Australasian Society for Infectious Diseases guidelines for the diagnosis and treatment of *Clostridium difficile* infection

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Clostridium difficile is a frequent cause of both nosocomial and antibiotic-associated diarrhoea, and is usually health care-associated. It is infrequently found in the gastrointestinal tract of healthy adults, but may colonise up to two-thirds of young children before they are weaned.[1] In healthy people, *C. difficile* does not cause problems; resistance to infection is thought to be due in part to commensal bowel flora and antibody-mediated immunity. Impairment of the normal resistance mechanisms, including disruption of host flora by most antibiotics, gastric acid suppression, immunosuppression or cytotoxic drugs may result in *C. difficile* colonising the gastrointestinal tract. For reasons that are not well understood, a proportion of colonised individuals progress to *C. difficile* infection (CDI) following overgrowth of toxin-producing strains of *C. difficile*.

C. difficile exists in both vegetative and spore forms; alcohol-based hand rub is effective against the vegetative form but probably not against spores. Although handwashing appears to be more effective because it physically removes spores (rather than killing them), the increased use of alcohol-based hand rub for hand hygiene has not been associated with a rise in *C. difficile* infection.[2] The hospital environment can become grossly contaminated with *C. difficile* spores that persist for long periods unless methods of cleaning and disinfection that remove or kill spores are used. *C. difficile* produces two major toxins (A and B) that are important in disease pathogenesis. Most strains produce both toxins, but about 3% of Australian strains produce toxin B only.[3]

Recently, a hypervirulent strain (PCR ribotype 027, also known as NAP-1 or BI) has been associated with high rates of nosocomial transmission, severe disease and increased mortality, particularly in patients aged over 65 years. This strain is characterised by increased production of toxins A and B, the presence of an additional potential virulence factor (binary toxin) and resistance to newer fluoroquinolone antibiotics, such as moxifloxacin.[4] Since the late 1990s, this strain has become common in North America, the United Kingdom and several European countries, mainly in hospitals, but more recently in the community in some European countries.[5] Isolates of the PCR ribotype 027 have recently been described in Australia (including local transmission at a hospital in Melbourne).[6,7] Another strain, PCR ribotype 078, has also been associated with severe disease. This strain is genetically similar to strains found in pigs in the Netherlands, but is not resistant to newer fluoroquinolones.[6,8] PCR ribotype 078 has not been reported in animals in Australia, although some strains have been recovered from humans.[6] Only one isolate of PCR ribotype 078 has been identified in New Zealand (S Roberts, Infectious Diseases Physician and Clinical Microbiologist, LabPLUS, Auckland District Health Board, Auckland, NZ, unpublished data). There is some evidence that other PCR ribotypes may be associated with severe disease and epidemic spread.

ABSTRACT

- *Clostridium difficile* is the most common cause of health care-associated and antibiotic-associated diarrhoea.
- These guidelines are intended to provide advice to clinicians on the clinical assessment, diagnosis and management of *C. difficile* infection (CDI).
- Hypervirulent strains of *C. difficile*, including PCR ribotype 027 strains recently identified in Australia, have been associated elsewhere with epidemic spread and high rates of severe disease and death.
- Diagnostic tests include stool culture, polymerase chain reaction-based assays, cell-culture cytotoxicity assays and enzyme immunoassays detecting *C. difficile* glutamate dehydrogenase, and/or toxin A and/or B.
- To treat an initial episode and a first recurrence, metronidazole is the preferred antibiotic, with oral vancomycin reserved for severe disease and subsequent recurrences.
- Surgery should be considered for fulminant disease.

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Aims

These guidelines provide advice for clinicians diagnosing and treating CDI, particularly as there is little clinical experience in treating severe disease in Australia and New Zealand. Guidelines for the prevention and control of CDI are being prepared separately.[9]

Guideline development

The *C. difficile* Working Party of the Australasian Society for Infectious Diseases (ASID) was formed in response to recent reports of the hypervirulent strain (PCR ribotype 027) in Melbourne. In light of these developments, an expedited review process was adopted. Published literature, including recent guidelines published by the Society for Healthcare Epidemiology of America in conjunction with the Infectious Diseases Society of America[10] and the European Society for Clinical Microbiology and Infectious Diseases,[11] was reviewed by the Working Party. The advice of experts was sought, including that of the Royal Australasian College of Surgeons and the Colorectal Surgical Society of Australia and New Zealand. Draft guidelines were sent to ASID members for comment; responses were made to all feedback received.

In which patients should CDI be suspected?

