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Management of *Clostridium difficile* infection

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ABSTRACT *Clostridium difficile*-associated diarrhoea is the most common cause of nosocomial diarrhoea and has a high morbidity and mortality among infected patients. Its prevalence and recurrence rates increase with age. Influencing local antibiotic practice can have an impact on infection rates, and this and other specific strategies to reduce the incidence and relapse rates of *C. difficile*-associated diarrhoea are needed. Reduction of *C. difficile*-associated diarrhoea rates would have enormous positive resource implications for health services, primarily by reducing length of hospital stay, and would also reduce mortality and morbidity in hospital inpatients.

KEYWORDS *Clostridium difficile*, cross-infection, diarrhoea, hospital-acquired infection, management, older people

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INTRODUCTION

Managing *Clostridium difficile*-associated diarrhoea (CDAD) infection has increasingly become a routine part of the physician's workload. National mandatory surveillance was introduced in the UK in 2004 and rates of CDAD infection have risen from 2.2 to 2.39 cases per 1,000 bed days between 2005 and 2006 (the annual total was 55,681 cases in 2006). *Clostridium difficile* is a Gram-positive, spore-producing, anaerobic bacillus that causes illness by producing exotoxins that act on the colon. Originally discovered in 1935, it was not until 1978 that this organism was recovered from the stool of patients with antibiotic-associated pseudomembranous colitis. It is now implicated as the pathogenic agent in this disease.

There have been a number of serious outbreaks related to CDAD infection in recent years that have brought this nosocomial infection to the attention of the public and the media. A hypervirulent strain of *C. difficile*, known as NAP1/027, has emerged, which produces higher levels of toxins A and B and an extra toxin (binary toxin). This strain caused outbreaks in Quebec, the UK and in parts of Europe and appears to cause more serious disease than other strains, with higher rates of attributable mortality. The NAP1/027 strain is resistant to fluoroquinolone antibiotics, and case-control studies of the outbreaks showed prior fluoroquinolone use to be a risk factor for disease. It has been detected globally and continues to pose a risk as an epidemic disease. In addition, populations previously not thought to be at risk for CDAD (e.g. community-dwellers without antibiotic exposure) have experienced outbreaks. Although the reasons for this increase in incidence are unknown, it is unlikely to be related to the NAP1/027 strain.

The *C. difficile* organism causes gastrointestinal infections in humans that range from asymptomatic colonisation to severe diarrhoea, pseudomembranous colitis, toxic megacolon and death. The mortality rate related to CDAD infection may be as high as 25% in older people. *Clostridium difficile* can also be found in the stool of healthy people in the community. This is asymptomatic carriage and occurs in approximately 5–7% of healthy adults, but this figure rises to approximately 20% of hospital inpatients. It has been suggested that antibiotic therapy reduces the colonisation resistance provided by other gut bacteria, precipitating active infection from this colonised state.

RISK FACTORS

Some of the risk factors for CDAD infection are intuitive and include increasing age and hospital stay, co-morbidity, multiple antibiotics and length of antibiotic course. Other risk factors such as presence of a nasogastric tube, anti-ulcer therapy and gastrointestinal procedures (e.g. endoscopy) may be less well recognised. Studies that have considered the effects of proton pump inhibitors (PPIs) have found that patients are about twice as likely to develop CDAD while taking this medication. The increased risk is likely to be due to increased survival of spores owing to the less acidic gastric environment. However, analysis also shows female gender gives similar odds ratios, so the effects of PPIs are likely to be small compared with prior antibiotic therapy. Particular antibiotics have also been implicated, such as clindamycin, cephalosporins and, more recently, fluoroquinolones such as levofloxacin. However, virtually all antibiotics have been associated with CDAD infection.

There is some evidence that herd immunity has an influence upon the case acquisition rate of CDAD, that is as the number of susceptible patients increases, the easier the infection spreads and therefore the greater the potential number of cases. This may further explain the higher incidence of outbreaks in care of the elderly wards and intensive care units. More than 80% of positive cultures are reported in those over the age of 65, with one study showing CDAD prevalence in an acute geriatric ward of 13.7%, and 20.4% in a chronic geriatric ward, with a nosocomial infection rate of 12.2%.

