Treatment of Clostridium difficile infection

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The treatment options for Clostridium difficile infection remain limited, although promising agents are currently being assessed. Metronidazole is the first-line drug of choice for those patients requiring specific anti-C. difficile treatment. Much of the interest in alternative therapies has centred on the difficult management issues posed by patients with multiple symptomatic recurrences of C. difficile infection. However, it is now clear that the majority of these episodes are due to reinfections with new C. difficile strains and not relapses caused by the original bacterium. Hence, the true efficacy of the alternative regimens remains unclear. Individuals susceptible to C. difficile reinfections need to be protected from exposure to C. difficile until their bowel flora recovers. While several biotherapeutic approaches to the treatment and prevention of C. difficile infection have been described, few controlled data are available. Preliminary studies with anti-C. difficile bovine immunoglobulin concentrates for treatment and prevention have produced promising results. Vaccination to prevent C. difficile infection, particularly in high-risk elderly patients managed within institutions where C. difficile is endemic, is a worthwhile therapeutic goal.

Introduction

Since a review of the treatment options for Clostridium difficile infection was published in 1992, there have been few additions to the therapeutic choice available to the clinician. However, several unproved therapies are used sporadically, and potential new approaches have been suggested. Progress in defining new treatments for C. difficile infection has been hindered by the heterogeneous nature of hospital-acquired diarrhoea, and in particular whether colitis and/or pseudomembranous colitis is present in individual cases. Study groups have usually been poorly defined in this context, and given the spontaneous resolution of symptoms in a proportion of cases (see below) the true efficacy of treatment approaches often remains uncertain. It is accepted that C. difficile is the major defined cause of hospital-acquired diarrhoea, and in particular whether colitis and/or pseudomembranous colitis is present in individual cases. Study groups have usually been poorly defined in this context, and given the spontaneous resolution of symptoms in a proportion of cases (see below) the true efficacy of treatment approaches often remains uncertain. It is accepted that C. difficile is the major defined cause of hospital-acquired diarrhoea, and in particular whether colitis and/or pseudomembranous colitis is present in individual cases. However, severe colonic inflammation or pseudomembrane formation, or because symptoms persist following cessation of the precipitating agent. There is, however, a major practical dilemma when deciding when to initiate treatment. It is difficult to withhold treatment from a patient with C. difficile toxin-positive diarrhoea, as it is currently not possible to predict who will spontaneously improve and who will have protracted and/or
worsening symptoms. This decision is made still more difficult as C. difficile infection frequently occurs in frail, elderly individuals in whom treatment delay may have serious consequences. Indeed, although it is rarely possible to prove that C. difficile is a cause of death, such infection has been significantly associated with mortality in the elderly. In practice, if the patient remains symptomatic (with no improvement) at the time of laboratory confirmation of the diagnosis, which is usually at least 24–48 h after the onset of diarrhoea, specific treatment is often instigated. A antibiotic(s) with a lower propensity to induce C. difficile infection should, if possible, be substituted for the implicated drugs whenever antimicrobial treatment has to be continued.7

First-line therapy

Two specific treatments of C. difficile infection are available, namely oral vancomycin 125 mg qds for 7–10 days, or metronidazole 400 mg tds for 7–10 days. No statistically significant differences in the response (c.80–100%) or relapse (c.15–25%) rates for oral vancomycin compared with oral metronidazole have been demonstrated.1,6 The mean duration of symptoms in patients with C. difficile infection is significantly shorter in patients treated with vancomycin (3.0 days; n = 22) compared with those given metronidazole (4.6 days; n = 28). It is, however, unknown whether this difference is significant in terms of realizable clinical benefit, especially since vancomycin (approximately £120 sterling for a 10 day course) is considerably more expensive than metronidazole (about £2 sterling). In particular, it has never been shown that the marginally better response time following oral vancomycin therapy can be correlated with a shorter hospital stay. If, however, large numbers of C. difficile cases are causing a shortage of isolation facilities, then a quicker symptomatic response should theoretically release such resources. Dosages of oral vancomycin greater than the standard 125 mg qds regimen are not more effective,9 but dose-ranging studies for metronidazole have never been published. In practice, the selective pressure for glycopeptide-resistant enterococci provided by oral vancomycin has prompted most hospitals now to use metronidazole as the first-line treatment for C. difficile infection and the former agent for ‘difficult’ cases (see below). It is worth noting that the optimum management of C. difficile-negative antibiotic-associated diarrhoea has not been established.

A particularly worrying recent report from Spain noted a significantly higher recurrence rate of C. difficile infection in HIV-positive patients (26%) compared with non-HIV cases (14%).10 The authors found that metronidazole resistance in vitro (NCCLS MIC breakpoint of 32 mg/L) was significantly more common in the HIV-positive cases than in the non-HIV cases (38% and 15%, respectively). This is the first account of apparently widespread metronidazole resistance in C. difficile, previously only sporadic cases had been reported. Given the problems of antimicrobial susceptibility testing of anaerobes, caution should be exercised before these results are accepted unchallenged.

