REVIEW

Pathogenesis and treatment of *Clostridium difficile* infection

I Tonna, P D Welsby

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This paper reviews the pathogenesis and management of *Clostridium difficile* diarrhoea, in particular the management of recurrent episodes.

Clostridium difficile is a Gram positive, spore forming anaerobic bacillus that in contrast with popular belief is not a normal commensal of the adult gastrointestinal tract.¹ The organism is acquired from an exogenous source and given certain conditions can induce disease. Consequences range from asymptomatic carriage, dehydration, metabolic changes, bowel perforation, and haemorrhage. The mortality is highest in the elderly population and is about 1.5% of all hospitalised cases of *C difficile* diarrhoea.² There are five major patterns of *C difficile* induced disease (see table 1).

PATHOGENESIS

There are two prerequisites for developing *C difficile* associated diarrhoea: disruption of the normal gastrointestinal flora, causing diminished colonisation resistance favouring *C difficile*, and acquisition of the organism from an exogenous source. Other factors include host susceptibility, virulence of the *C difficile* strain concerned, and the nature and extent of antimicrobial exposure.³

In normal people there are more than 500 species of bacteria in the colon. A gram of faeces normally contains up to 10¹² bacteria that resist colonisation and impair multiplication of *C difficile*. Lactobacilli and group D enterococci display most antagonistic activity,⁸ and eradication or reduction of such bacteria by antibiotics creates an environmental vacuum for *C difficile* to fill. People have significant variations in their intestinal microflora and the elderly population are most at risk of *C difficile* diarrhoea, possibly because their protective bacteroides diversity is more likely to be affected by antibiotics, which then permit growth of *C difficile*.^{4 9}

There are more than 400 strains of *C difficile*. Infection is acquired faeco-orally and *C difficile* multiplies in the colon. Only toxin producing strains produce disease.¹⁰ Toxins are endocytosed by colonic epithelial cells and damage the actin cytoskeleton, causing cell death. There are two toxins that together are normally required to cause *C difficile* associated diarrhoea. Toxin A disrupts colonic mucosal cell adherence to colonic basement membrane and damages villous tips. Toxin B enters the cell by endocytosis and induces apoptosis. Toxin B is 1000 times more potent in its cytotoxic effect than toxin A. Both toxins stimulate monocytes and macrophages, which in turn release interleukin 8, resulting in tissue infiltration with neutrophils.¹¹

However, infection with “virulent” strains of toxin producing *C difficile* can be asymptomatic implying that other factors, including the environment within the gut are important.^{12–15}

The extent of clinical manifestations depends on the immune response to *C difficile*. Patients with low anti-toxin A IgG levels manifest more severe disease unlike those with higher levels who usually recover spontaneously.⁵

TREATMENT

In mild cases, oral rehydration plus withdrawal of the causative antibiotic is often successful.¹⁶ Identification of *C difficile* or its toxins should not lead to reflex prescription of metronidazole or vancomycin. Oral rehydration alone may succeed because it allows host immunological responses to deal with the infection and does not create additional ecological vacuums for *C difficile* to re-emerge into once metronidazole or vancomycin is stopped. Oral metronidazole or vancomycin can be used if symptoms are severe. Metronidazole is preferred because it is less expensive, well tolerated when given for short periods, is effective as vancomycin, and does not encourage vancomycin resistant enterococci.¹⁷ Parenteral antibiotic therapy is less effective than the oral route. Intravenous metronidazole is of dubious efficacy. Although there were case reports of some clinical benefit when used in patients in whom oral administration was impractical, further trials are needed to assess the effectiveness of intravenous compared with oral metronidazole.¹⁸ Vancomycin is not excreted into or absorbed from the gastrointestinal lumen. Consequently, parenteral administration of the drug will not reach the site of infection. Nasogastric tube or enema administration may be necessary.^{5 6 19}

There are two main reasons for recurrences after successful treatment with metronidazole or vancomycin:

- (1) Neither antibiotic eliminates *C difficile* spores. Once metronidazole or vancomycin are stopped spores will germinate and *C difficile* will proliferate in the ecological vacuum with return of diarrhoea.²⁰
- (2) Administration of any antibiotic may induce expression of *C difficile* virulence factors that will be most developed just before the antibiotic is stopped. Hence, diarrhoea will recur after the treatment is stopped. It is known that toxin production occurs after the end of the exponential growth phase, whereas much lower levels are seen in early and mid-exponential growth phase.²¹ In such situations, the relapse would be expected to occur soon after stopping metronidazole or vancomycin or even during the course of treatment.