PREVENTION

A variety of preventative strategies have been trialled. Interventions are directed not only towards the control of the bacteria but also of the antibiotics associated with the infection. *Clostridium difficile*-associated diarrhoea is spread by the faeco-oral route, and infection can be acquired either spontaneously (usually after antibiotics) or by picking up spores (from surfaces or from the hands of others), which are then ingested. Although alcohol gel does have some activity against the spores of CDAD, hand-washing is considered the optimal method to avoid transmission of CDAD.

In addition to infection control measures, restrictive antibiotic practices in elderly care wards have been shown to reduce the incidence of CDAD infection. In particular, limiting the use of cephalosporins appears to be a consistently successful method of reducing CDAD infection. Previously a vogue emerged for using fluoroquinolones instead of cephalosporins on restrictive antibiotic policies, but given the outbreaks of the NAP1/027 strain, enthusiasm for this substitute has waned. Several trials have used a combination of education, cleaning and restrictive antibiotic policy, and these studies report encouraging results with sustained lower levels of CDAD infection. Clearly implementing such prevention strategies requires the co-operation and enthusiasm of a wide range of people, but it does appear to be successful.

Prebiotics and probiotics have created considerable clinical and public interest over the past few years as having potential to prevent and treat CDAD and a whole host of other possible beneficial effects. Probiotics are defined as live microbes that, when ingested, confer health benefits to the host. Common examples of probiotic bacteria are *Lactobacilli* (*casei*, *rhamnosus* and *acidophilus*) and the probiotic yeast *Saccharomyces boulardii* (or Brewer's yeast). Prebiotics are foods that promote the growth or function of probiotic micro-organisms; examples include oats, wheat and barley. Probiotics have shown promise for primary prevention of CDAD, and several studies using either *Lactobacilli* or *Saccharomyces* have demonstrated lower incidence of CDAD in those in the probiotic arm of the trial. Some studies have failed to show benefits, but the overall impression is that probiotics are useful in primary prevention. The case for probiotics has, however, been slightly hampered by case reports of life-threatening fungaemias and bacteraemias in immunocompromised patients, and caution is needed when prescribing in this group of patients. Prebiotics such as oligofructose are another interesting possibility for prevention or treatment of CDAD, and although early trials show promise, further research in this area is needed.

CLINICAL PRESENTATION

Clostridium difficile-associated diarrhoea infection should be considered as a differential diagnosis in all hospital inpatients who present with diarrhoea (including new admissions). Antibiotics may have been given in the community, patients may have been exposed to others with CDAD or may have been recently discharged from hospital. A history of the diarrhoea, including the potential risk factors described above, in conjunction with a thorough clinical examination to exclude colitis, bowel perforation and other diagnoses, is mandatory. Particular attention should be paid to features suggestive of a systemic inflammatory response, such as fever, tachycardia and tachypnoea, as these may suggest a colitis or more severe infection.

In addition to stool cultures, blood tests (particularly white cell count and potassium and albumin levels) should be taken. Several series have considered those who experience severe or relapsing CDAD infection and found that this group tend to have low albumin, low potassium and markedly elevated white cell counts. In this more severe group, some would advocate vancomycin as a first-line therapy. Those who have evidence of severe illness, either at presentation or over the course of treatment, may need further abdominal imaging, such as erect chest radiograph, abdominal radiograph and computed tomography scanning, to exclude other diagnoses that may co-exist (e.g. Crohn's disease, diverticulitis).

