Prevention and medical management of Clostridium difficile infection

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The incidence of Clostridium difficile infection in the United Kingdom has increased since the late 1990s. 1 High profile outbreaks in the United States, Canada, and northern Europe have been associated with a previously uncommon but highly virulent strain known as ribotype 027. A recent review in the BMJ examined the role of surgery in treating C difficile colitis. 2 This review focuses on the prevention and medical management of C difficile infection. Because few randomised controlled trials (RCTs) exist on this subject, our recommendations are based mainly on non-RCT studies and clinical governance reports.

Who becomes infected with C difficile?

C difficile can be cultured from the stool of 3% of healthy adults and as many as 35% of hospital inpatients. 1 Lower rates of nosocomial colonisation are seen in some studies, and may be dependent on patient population, length of hospital stay, and local infection control procedures. 2 3 4 Most colonised people remain asymptomatic. Clinical disease develops when the normal gut flora is disrupted, usually by antibiotic exposure, thereby creating conditions that favour C difficile proliferation within the colon. Although C difficile infections in England have started to decline overall, 36 097 infections in patients aged 2 years and over were reported to the UK Health Protection Agency (HPA) for the financial year ending March 2009 (www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1252326222452). Elderly hospital inpatients are the main group affected, but the epidemiology of the disease is changing. Community associated infections have been increasingly recognised, as have infections in pregnant women and children, populations previously regarded as being at low risk. 5

How does C difficile infection present and how is it diagnosed?

Gastrointestinal diseases associated with C difficile infection range from mild diarrhoea to fulminant colitis. Some “silent” infections present with abdominal pain and distension, in the absence of appreciable diarrhoea. These features may indicate severe disease, which in turn causes ileus or toxic megacolon. 6 7 UK national guidelines define C difficile infection as one episode of unformed stool, not attributable to any other cause, occurring at the same time as a positive C difficile toxin assay. 8 The toxin may be detected by commercial immunoassay kits, nine of which were tested against a “gold standard” cytotoxin or toxigenic culture assay. 9 Compared with the cytotoxin assay, sensitivities ranged from 67% to 92% and specificities from 91% to 99%. Because most patients with diarrhoea do not have C difficile infection, these equate in practice to negative predictive values greater than 95%, but positive predictive values that may be lower than 50% (for example, in samples from the community, where prevalence is low). When C difficile infection is uncommon or clinically unlikely, positive test results must therefore be interpreted with care and a confirmatory test should be considered. 10 11 In suspected cases of silent infection, endoscopy or abdominal computed tomography may be needed. Characteristic findings include thickening of the colonic wall, dilation, and pseudomembrane formation. 2

How can it be prevented?

Prevention has two aspects—prevention of acquisition of C difficile and prevention of infection in colonised people. This requires a multifaceted approach based on the five main strategies outlined in the UK Department of Health Saving Lives campaign (www.clean-safe-care.

SUMMARY POINTS

The incidence of Clostridium difficile infection has increased in the past decade
National and local surveillance of C difficile infection is crucial to guide implementation of control measures
Prudent antibiotic prescribing, correct hand hygiene, use of personal protective equipment, environmental decontamination, and isolation or cohort nursing may prevent infection
Treatment is with oral vancomycin or metronidazole, according to disease severity, with escalation of treatment in the event of non-response

SOURCES AND SELECTION CRITERIA

We searched PubMed and Google Scholar for articles published from 2006 to 2009 on the treatment and prevention of Clostridium difficile infection and screened the reference lists of retrieved publications. We also consulted the Cochrane Library and the recent best practice guidance from the Health Protection Agency. 1

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Table 2 | Faecal concentrations of oral and intravenous vancomycin and metronidazole.13-15

<table>
<thead>
<tr>
<th>Drug preparation</th>
<th>Typical faecal concentration</th>
<th>MIC90* (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral vancomycin (total 2 g daily)</td>
<td>Mean 3100 µg/g stool</td>
<td>0.75-2.0</td>
</tr>
<tr>
<td>Intravenous vancomycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral metronidazole (total 1.2 g daily)</td>
<td>0.4-14.9 µg/g stool</td>
<td>0.2-2.0</td>
</tr>
<tr>
<td>Intravenous metronidazole (total 1.5 g daily)</td>
<td>5.1-24.2 µg/g stool</td>
<td></td>
</tr>
</tbody>
</table>

*Minimum inhibitory concentration needed to inhibit 90% of strains.
†Watery or semiformed stool.