Occasionally, patients with C. difficile infection are unable to take oral medication. Either metronidazole or vancomycin can be given via a nasogastric tube in such cases. Alternatively, owing to the unpredictable colonic concentrations of both metronidazole and vancomycin that are obtained following iv administration, empirical iv therapy should consist of both antibiotics.

Management of symptomatic recurrences

It is not uncommon to see patients with multiple clinical relapses of C. difficile infection.1 For example, in a recent UK study, repeat courses of antibiotic treatment were given to 37% of those patients requiring specific therapy for C. difficile infection, but it was not known whether the high clinical failure rate was due to relapses or to reinfections.11 Patients with symptomatic recurrences of C. difficile infection pose a therapeutic dilemma: should metronidazole or vancomycin be prescribed for ‘apparent’ treatment failures? While reported relapse rates for treatment with metronidazole or vancomycin are not significantly different (5–23% and 9–24%, respectively11), ‘relapse’ is normally defined clinically, i.e. as a symptom-free period followed by a recurrence of diarrhoea. A iso, it should be remembered that approximately a quarter of patients whose symptoms of C. difficile resolve still excrete the bacterium in faeces.12,13 A recent study of risk factors for recurrences of C. difficile infection included patients whose symptoms had ceased for only 1 day.14 Clearly, such an approach is likely to over-diagnose recurrences of infection.

Two series of case histories involving 10 and 11 patients respectively have shown, using DNA fingerprinting, that at least half of these so-called relapses are reinfections with a different strain.15,16 In a more recent and larger study, differing C. difficile DNA fingerprints were documented in 15/27 patients, and hence at least 56% of the clinical recurrences of infection were in fact due to reinfection as opposed to relapse.5 A iso, as an endemic C. difficile clone was present in 18 out of 27 patients (67%) and accounted for 53% (31/58) of all isolates, it is probable that the great majority of symptomatic recurrences were reinfections with either a different or the same C. difficile strain.

It has been common practice to switch from metronidazole to vancomycin (or vice versa) in patients with symptomatic recurrences. However, these data5 weaken the justification for the prescription of oral vancomycin as a second-line agent in such patients. There is
considerable pressure to assess new and unproved treatment options for individuals with multiple symptomatic recurrences of *C. difficile* infection. Having shown that reinfections account for the majority of such cases, there is little rationale for using ‘experimental’ treatment regimens, such as those discussed below, for reinfections as opposed to relapses. Indeed, we should remain sceptical about new treatments for ‘relapses’ of *C. difficile* infection, unless it is clear that the problem is not really one of ‘reinfection’. In patients with multiple relapses, 4–6 week regimens of tapering, followed by pulsed, doses of vancomycin have been given, supposedly first to kill vegetative *C. difficile*, and then to allow antibiotic resistant spores to germinate and subsequently also be killed. However, given the above findings it is likely that the frequent success of this regimen is due to the prolonged antibiotic course simply preventing reacquisition of *C. difficile*, during the period when the patient’s bowel flora remains ineffectual against bacterial colonization. A combination of oral vancomycin and rifampicin given for 7–10 days has also been used with some success in small numbers of patients with multiple symptomatic recurrences.

There have been occasional case reports of symptoms worsening in unconfirmed cases of *C. difficile* infection following the administration of an anti-motility agent. This observation was not confirmed in a more recent study of patients with mild to moderate *C. difficile* infection. While anti-motility agents may aid the nursing of patients with diarrhoea, their use should be avoided in severe cases of *C. difficile* infection, because of the theoretical potential accumulation of toxins in the gut.

Measures must be taken to ensure that further strain acquisition by index cases does not occur. Unfortunately, patients with symptomatic *C. difficile* infection are likely to remain susceptible to such acquisition due to impaired colonization resistance secondary to disrupted gut flora. It is poorly understood why some individuals in particular suffer multiple symptomatic recurrences of *C. difficile* infection. There is evidence of a poor immune response to *C. difficile* toxins in these patients, and it is known that antibodies to *C. difficile* are reduced in some elderly individuals. Such observations have stimulated research into immunological approaches to treatment (see below).

**A latternate treatment approaches**

These can be divided broadly into antibacterial, biotherapy and immunological approaches, with the latter two categories being the main areas of study in recent years. Alternative antibiotics to metronidazole and vancomycin include bacitracin, which has to be prepared in-house using sterile gelatin capsules and is less effective than vancomycin, and fusidic acid, which has also been used with some success in limited numbers of patients. A recent study compared the efficacies of oral fusidic acid, metronidazole, teicoplanin and vancomycin for the treatment of *C. difficile*-associated diarrhoea. Unfortunately, relatively few patients were enrolled (28–31 per group) and, therefore, significant differences observed between the antibiotics were few and were limited to results in favour of teicoplanin when compared with fusidic acid and/or metronidazole for the overall analysis of the clinical relapse and/or microbiological failure. When the results for the 55–71% of patients in each treatment group who had colonoscopically proven colitis were compared, no significant differences were observed. The authors concluded that metronidazole remained the first-line treatment of choice. The use of anion-exchange resins to bind *C. difficile* toxins is no longer fashionable, partly because vancomycin can bind to these agents in vitro.