TREATMENT

Table 1 describes standard management measures for all patients with CDAD diarrhoea, regardless of severity. Until recently, studies had shown that the antibiotics vancomycin and metronidazole were equally effective, with one study reporting 94% of those treated being cured clinically, with comparable (16%) rates of clinical recurrence in both groups. Therefore, on the basis of cost (and to prevent emergence of vancomycin-resistant *enterococci*) oral metronidazole has been the recommended first-line antibiotic. However, a recent double-blind, placebo-controlled randomised controlled trial by Zar et al. showed that vancomycin was significantly more likely to produce cure in severe CDAD than

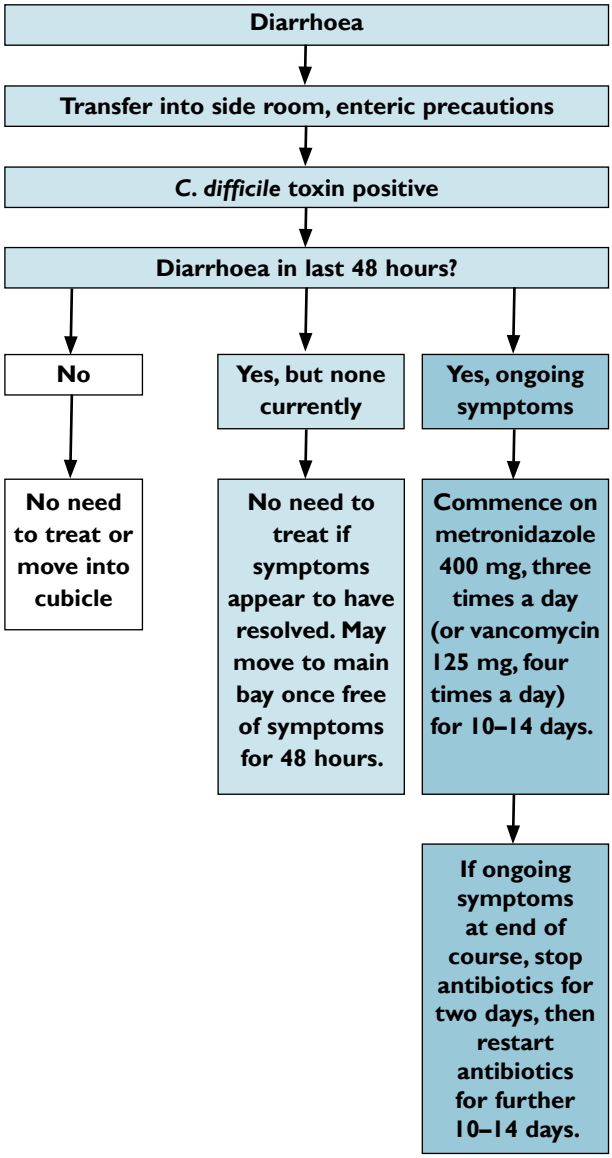

FIGURE 1 Management of CDAD.

metronidazole (97% vs 76%, respectively). The main flaw of the study was that it compared metronidazole 250 mg four times daily with vancomycin 125 mg four times daily to ensure adequate blinding, which is only two-thirds of the usual total dose of metronidazole used. Nevertheless, cure rates for mild CDAD were 90%, which is comparable with previous studies that have used the standard dose of metronidazole and considered all severities of CDAD as one group. Further discussion of optimal first-line treatment of severe CDAD is warranted in light of this new evidence.

Asymptomatic carriage of *C. difficile* toxin in patients without diarrhoeal symptoms warrants no treatment. Indeed, treating asymptomatic patients is not associated with long-term eradication of the organism and one study has shown that this group is in fact less likely to develop CDAD, suggesting a protective mechanism. Treatment is described in Figure 1.

TABLE 1 Standard management for all patients testing positive for *C. difficile* toxins

- Barrier nurse in side room where possible.
- Stop antibiotics where possible.
- Avoid starting antibiotics where possible.
- Stop all laxatives.
- Commence stool chart.
- Daily examination of abdomen for tenderness or distension (indicative of colitis).
- Regular blood tests to check potassium, white cell count and albumin.

RELAPSE AND RECURRENCE

Relapse and recurrence have been shown to occur in 15–25% of treated patients for CDAD. Older age and frailty are predictors for recurrent disease. Relapse or recurrence is characterised by further diarrhoea after initial remission. Repeat testing of stool samples in this instance is unhelpful as toxin remains detectable in stool for many weeks after an initial episode of CDAD. Usually a second course of metronidazole will be used, but if further relapse occurs, vancomycin is seen as the drug of choice. Some studies have considered the use of pulsed-tapered regimens, where gradually reducing doses of vancomycin are given followed by 'pulses' of vancomycin every few days. These studies are unfortunately case series or small non-blinded clinical trials, and although results appear favourable, large robust trials are needed with proper randomisation and blinding before conclusions can be drawn.