How can antibiotic stewardship help prevent *Clostridium difficile* infection?

Many authors have produced “hit lists” of antibiotics with the potential to cause *Clostridium difficile* infection,8 but this approach has problems.9 Classification into low, medium, and high risk antibiotics is practically useful (table 1), but any antibiotic, at any dose, for any length of time, will alter the colonic microbiota, potentially allowing *Clostridium difficile* to proliferate and cause disease.10 Prospective observational cohort studies suggest that restricting the use of the high risk agents, clindamycin and third generation cephalosporins, results in fewer cases of *Clostridium difficile* infection.10-12 Although use of fluoroquinolones has been linked to the spread of the ribotype 027 strain, risk analyses have been confounded by antibiotic polypharmacy, duration of antibiotic treatment, and infection control practices.13 In addition, observational data suggest that different fluoroquinolones differ in propensity to cause *Clostridium difficile* infection, with gatifloxacins having the highest risk.9

To reduce overprescribing and inappropriate antibiotic use, the Saving Lives campaign makes the following “best practice” recommendations for antimicrobial prescribing: antibiotics should be prescribed according to local policies and guidelines for treatment and prophylaxis, avoiding broad spectrum agents; the indication for starting an antibiotic should be documented in the medical record, along with a stop or review date; intravenous antibiotics should be avoided, and the shortest treatment course likely to be effective should be prescribed; prescriptions should be reviewed daily; and single antibiotic doses should be used for surgical prophylaxis if possible.

Hospital initiatives focusing on antibiotic stewardship include antibiotic ward rounds, antibiotic care bundles,15 electronic prescribing, restricted antibiotics that require microbiology approval, and computerised decision support networks.16 Antibiotic pharmacists may play a major role in this regard.17

What infection control measures should be instituted?

*Clostridium difficile* infection has been estimated to increase hospital stay by an average of 21 days,18 although more recent studies have suggested a less pronounced effect.19-21 While in hospital, infected patients may continue to excrete infective *Clostridium difficile* spores. Hand washing is paramount in preventing hospital acquired infections (www.nhs.uk/cleanyourhands). Alcohol based hand gels are highly effective against non-spore forming organisms, but they do not kill *Clostridium difficile* spores or remove them from hands. Experimental studies have shown that alcohol based hand gels are significantly less effective at reducing contamination with *Clostridium difficile* spores than washing with soap and water.17 UK national guidelines recommend that healthcare workers wash their hands before and after contact with patients with suspected or confirmed *Clostridium difficile* infection, and that disposable gloves and aprons are used when handling body fluids and caring for such patients.1

*Clostridium difficile* spores can survive in the environment for months or years, and environmental contamination has been linked to the spread of *Clostridium difficile* infection in healthcare settings.17 UK national guidelines therefore recommend various forms of environmental decontamination:1 rooms or bed spaces of infected patients should be cleaned daily using chlorine containing cleaning agents or vaporised hydrogen peroxide.22-26 Keeping surfaces free of *Clostridium difficile* spores has been linked to a significantly lower rate of nosocomial *Clostridium difficile* infection with use of disposable

TIPS FOR NON-SPECIALISTS

- Avoid antibiotics with a high risk of inducing *Clostridium difficile* infection, especially in patients with a history of infection
- Isolate patients with suspected *Clostridium difficile* infection, use gowns and gloves when seeing them, and remember to wash hands rather than use alcohol gel
- Pay careful attention to the supportive care (such as fluid and electrolyte replacement) of infected patients
- Stop precipitating antibiotics if possible, and if not, substitute with a lower risk agent
- Reserve metronidazole for initial treatment of patients with mild or moderate disease, then escalate treatment according to agreed local and national protocols
- Discuss patients with recurrent infection with your local microbiology department
thermometers (0.16/1000 patient days) compared with electronic thermometers (0.37/1000 patient days; relative risk 0.44; 95% confidence interval 0.21 to 0.93), and a similar reduction was seen by an observational study that compared rates before and after the introduction of tympanic thermometers."\(^6\)

No RCTs or systematic reviews have assessed the value of isolation measures in preventing *C difficile* infection, but a systematic review of isolation in the hospital management of meticillin resistant *Staphylococcus aureus* (MRSA) suggested it was effective as part of a broader infection control strategy.\(^7\) UK national guidelines recommend that patients with potentially infective diarrhea should be moved immediately into a single room with en suite facilities, \(^1\) but this practice has difficulties. For example, moving frail elderly patients may increase the risk of delirium.\(^16\) In a large outbreak, or highly endemic settings, isolating affected patients in single rooms may not be possible. The creation of *C difficile* isolation wards in hospitals with high levels of disease was successful in certain outbreaks.\(^8\) Because the positive predictive value of the toxin immunoassays is suboptimal, however, transferring patients to cohort areas risks putting people without *C difficile* (false positives) at increased risk of acquiring the infection.