Several small series of patients have been treated for, or received prophylaxis against, antibiotic-associated diarrhoea with biotherapy, including *L. acidophilus*, *L. casei*, *L. reuteri* and *S. boulardii*. A large USA multicentre trial of *S. boulardii* compared with established treatments of *C. difficile* infection was set up, but it is not clear why the results of this have not been published. It should be noted that *Saccharomyces cerevisiae* (brewer’s yeast) is distinct from *S. boulardii*. Use of inexpensive
over-the-counter preparations of brewer’s yeast cannot, therefore, be considered to be cheap ‘equivalents’ to the commercial preparation of S. boulardii. A recent excellent review of biotherapy for the treatment of diarrhoea is recommended for further information.

The nature and role of the immune response to C. difficile infection is an area of interest which may ultimately lead to the development of effective vaccines or other forms of immunotherapy. One promising approach has been the study of an anti-C. difficile bovine immunoglobulin concentrate. Bovine colostrum is rich in IgG, unlike human colostrum which is enriched with IgA, and levels of specific IgG antibodies can be increased markedly following immunization with C. difficile toxoids. A bovine immunoglobulin concentrate has been reported to inhibit the cytotoxicity and enterotoxicity of C. difficile toxin and, following oral administration of the preparation, human faeces have been shown to contain neutralizing antitoxin activity. Further human studies are awaited with interest; these may include modifications to the immunization process in order to maximize the neutralizing antitoxin activity, and enteric coating of the preparation to ensure high dose delivery to the large intestine.

Prophylaxis against C. difficile infection

The most obvious prophylaxis against C. difficile infection is either the avoidance of precipitating antibiotics or the prevention of acquisition of the bacterium. These approaches are discussed elsewhere in this supplement. As with treatment options for C. difficile, three therapeutic approaches have been explored, namely antibacterial, biotherapeutic and immunological ones. Antibacterial prophylaxis is theoretically the least attractive of these, as any oral antibiotic will inevitably adversely affect the normal gut flora, assuming that sufficient quantities reach the large intestine. As such, it is likely that the period of susceptibility to colonization by C. difficile will be increased. In any case, the only human study of antibacterial prophylaxis against C. difficile infection found that neither oral metronidazole nor vancomycin was effective at preventing the asymptomatic faecal excretion of C. difficile.

The most convincing studies of biotherapy prophylaxis involve the use of a commercial preparation of S. boulardii. Two large studies have noted a reduction in diarrhoea in patients given prophylactic S. boulardii concurrently with antibiotics (until about 2 weeks after cessation of antibiotic therapy). However, in one of these, diarrhoea was not significantly reduced in the subset of patients who were C. difficile-positive, although this may reflect limited study power. Also, as the mean age of subjects in this latter study was 48 years, the population studied differed markedly from the elderly patients on geriatric wards, who are at particularly high risk of C. difficile infection. Interestingly, neither acquisition of C. difficile nor production of toxin was reduced in this study, suggesting that S. boulardii in some way blocks toxin activity as opposed to preventing colonization. In a rat ileal model, S. boulardii was shown to prevent binding of toxin A, whereas heat-inactivated S. boulardii did not block toxin. Further controlled studies are warranted to establish whether manipulation of the gut ecosystem can effectively prevent either C. difficile acquisition (preferably) or toxin activity.

Prophylaxis with bovine colostral immunoglobulin collected following immunization with a C. difficile culture filtrate was found to prevent diarrhoea in clindamycin-treated C. difficile-exposed hamsters. Theoretically, vaccination against C. difficile toxin(s), particularly in individuals at high risk, could prevent infection. In a recent study, a plasmid was engineered to express a fusion protein containing amino acid residues from the non-toxic, receptor-binding, carboxy-terminus of C. difficile toxin A and the secretion signal of Escherichia coli haemolysin A. When the plasmid was introduced into Vibrio cholerae, the fusion protein was secreted by a number of V. cholerae strains and recognized by both monoclonal and polyclonal anti-C. difficile toxin A antibodies. The plasmid was next introduced into an attenuated V. cholerae strain, which was then administered orally to rabbits. Colonization studies showed that the V. cholerae vector was recoverable from rabbit ilea for up to 5 days after oral inoculation, and systemic anti-C. difficile toxin A immunoglobulin G antibody responses were observed. Vaccination also led to significant protection against toxin A in an ileal loop assay. It is likely that much of the future activity towards the discovery of new therapeutic measures against C. difficile infection will be concentrated on active or passive immunological modalities. The challenge will be to provide a long-lasting protective therapy which is effective in the elderly. Unfortunately, vaccine efficacy in this age group often remains sub-optimal.

References