CDI should be suspected in any hospitalised patient who develops diarrhoea or any person in the community who develops diarrhoea

after a course of antibiotics or in association with immunosuppressive therapy. Although severe CDI appears to particularly affect hospitalised patients over 65 years of age, the epidemiology has evolved over time, with severe cases reported in people in the community and in peripartum women who lack traditional risk factors.[12] Diarrhoea is usually watery, but may occasionally be bloody.[13] Other symptoms associated with CDI include fever, loss of appetite, nausea and abdominal pain. An elevated white cell count is found in 40% of affected patients, and hypoalbuminaemia in 76%.[13]

CDI usually occurs 5 to 10 days after commencing antibiotic therapy, although symptoms have been described as early as 2 days and as late as 10 weeks after antibiotic treatment. Other reported risk factors include the use of cytotoxic chemotherapy, renal impairment, prior gastrointestinal surgery, severe underlying comorbid conditions, gastric acid-suppressive therapy and prolonged hospital stay.[13,14] Although many antibiotics have been implicated, broad spectrum agents such as ampicillin, amoxycillin, third or fourth generation cephalosporins and clindamycin are most commonly implicated, and interventions that involve restriction of antibiotics appear to be effective in reducing rates of endemic CDI.[15,16] More recently, studies have noted a strong association between the newer fluoroquinolones (such as moxifloxacin and gatifloxacin) and the hypervirulent PCR ribotype 027 strain of *C. difficile*, which has a high prevalence of resistance to these agents.[17]

Since asymptomatic carriage of *C. difficile* is common in young children, its role in diarrhoea following antibiotic therapy (which is common in this group) is difficult to assess. Reports of pseudomembranous colitis in children are uncommon, although immunocompromised children appear to be vulnerable.[13] Recent reports from North America have noted an increase in the incidence of CDI diagnoses in infants and children, paralleling the rise in adult incidence; however, the extent to which this represents true disease (rather than colonisation or changes in testing practices) is uncertain.[18]

The differential diagnosis of antibiotic-associated diarrhoea includes infection with other pathogens such as norovirus (usually associated with prominent vomiting, a self-limited course, and a characteristic serial interval in outbreaks), bacterial pathogens (eg, *Campylobacter* spp.), the use of laxatives or enteral feeds, ischaemic colitis and inflammatory bowel disease.[19]

1 Clinical assessment of *Clostridium difficile* infection (CDI)

Definition	Criteria
CDI	• Clinical features of CDI (diarrhoea, ileus, toxic megacolon) AND • Microbiological evidence of toxin-producing *C. difficile* OR • Pseudomembranous colitis on colonoscopy
Severe CDI	***Any of the following features are suggestive of severe CDI.*** Clinical • Fever (> 38.5°C), rigors • Haemodynamic instability • Peritonitis or evidence of bowel perforation • Ileus or toxic megacolon Laboratory • White blood cell count >15 × 10^9/L and < 20% neutrophils • Elevated lactate level • Rise in creatinine level (> 50% above baseline) • Albumin level < 25 mg/L Other investigations • Large intestine distension, colonic wall thickening, fat stranding, unexplained ascites (imaging) • Pseudomembranous colitis (colonoscopy)
Treatment failure	• Lack of improvement or increasing stool frequency after 3 days of treatment • New signs of severe CDI
Recurrence	• Increasing stool frequency over 2 consecutive days OR • New signs of severe CDI after apparent improvement • Re-testing of patients is generally not helpful as colonisation may persist for some weeks. ◆

How should patients with suspected CDI be assessed?

Clinical features of severe CDI include fever (> 38.5°C), an acute abdomen, the presence of ileus (and absence of diarrhoea), and/or toxic megacolon (Box 1).[11] Risk factors for poor outcome include age over 60 years, significant underlying comorbid conditions/organ dysfunction, and having an immunocompromised status. Laboratory findings associated with severe disease include lactic acidosis, elevated white cell count, low albumin level, and acute renal impairment. In some patients, fevers of up to 40°C and white cell counts exceeding 50 × 10^9/L may be present. The development of an ileus (in patients without diarrhoea) and later toxic megacolon, are important signs of severity that mandate urgent surgical referral.

The presence of pseudomembranes on colonoscopy and radiological evidence of dilatation of the large bowel without involvement of the small bowel, thickening of the bowel wall (including the "accordion" sign and "double-halo" sign associated with submucosal oedema), perforation or unexplained ascites (associated with hypoalbuminaemia) are strongly suggestive of severe CDI.[19,20] Findings of radiological studies may be normal or non-specific initially, but patients should be carefully followed for the development of new signs of severity that may indicate clinical deterioration.

How can CDI be diagnosed?