### Are there any other ways of preventing *C difficile* infection?

The rising incidence of *C difficile* infection since the late 1990s has coincided with the widespread use of proton pump inhibitors (use increased 10-fold in the UK from 1992 to 1995), raising concerns that the two may be linked.\(^17\) Hospital and community studies have produced conflicting results,\(^6\)\(^9\)\(^12\)\(^22\) but a meta-analysis of case-control and cohort studies including 126 999 patients suggested a significant association between proton pump inhibitors and *C difficile* infection (odds ratio 2.05; 1.47 to 2.85).\(^11\)

Probiotics (live micro-organisms such as *Lactobacillus* or *Bifidobacterium* taken as supplements or in yoghurt drinks to rebalance the gut flora) and prebiotics (carbohydrates such as oligofructose, inulin, and other non-digestible foodstuffs that stimulate the growth or activity of gut bacteria) have been proposed as preventive methods for *C difficile* infection.\(^15\) A recent double blind RCT showed that a probiotic *Lactobacillus* preparation helped prevent *C difficile* infection in a highly selected subgroup of patients receiving antibiotics,\(^21\) but the findings may not be generalisable.\(^26\) A previous meta-analysis failed to provide sufficient evidence for the routine clinical use of probiotics to prevent or treat *C difficile* infection.\(^22\) Data on prebiotics are sparse.

### How is *C difficile* managed medically?

Patients with *C difficile* infection may develop electrolyte imbalance, dehydration, malnutrition, and pressure sores, so their supportive medical care must be optimised. After outbreaks at Maidstone and Tunbridge Wells NHS Trust in 2005-6, the UK Healthcare Commission criticised the general management of infected patients for inadequate monitoring and doctor review, poor fluid replacement and nutritional support, and lack of multidisciplinary assessment.\(^6\)

In early studies, 15-23% of patients who developed *C difficile* infection became asymptomatic through stopping the offending antibiotic alone—allowing normal flora to recolonise the colon—whereas continuing systemic antibiotics has been associated with a poor response to treatment.\(^3\) When treatment cannot be stopped, because of concurrent infection that requires ongoing systemic antibiotics, an antibiotic with a low risk of causing *C difficile* infection may be substituted (table 1). The use of antimicrobial agents during active infection has been associated with toxic megacolon.\(^3\)\(^7\)\(^W21\)

### Which antibiotics are used to treat *C difficile* infection?

Oral vancomycin was the first drug shown to be effective for *C difficile* infection, followed by oral metronidazole, and these agents remain the mainstay of treatment.\(^1\) Whereas intravenous vancomycin is almost exclusively excreted in the urine, oral vancomycin achieves faecal concentrations many times higher than the minimum inhibitory concentrations of *C difficile* strains reported to date (table 2). After ingestion by healthy volunteers, metronidazole is completely absorbed from the gastrointestinal tract, and is undetectable in the faeces.\(^6\)\(^22\) When diarrhoea is present, however, metronidazole may achieve therapeutic values in faeces when given orally or intravenously, perhaps because of seepage across inflamed colonic mucosa.\(^22\) UK surveillance data support the emergence of reduced susceptibility to metronidazole in some *C difficile* isolates, but the clinical importance of this is unclear.\(^23\)

### What is the appropriate choice for initial antibiotic treatment?

In patients with severe *C difficile* infection (any of white blood cell count >15×10⁹/l, acutely rising serum creatinine (>50% above baseline), temperature over 38.5°C, or clinical or radiographic evidence of severe colitis), UK national guidelines recommend initial treatment with oral vancomycin, on the basis of evidence from two recent RCTs that compared vancomycin and metronidazole.\(^1\) These trials, which stratified for disease severity, showed a lower rate of treatment failure with vancomycin in patients with severe *C difficile* infection,\(^6\)\(^26\)\(^27\) Only one has been fully published; it found cure rates of 76% with metronidazole versus 97% with vancomycin (P=0.002) in patients with severe disease.\(^26\) Retrospective and prospective observational studies have also shown that response time is shorter for vancomycin than for metronidazole, which may be important in patients with severe disease.\(^26\)\(^27\) In patients with mild or moderate disease, neither RCT showed that vancomycin was significantly superior.\(^26\)\(^27\) UK national guidelines therefore still recommend oral metronidazole for initial treatment in these patient groups, because it is cheaper than oral vancomycin, and because of concern that overuse of vancomycin may result in the selection of vancomycin resistant enterococci.\(^1\) Observational data suggest, however, that metronidazole, as well as vancomycin, may promote persistent overgrowth of vancomycin resistant enterococci.\(^28\)
What if the patient fails to respond to initial treatment?