See end of article for authors' affiliations

Correspondence to:
Dr P D Welsby, Infectious
Diseases Unit, Western
General Hospital,
Edinburgh EH4 2XU, UK;
P.Welsby@ed.ac.uk

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Table 1 Clinical range of *Clostridium difficile* infections⁷

Infection pattern	Characteristics
Asymptomatic carriage (up to 5% of healthy adults, 20% in patients hospitalised for one week, 50% in patients hospitalised for four weeks) ³	Most common occurrence, the infected person acts as a reservoir of infection
"Simple" antibiotic associated diarrhoea (20% of all cases with presumed antibiotic associated diarrhoea) ⁴	Possibility of dissemination of organisms within hospital environments No systemic symptoms Common during treatment with antibiotics Diarrhoea usually stops after the antibiotic is withdrawn Mild oedema and hyperaemia of the rectum on sigmoidoscopy, but with normal colonic mucosa
Diarrhoea without pseudomembrane formation (20% have proximal disease undetected on routine flexible sigmoidoscopy) ⁵	Systemic manifestations including low grade fever and leucocytosis Abdominal pain Endoscopically there may be patchy erythematous colitis
Pseudomembranous enterocolitis (10% of <i>C. difficile</i> associated diarrhoea) ⁶	Typical elevated yellowish plaques on colonoscopy
Fulminant colitis (3% of <i>C. difficile</i> associated diarrhoea) ⁶	High risk of complications such as perforation, megacolon, or death

Recurrence rates of *C. difficile* diarrhoea vary between 15% to 35% but may be as high as 55%.^{22–24} Most relapses occur within two months.²² Recurrences can occur when original strains re-establish themselves or if infection with a different strain of *C. difficile* occurs.

TREATMENT OF SYMPTOMATIC RELAPSES OF CLOSTRIDIUM DIFFICILE ASSOCIATED DIARRHOEA

Symptomatic return occurs when diarrhoea reappears along with positive tests for *C. difficile* toxin in the faeces. The diagnosis is made when *C. difficile* toxin is identified in the stools. The presence of the organism in the stool does not necessarily mean that the diarrhoea is attributable to *C. difficile*.

There are a number of options for treating relapses of *C. difficile* diarrhoea:

- (1) If diarrhoea is mild, simple supportive treatment is advocated to allow the intestinal flora to stabilise, allowing the diarrhoea to settle.¹⁶
- (2) If diarrhoea is severe, another course of oral metronidazole or vancomycin should be given.¹⁶
- (3) There are 10 other options to be considered in problematic relapses (box).

Further courses of metronidazole or vancomycin have been administered either as:

- A prolonged repeat of treatment for 10–16 days.²⁰ High dose vancomycin (2 g/day) was associated with a lesser rate of

recurrence of diarrhoea than medium/low dose vancomycin (44% v 71%–54%). Medium dose metronidazole (1.5 g/day) had a recurrence rate of 40% whereas it was 44% with the low dose form (<1 g/day). The number of patients treated with high dose metronidazole (n = 2) did not have sufficient power to reach statistical significance.

- A tapering regimen with metronidazole or vancomycin started at a high dose (>2 g/day of vancomycin or 2 g/day of metronidazole).²⁰ The vancomycin dose was decreased over 10–30 days to a dose of 125 to 750 mg/day depending on the preference of the physician. The best response was found in those cases given a starting dose of vancomycin 500 mg/day tapering to 125 mg/day over three weeks. This was associated with a 20% recurrence of diarrhoea. The number of patients treated with tapering doses of metronidazole (n = 1) was too low to be commented upon.
- A pulsed regimen.²⁰ Vancomycin was given in pulsed 125–500 mg doses every three days for three weeks (dose being determined by the responsible physician). When the 500 mg pulse was used this was associated with the lowest recurrence rate of diarrhoea (14%). Only one patient was given pulsed metronidazole, thus no clinically significant data could be extrapolated.
- A combination of the above.²⁰ Some of the patients were first treated with a tapering regimen of vancomycin followed by short courses of pulsed doses for 3–10 days. The recurrence rate was 20%.