Several studies have shown that recurrent infection represents the majority of second infections, and that another major predictor for relapse/recurrence is poor host antibody antitoxin response to *C. difficile* toxins. Other studies have therefore considered the use of passive immunoglobulin with some success, but numbers are too small to be conclusive and further studies are needed. Nevertheless, patients with severe (evidence of colitis), refractory or recurrent (more than two episodes of diarrhoea) disease should be considered for treatment with intravenous immunoglobulin. Another useful therapy may be probiotics, and a number of studies have compared the use of *Saccharomyces boulardii*, in particular, with improved resolution rates.

A handful of case studies have considered the use of corticosteroids (some cases were children) successfully, but corticosteroids are not routinely used in clinical practice. Other techniques to restore the gut flora have been tried and reported largely as single case reports, such as rectal infusion of normal faeces and saline enema of normal colonic bacteria, but these remain unattractive and unproven therapies. Notably, there are a few reported cases of methicillin-resistant *Staphylococcus aureus*

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enterocolitis causing very similar symptoms to CDAD. These cases are usually *C. difficile* toxin-negative but show profuse growth of *Staph. aureus* on culture. Many laboratories now test only for *C. difficile* toxins rather than culturing the organism, so if toxins are negative despite a strong clinical suspicion, liaison with the microbiology team regarding additional tests may be helpful.

A pragmatic approach to treating relapse or recurrence, therefore, would be to use metronidazole as a second treatment course unless the patient has severe disease (low albumin, etc.), in which case vancomycin would be appropriate. Vancomycin should be used for a third course and could be combined with either *Saccharomyces boulardii*, or a tapered-pulsed course of vancomycin could be trialled. Immunoglobulin could also be trialled. Although much of this is not based on robust evidence, it is currently the best evidence available until larger trials are performed.

COST

Clostridium difficile-associated diarrhoea is costly in terms of mortality, morbidity and healthcare resources. Those who develop CDAD stay significantly longer in hospital compared with controls (including an average 14 days in a side room), and are significantly more likely to die. It has been estimated that CDAD infection in the UK results in an increase in total identifiable cost of more than £4,000 per case, with >94% of this additional cost being a result of the increased length of hospital stay.

KEY POINTS

- *Clostridium difficile* is a common cause of nosocomial diarrhoea.
- *Clostridium difficile* infection occurs predominantly in older people.
- Increasing age is a risk factor for recurrent disease.
- Management of *C. difficile* infection is primary prevention, with restrictive antibiotic practices being of proven benefit in older age groups.
- Secondary prevention of *C. difficile* infection is with antibiotic treatment, with metronidazole as first-line treatment.

FURTHER READING

- Kyne L, Merry C, O'Connell B et al. Factors associated with prolonged symptoms and severe disease due to *Clostridium difficile*. *Age Ageing* 1999; 28(2):107–13.
- Kyne L, Kelly CP. Recurrent *Clostridium difficile* diarrhoea. *Gut* 2001; 49:152–53.
- Ludlam H, Brown N, Sule O et al. An antibiotic policy associated with reduced risk of *Clostridium difficile*-associated diarrhoea. *Age Ageing* 1999; 28(6):578–80.
- Rudensky B, Rosner S, Sonnenblick M et al. The prevalence and nosocomial acquisition of *Clostridium difficile* in elderly hospitalized patients. *Postgrad Med J* 1993; 69:45–7.
- Starr J. *Clostridium difficile* associated diarrhoea: diagnosis and treatment. *BMJ* 2005; 331:498–501.
- Wilcox M. *Clostridium difficile* setting the scene. *J Antimicrobial Chemo* 1998; 41(suppl.C):1–3.
- Zar FA, Bakkanagari SR, Moorthi KM et al. A comparison of vancomycin and metronidazole for treatment of *Clostridium difficile*-associated diarrhoea, stratified by disease severity. *Clin Infect Dis* 2007; 45:302–7.

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