Treatment failure is defined as no response after one week, although most patients show signs of improvement within 48–72 hours. UK national guidelines recommend that antibiotics be reviewed daily and a plan agreed for escalating treatment in the event of non-response. If diarrhoea does not improve, patients initially treated with metronidazole may be changed to vancomycin. In severe disease, aggressive treatment with escalating doses of vancomycin, up to 500 mg four times daily, may be used, although no robust evidence supports this approach, and an early randomised trial comparing vancomycin 500 mg four times daily with 125 mg four times daily in 46 inpatients found no difference in outcomes. In patients with adynamic ileus (which may reduce passage of oral preparations to the colon), intravenous metronidazole may be added, but the efficacy of this route of administration is unclear. Vancomycin administered as a retention enema may increase colonic antibiotic exposure, and in a recent case series examining this as adjunctive treatment, eight of nine patients completely recovered. Finally, surgery may be life saving in severe disease. Figure 1 shows a possible management cascade for *C difficile* infection adapted locally from UK national guidelines for use in our centre.

Are there any other treatment options for refractory disease?

Several antibiotics have been used for the treatment of refractory infection. UK national guidelines suggest considering the addition of rifampicin 300 mg twice daily for severe disease, although the only RCT assessing rifampicin as an adjunct to metronidazole for *C difficile* infection was halted early because of lack of efficacy. A recent case series described the successful use of intravenous tigecycline for *C difficile* infection in four patients refractory to vancomycin and metronidazole. UK national guidelines also recommend the use of intravenous immunoglobulin (400 mg/kg) in selected severe cases, although results from case reports and small series have been inconsistent and no RCTs are available to support this position.

How is recurrent *C difficile* infection diagnosed?

Recurrent *C difficile* infection (relapse of diarrhoea after initial resolution of symptoms) usually occurs within one to three weeks but has been described up to two months after the initial episode. The risk of recurrence after a single episode is high, with 8–50% of patients having at least a second episode after treatment with metronidazole or vancomycin. Risk factors include previous relapses, age

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**ONGOING RESEARCH**

- To determine the epidemiology of community acquired *Clostridium difficile* infections in younger patients who have not received antibiotics or had contact with the healthcare system
- To determine the contribution of factors such as *C difficile* in food animals, salads and other food stuffs, pets, soil, and water
- To define diagnostic algorithms that optimise test combinations for the laboratory diagnosis of *C difficile* infection
- There is considerable interest in the development of monoclonal antibodies and toxin specific vaccines to prevent or treat *C difficile* infection, and tovalenec, a novel toxin binding polymer, is undergoing clinical trials
- Randomised controlled trials (RCTs) are urgently needed to examine treatment for fulminant, refractory, and recurrent *C difficile* infection, including new antibiotics such as tigecycline, and non-antimicrobial agents such as intravenous immunoglobulin
- An RCT examining faecal transplantation is under way in the Netherlands
greater than 65 years, severe underlying illness, and additional antibiotic use after treatment for C difficile infection has been stopped. Paradoxically, the antibiotics used to treat C difficile infection may themselves interfere with the re-establishment of the normal colonic flora, contributing to the propensity for recurrent disease.

Patients may remain positive for C difficile toxin despite clinical cure, and UK Department of Health surveillance regards serial positive results within 28 days of the first specimen as a single episode. UK national guidelines do not recommend retesting for C difficile toxin within 28 days if patients remain symptomatic, but repeat testing may be appropriate at any time if symptoms relapse after resolution and recurrence needs to be confirmed.

