond well to medical therapy that includes discontinuation of the inciting antibiotic and treatment with metronidazole or vancomycin.[1] However, despite successful treatment of initial episodes, 15–25% will have recurrence of diarrhoea following withdrawal of specific antibiotic therapy.[1 2] Treatment of this form of *C difficile* disease can be particularly problematic.

Approaches to management include conservative therapy, treatment with specific anti-*C difficile* antibiotics, use of anion binding resins, therapy with microorganisms (probiotics), and immunoglobulin therapy (table 1).

Table 1 Approach to management of recurrent Clostridium difficile diarrhoea

First recurrence
- Confirm diagnosis
- Symptomatic treatment if symptoms are mild
- 10–14 day course of metronidazole or vancomycin

Second recurrence
- Confirm diagnosis
- Vancomycin* taper
  125 mg q 6 h for 7 days
  125 mg q 12 h for 7 days
  125 mg qd for 7 days
  125 mg qod for 7 days
  125 mg every 3 days for 7 days

Further recurrences
- Vancomycin in tapering dose as above plus cholestyramine 4 g bid or
- Vancomycin 125 mg qid and rifampicin 600 mg bid for 7 days or
- Therapy with microorganisms (eg, *Saccharomyces boulardii* in combination with metronidazole or vancomycin) or
- Intravenous immunoglobulin

*Metronidazole may be substituted for vancomycin although there are no published data regarding its efficacy in this treatment regimen
q 6 h, every 6h; qd, every day; qod, every other day; bid, twice daily; qid, four times daily.
(Table adapted with permission from Linevsky JK, Kelly CP. Clostridium difficile colitis. In: Lamont JT, ed. *Gastrointestinal infections: diagnosis and management*. New York: Marcel Dekker, 1997:293–325).

First recurrence

CONSERVATIVE THERAPY

Conservative management of recurrent diarrhoea is preferable to retreatment with metronidazole or vancomycin as these agents perpetuate disturbance of the normal intestinal flora predisposing patients to further recurrences.[2] However, it is often difficult to withhold antibiotic therapy as many patients with recurrent disease are not able to tolerate ongoing diarrhoea. Persistent or worsening diarrhoea caused by recurrent *C difficile* infection is a clear indication for active treatment.

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RETREATMENT WITH SPECIFIC ANTI-*C DIFFICILE* ANTIBIOTICS

The most common therapy for recurrent *C difficile* diarrhoea is a second course of the same antibiotic used to treat the initial episode.[2] In one large observational study, 92% of patients with recurrent *C difficile* diarrhoea responded successfully to a single repeated course of therapy, usually with metronidazole or vancomycin.[3] Unfortunately, despite successful treatment of a recurrent episode, up to 65% of patients may have multiple recurrences.[4]

Second and further recurrences

A variety of treatment schedules have been suggested for patients with multiple recurrences of *C difficile* diarrhoea. One approach is to give a prolonged course of vancomycin (or metronidazole) using a decreasing dosage schedule followed by pulse therapy.[5] A combination of vancomycin and rifampicin was used successfully in a small uncontrolled study of seven patients with relapsing disease.[6] Anion exchange resins, such as cholestyramine, bind *C difficile* toxins and may be used in conjunction with antibiotics to treat frequent relapsers.[2] However, as cholestyramine may bind vancomycin as well as toxins, it should be taken at least 2–3 hours before or after vancomycin.

Biotherapy (therapy with microorganisms or "probiotics") is an attractive approach to the management of recurrent *C difficile* diarrhoea because it aims to restore the "colonisation resistance" of the normal colonic flora. Several agents and routes of administration have been evaluated, including brewer's or baker's yeast (*Saccharomyces cerevisiae*) taken by mouth, *Lactobacillus GG* given as a concentrate in skim milk, a mixture of colonic bacteria in saline administered as a rectal infusion, fresh faeces administered as a rectal enema, oral administration of non-toxigenic *C difficile*, and *Saccharomyces boulardii* given in capsule form.[1 2] Unfortunately, many of these studies have been small, open labelled, and uncontrolled.

S boulardii is a non-pathogenic yeast that has been reported to reduce the incidence of antibiotic associated diarrhoea. A randomised, double blinded, placebo controlled trial demonstrated that *S boulardii* (500 mg twice a day for four weeks) in combination with metronidazole or vancomycin significantly reduced recurrences compared with placebo in patients with multiple episodes of *C difficile* diarrhoea (recurrence rate 35% *v* 65%; p=0.04).[4]

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There is now substantial evidence that the immune response to *C difficile* toxins plays a major role in determining host susceptibility to disease.[7 8] Several investigators have found that serum antibody levels against *C difficile* toxins are low in patients with recurrent *C difficile* diarrhoea.[8] In a study of six children with relapsing *C difficile* colitis, Leung *et al* found that these children had low serum levels of IgG antibody against toxin A. Treatment with normal pooled intravenous gamma globulin (400 mg/kg every three weeks) that contains IgG anti-toxin A was associated with a marked increase in serum antitoxin antibody levels and resolution of recurrent *C difficile* diarrhoea.[9] Although this approach to the management of recurrent *C difficile* diarrhoea is promising, further controlled studies are required before gamma globulin can be recommended as therapy for this condition.

In summary, the management of recurrent *C difficile* diarrhoea can be a challenge to healthcare providers. Several treatment approaches have been recommended but experience to date is largely anecdotal. Further randomised controlled clinical trials are necessary to evaluate the efficacy of biotherapy and immunotherapy. Future approaches to the control of nosocomial *C difficile* infection and subsequent recurrence may involve active or passive immunisation of at risk individuals.[8 10] Until that time, the basic principals of management should involve (a) treatment of *C difficile* diarrhoea and (b) reduction of the susceptibility of the individual to *C difficile* reinfection by judicious use of antibiotics and attention to infection control issues.

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