Only a third of patients with antibiotic-associated diarrhoea have confirmed CDI, so diagnostic tests are essential. Testing should only be performed on unformed (liquid) stools, because a positive result in a formed stool only signifies colonisation. When ileus is present, rectal swabs are suitable specimens. Repeat testing of faecal specimens (by enzyme immunoassay [EIA] for toxin A and B or polymerase chain reaction [PCR]) within 7 days does not increase the diagnostic yield significantly.[21,22]

2 Treatment of severe and non-severe *Clostridium difficile* infection (CDI)

Treatment	Non-severe infection	Severe infection
General measures	• Avoid and/or stop therapy with antiperistaltic agents and opiates • Promote the use of narrow spectrum antimicrobial agents • Stop therapy with other antibiotics if possible; if not, a prolonged course of treatment for CDI may be required • Perform serial clinical assessment • Perform serial assessments of white cell count, and lactate, creatinine and electrolyte levels	
Treatment of initial episode	• Metronidazole, 400 mg orally, three times daily for 10 days • If unable to tolerate oral treatment: metronidazole, 500 mg intravenously, 8-hourly for 10 days	• Vancomycin, 125 mg orally, four times daily for 10 days • If unable to tolerate oral therapy: metronidazole, 500 mg intravenously, 8-hourly for 10 days plus a retention enema of vancomycin, 500 mg in 100 mL of normal saline every 4–12 h and/or vancomycin, 500 mg four times daily by nasogastric tube
Indications for surgery		*Any of the following are indications for surgical review* • Bowel perforation, toxic megacolon • Deterioration (including severe ileus, rising lactate level, rising white cell count, ongoing severe sepsis) despite antibiotic treatment
Treatment of first recurrence	• As for initial episode	• As for initial episode
Treatment of second or subsequent recurrence	• Vancomycin in a pulsed/tapering course (eg, 125 mg orally, four times daily for 14 days, then 125 mg twice daily for 7 days, then 125 mg every second day for 2–8 weeks; (other regimens also described)	
Alternative treatments with evidence of efficacy, role unclear	• Bacitracin, 20 000 units orally, four times daily for 7 days • Fusidic acid, 500 mg orally, three times daily for 10 days • Teicoplanin, 100–400 mg orally, twice daily for 10 days • Tigecycline, 100 mg intravenous loading dose, then 50 mg twice daily for 14–21 days • Rifampicin, 300–600 mg orally, twice daily (in combination with vancomycin for relapse) for 7–10 days • Rifaximin, 200 mg orally, three times daily for 10 days • Nitazoxanide, 500 mg orally, twice daily for 7–10 days • Tolevamer, 6 g orally, daily for 14 days • Antibodies to *C. difficile* toxins A and B (anti-TcdA and anti-TcdB, 10 mg/kg, single dose in combination with metronidazole or vancomycin) • Faecal enema — consider logistical issues; donor screening required • Intravenous gammaglobulin ◆	

Assays that are available to diagnose CDI fall into five groups (Box 2).

- Faecal culture determination of the toxigenic status of the infecting *C. difficile* isolate ("toxigenic culture"). This is relatively slow but sensitive and specific. These tests are regarded as the gold standard and are necessary for epidemiological typing studies.
- Screening EIA to detect *C. difficile* glutamate dehydrogenase (GDH); these tests are sensitive but less specific.
- EIAs to detect toxins A and/or B, which are variably sensitive, but more specific than GDH assays. Some test kits combine detection of GDH and toxins A and/or B.
- Cell culture cytotoxicity assays that directly detect stool cytotoxic activity. These are sensitive and specific, but technically difficult and also relatively slow.
- PCR-based assays to detect conserved gene targets within the pathogenicity locus of *C. difficile*. These tests appear to be sensitive and specific, but commercial tests are expensive.

The detection of *C. difficile* toxin in a cell-based cytotoxic assay (CCA) or toxigenic culture of *C. difficile* obtained from stool are generally regarded as the gold standards for diagnosis.[23,24] However, both culture of stool and CCA have relatively slow turnaround times (> 48 hours) and CCA is technically difficult, poorly standardised, and requires expertise to read. Culture is required to obtain isolates for genotyping for epidemiological studies, including detection of the hypervirulent strains at reference laboratories.