How do recommendations differ for recurrent disease?
Because recurrence may represent reinfection rather than relapse, and because evidence for clinically relevant resistance to metronidazole or vancomycin is lacking, the antibiotic that was used to treat the initial episode may be used for the first recurrence (unless this is metronidazole and the recurrence meets criteria for severe C difficile infection). In second and subsequent recurrences, however, vancomycin is recommended. This is because stool concentrations of metronidazole wane during recovery, with much lower concentrations in formed than in watery or semiformal stools, and because long term use of metronidazole may be associated with adverse effects, such as peripheral neuropathy.

Observational studies have examined the use of long term, tapering, or pulsed courses of vancomycin. Slowly falling concentrations of antibiotics in the colon may suppress C difficile proliferation, while allowing normal colonic flora to recover, or allow C difficile spores to germinate, making them susceptible to subsequent intermittent doses. None of the proposed regimens has been tested in an RCT, and they may all apply considerable selection pressure for vancomycin resistant enterococci. Other antimicrobial regimens, such as a short course of vancomycin and rifampicin, or rifaximin (a poorly absorbed rifamycin derivative not licensed in the UK) used as a “chaser” after vancomycin, have been reported to be successful in small numbers of patients. Low concentrations of serum antibodies against C difficile toxin A correlate with the risk of recurrent C difficile infection, and a recent phase II RCT found a significant reduction in C difficile recurrence in patients treated with experimental monoclonal antibodies against toxins A and B. Pooled intravenous immunoglobulin may also neutralise these toxins, and a small case series reported a successful clinical response to intravenous immunoglobulin in three of five patients with recurrent infection. Although recommended in the UK Department of Health clinical guidelines for immunoglobulin use for selected patients with multiple recurrent C difficile infection in whom all other treatments have failed or are inappropriate, no RCTs support the use of intravenous immunoglobulin, and cost and availability may preclude its widespread adoption. Finally, evidence is emerging for the efficacy of faecal transplantation in patients with relapsing C difficile infection, mostly from small retrospective case series. Fresh stool from a healthy donor is administered by enema or nasogastric tube in an effort to reconstitute the normal colonic flora. Concerns remain about the safety of this approach, as well as its acceptability.

Conclusions
Many cases of C difficile infection could be prevented by prudent antibiotic prescribing and vigorous infection control measures, which may also reduce other healthcare associated infections and limit the spread of multiresistant organisms such as MRSA and vancomycin resistant enterococci. Although evidence from RCTs supports guidance on the initial antibiotic treatment of C difficile infection, more data are urgently needed on the management of refractory, fulminant, and recurrent disease.

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Provenance and peer review: Not commissioned; externally peer reviewed.

4 Centre for Disease Control and Prevention. Severe Clostridium difficile associated disease in populations previously at low risk. MMWR 2005;54:1201-5.

ADDITIONAL EDUCATIONAL RESOURCES

Resources for patients
NHS Choices (www.nhs.uk/Conditions/Clostridium-difficile/Pages/Symptoms.aspx)—Advice about C difficile
Patients Association (http://www.patient-association.org.uk)—Website with several reports on infection control

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9 Dial S, Keouzh A, Dascal A, Barkun A, Suisse S. Patterns of antibiotic use and risk of hospital admission because of Clostridium difficile infection. CMAJ 2008;179:767-72.


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ANSWERS TO ENDGAMES, p 661. For long answers go to the Education Channel on bmj.com

PICTURE QUIZ

Progressive dysphagia, dysarthria, dystonia, and tremor

1 The brain images show increased T2 weighted signal in the pons, midbrain, thalami, and basal ganglia. Putaminal volume loss is also seen on a background of generalised cerebral and cerebellar volume loss, as are intrinsic low signal changes within the putamina. The most likely diagnosis is Wilson’s disease.

2 The primary diagnosis is Wilson's disease. The differential diagnoses are Parkinson plus syndromes, pantothenate kinase associated neurodegeneration (formerly Hallervorden-Spatz disease), hereditary hypocupraspinemia, and acaeruloplasminaemia (a rare familial disorder).

3 Other signs include hepatic signs—such as weight loss, asterixis, palmar erythema, jaundice, and Dupuytren’s contracture; and neuropsychiatric signs—such as apraxia, behavioural changes (for example, depression and psychosis), lack of coordination, and abnormal gait.

4 Other tests include serum free copper, serum caeruloplasmin, 24 hour urinary copper, hepatic copper (liver biopsy), and mutation analysis or haplotype analysis.

5 Maintenance treatment with zinc acetate or trientine. Acute treatment for symptomatic patients should include chelating agents—penicillamine, trientine, or ammonium tetrathiomolybdate (on trial).