The best results were seen when pulsed regimens were used. Pulsed regimens may be superior because they allow spores to germinate during the antibiotic free period with the resulting *C. difficile* being killed by the next pulse and allowing the normal colonic flora to re-establish itself during the pulse free period.²⁰

Colestyramine binds *C. difficile* toxin but is of unproved clinical benefit and therefore cannot be recommended.²⁵

Oral probiotic therapy (use of live non-pathogenic bacteria to "reestablish the gut flora" and provide colonisation resistance against *C. difficile*) uses organisms resistant to gastric acid. *Lactobacillus acidophilus* and *Saccharomyces boulardii* produce proteases that digest *C. difficile* toxins.²⁶ The initial trial used known quantities of *S. boulardii*. Use of probiotic yoghurts with similar organisms (for example, *S. cerevisiae*) may not have the same effect.²⁸ The optimum dose of any probiotic is unknown, but a study using 1 g/day of *S. boulardii* with 2 g/day vancomycin for 28 days was found to be 67% more effective than

Treatment options of severe relapses

- Tapering doses of vancomycin²⁰
- Pulsed regimen of vancomycin²⁰
- Use of colestyramine²⁵
- Use of probiotics^{26–29}
- Combined use of probiotics with high dose vancomycin²⁹
- Intravenous gammaglobulin administration^{31–34}
- Faecal enemas³⁵
- Whole gut lavage³⁶
- Stool administered via colonoscope after whole gut lavage³⁵

vancomycin alone.²⁹ Probiotics are attractive therapeutic options because they are inexpensive, are palatable, and rarely cause harm except perhaps in the immunocompromised.³⁰

It is possible that patients who develop relapses are a subgroup of those infected who are slow to mount immunoglobulin responses, especially those treated early with vancomycin or metronidazole. The larger the immunoglobulin response to *C difficile* toxin A during initial episodes of diarrhoea, the lower the rates of recurrent diarrhoea. Patients with low levels of immunoglobulin G to toxin A had a 48-fold increase in risk of relapse. Passive immunisation against *C difficile* might be possible because normal pooled human immunoglobulin preparations contain significant titres of *C difficile* antitoxins. Five children were treated successfully with intravenous immunoglobulin,³² and adult successes have also been reported.^{33–34}

Although aesthetically unpleasant, *C difficile* diarrhoea can be treated by introducing normal intestinal flora in faeces from healthy persons via a colonoscopy after whole gut lavage or even via a nasogastric tube.^{35–37}

CAN C DIFFICILE DIARRHOEA BE PREVENTED?

Prevention entails:

- (1) avoiding exposure to *C difficile* and its spores
- (2) avoiding the use of unnecessary antibiotics
- (3) supporting the immune system to deal with *C difficile* or its toxins

C difficile spores can survive up to five months in the environment and transmission often occurs in hospitals where *C difficile* infected patients are close to susceptible patients.⁶ Transmission occurs via the hands of healthcare personnel. Hand washing, glove use, and appropriate isolation of those infected are important.³

Antibiotics should be given only when indicated and should be avoided if possible for the two months after successful treatment of *C difficile* diarrhoea.¹⁶ Although the number of clinical trials are small, there is evidence that administration of probiotics may prevent antibiotic associated diarrhoea when given together with antibiotics.³⁸ On the other hand, use of these live organisms to treat antibiotic associated diarrhoea remains to be proved.

Anti-toxin A IgG induced by vaccination was protective in hamsters³⁹ and a *C difficile* toxoid vaccine resulted in high toxin A IgG in humans after four intramuscular doses.⁴⁰ Whether such antibody responses confer immunity against symptomatic *C difficile* diarrhoea, particularly in the elderly population, is unknown. Even if a vaccine were available, to whom should it be given? Should it be given to all elderly patients (and if so what is the cut off age?), to all patients after a first episode of *C difficile* diarrhoea, or to the whole population? Cost effectiveness would need to be considered.

Authors' affiliations

I Tonna, P D Welsby, Infectious Diseases Unit, Western General Hospital, Edinburgh, UK

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