EIA for *C. difficile* GDH (or "common antigen") may be used as a screening test. This assay is rapid and inexpensive and has a high negative predictive value, but positive GDH test results require confirmation by a second test. EIA to detect toxins A plus B are rapid and widely used. They are relatively insensitive and their positive predictive value is only moderate, especially when disease prevalence is low.[25] Unless used with a GDH assay, EIAs perform poorly as a primary screening test. PCR-based assays for detection of genes encoding toxin B (*tcdB*) are commercially available, as are in-house assays targeting various targets within the pathogenicity locus of *C. difficile*, which includes genes *tcdA* and *tcdB*, and adjacent accessory genes *tcdC*, *tcdR* and *tcdE*. Although these assays have high sensitivity and specificity, the commercial assays are expensive. Some PCR-based assays identify non-toxigenic or hypervirulent *C. difficile* strains. The optimal diagnostic algorithm (for sensitivity and cost) is controversial, but likely to evolve as better, more cost-effective tests become available. Currently, many laboratories use a combination of a sensitive, but not necessarily highly specific, screening test (such as a GDH assay), followed by a more specific test on specimens that test positive to confirm the

presence of toxin (eg, an EIA for toxin A and/or B, PCR or toxigenic culture).

Confirmation of a hypervirulent strain requires culture of the organism. Some PCR assays may directly detect a characteristic gene deletion found in hypervirulent strains, but this should be confirmed by further typing. In laboratories that culture for *C. difficile*, moxifloxacin resistance may be used as a screening test for PCR ribotype 027.

Which antibiotic should be used for treatment of an initial CDI episode?

The current antibiotic of choice for mild to moderate disease is metronidazole; vancomycin should be reserved for severe disease (Box 2) because of concerns about generating antibiotic-resistant organisms such as vancomycin-resistant enterococci. In patients with colitis, adequate metronidazole concentrations in the colon are similar after oral and intravenous administration. Hence, if tolerated, the oral route is preferred. Where possible, therapy with the initiating antibiotic should be ceased and antiperistaltic agents and opiates should be avoided. In most clinical trials, a 10-day course of treatment was used. However, a longer course of treatment may be indicated if there is an ongoing need for treatment with antibiotics that precipitated the CDI, although metronidazole should not be used for longer than 4–6 weeks because of the potential for peripheral neuropathy.[26]

In severe CDI, vancomycin is more effective and is associated with lower rates of treatment failure and relapse than metronidazole. However, recent observational studies suggest that the effectiveness of vancomycin and metronidazole are similar since the emergence of PCR ribotype 027.[27-29] Vancomycin is not absorbed after oral administration, and much higher gastrointestinal concentrations are achieved when it is given orally rather than intravenously, whereas concentrations of metronidazole given by either route are low in stool.[30,31] Although a capsule formulation of vancomycin is available, the intravenous preparation is substantially cheaper and is commonly used for oral administration. A gradual decrease in susceptibility of *C. difficile* to metronidazole has been reported in some strains, but not PCR ribotype 027 strains, and is thus unlikely to explain the lower efficacy of metronidazole in severe disease.[32]

For patients who fail to respond to initial therapy after 2–3 days, switching to oral vancomycin (in patients started on metronidazole therapy) or increasing the dose of vancomycin (eg, 500 mg orally, four times daily) should be considered.[33] Vancomycin can be administered as a retention enema, particularly in cases of ileus.[34] The roles of intravenous immunoglobulin, faecal enemas (see below) and adjunctive antibiotics in the treatment of refractory severe CDI are uncertain, although tigecycline has been used with success in small studies.[33,35]

Other agents have been studied and may be alternative therapies for mild to moderate disease in patients for whom metronidazole is contraindicated (Box 2). In particular, tigecycline and fusidic acid are readily available alternatives. However, there are only small case series supporting the use of tigecycline,[35] and fusidic acid may be less efficacious than vancomycin.[36] A Cochrane review published in 2007 identified 12 clinical trials evaluating eight different antibiotic treatments for *C. difficile* diarrhoea.[36] In direct comparisons, no definite conclusions could be made on relative efficacy, although oral teicoplanin appeared to be marginally more efficacious than vancomycin and fusidic acid. The efficacy of antibiotic treatment in mild disease has not been established, as only one small placebo-controlled trial has been performed.[37] Only one study of combination antibiotics (metronidazole and rifampicin) was identified, and the combination did not appear to be more efficacious than metronidazole alone.[38] A recently published trial of monoclonal antibodies to *C. difficile* toxin A and B showed reduced rates of relapse in patients infected with PCR ribotype 027 and in patients with more than one previous recurrence, but had no benefit in treating acute CDI.[39]

How should patients be monitored?

In general, the condition of patients with CDI may not improve for 2–3 days and, if they are otherwise stable, treatment success cannot be assessed until this time.[11] A clinical improvement is indicated by a decrease in the frequency of diarrhoea and the resolution of any signs of severity the patient showed at presentation.

Where severe CDI is suspected, serial assessment of creatinine and lactate levels and white cell count should be performed. Clinical deterioration or a rise in any of these markers should prompt consideration of other treatment strategies, including surgery. Other complications of severe CDI include dehydration, electrolyte disturbances, hypoalbuminaemia and sepsis-related organ dysfunction.[10]

Response should not be assessed on the basis of repeat stool testing. In clinical trials, asymptomatic carriage of *C. difficile* at 30 days was reported in 25%–30% of patients.[40,41] This suggests that repeat testing is not indicated within 30 days of a primary episode, and retreatment should be based on clinical evidence of recurrent disease, which may be the result of reinfection with another strain or relapse with the original infecting strain.[42] After this time, the clinical utility of repeat testing depends on the test used, but a negative result from a sensitive test may be useful to exclude recurrence and prompt a search for alternative diagnoses.

What are the indications for surgery?

Surgery is generally indicated if there are signs of bowel perforation, toxic megacolon, and/or ongoing severe sepsis despite antibiotic treatment. The timing of surgery is important as severe physiological derangement is associated with poor outcomes, suggesting that surgery should be performed early in a patient whose condition is deteriorating.[43] In one review, a rising white cell count was suggested as a trigger for surgical review.[44] Risk factors associated with poor outcome after surgery include a serum lactate level over 5 mmol/L, age over 75 years, white cell count greater than 50×10^9/L, immunosuppression and shock.[43] Subtotal colectomy with an end-ileostomy is most commonly performed, and segmental resection is not generally recommended.[44]

Which antibiotics should be used for recurrences?

It is thought that the most common reason for recurrence of *C. difficile* disease after successful treatment is recolonisation from the environment.[42] Resistance to metronidazole and vancomycin is uncommon in Australia and New Zealand. Therefore, the preferred treatment for a first recurrence is readministration of metronidazole, with vancomycin reserved for severe cases (Box 3).

For second or subsequent recurrences, there is some concern about the cumulative toxicity of metronidazole, and an alternative antibiotic would be preferable. Most experience is with various

3 Practice points for managing *Clostridium difficile* infection (CDI)

Aim	Action
Recognition and clinical assessment	• Suspect and test for CDI in all hospitalised patients with diarrhoea, and in all patients who present with diarrhoea after antibiotic therapy (note that gastric acid suppression and chemotherapy also appear to be risk factors) • Monitor all patients for clinical deterioration and signs of severe disease by serial assessment of clinical, laboratory and radiological parameters
Diagnosis	• Test only unformed stool samples — repeat tests are not generally useful • Interpret test results based on the test strategy used at the laboratory, as a number of laboratory tests of varying sensitivity and specificity are available • Contact the laboratory to arrange additional studies to test for hypervirulent strains in patients who develop severe CDI • Monitor rates of CDI in hospitals
Treatment	• Use metronidazole orally or intravenously for mild to moderate disease, and reserve oral vancomycin for severe disease; treat for 10 days (if there is an ongoing need for other antibiotic therapy, then a longer course of treatment may be indicated) • Refer patients with severe disease to a surgeon early • Retreat first recurrent episodes with metronidazole or vancomycin as for an initial episode
Prevention	• Implement effective infection control measures (including hand hygiene, patient isolation and environmental cleaning) • Implement effective antibiotic stewardship measures, including restriction of fluoroquinolones, broad spectrum β-lactams and lincosamides (clindamycin or lincomycin) ◆

regimens of vancomycin, including tapering and/or pulsed courses.[10] The roles of alternative agents (such as bacitracin, tigecycline and fusidic acid) are unclear, but they may be options for treating recurrence of mild to moderate disease. Cholestyramine and other anionic binders are probably not effective in reducing recurrence, and also adsorb vancomycin. Faecal enemas (or preparations administered by nasogastric tube) to restore commensal flora ("stool transplant") have been used successfully in a number of refractory cases of recurrence, but significant logistical issues must be considered, including donor screening, the processing of the donor specimen and the route of administration.[45,46] A detailed protocol for the administration of faecal enemas has recently been published.[47]

Do probiotics have a role?

A Cochrane review performed in 2008 identified only four small studies of probiotics in the treatment of CDI.[48] Only one of these studies demonstrated a benefit — in patients receiving *Saccharomyces boulardii* — in reducing recurrence.[49] Cases of invasive disease associated with the use of probiotics have been described.[50] Based on the lack of efficacy and the potential for adverse events, the routine use of probiotics cannot be recommended for treating CDI, particularly in critically ill patients.

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Competing interests

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