DIRC Drug Information and Research Centre
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Therapeutic options

FOCUS ON *CLOSTRIDIUM DIFFICILE* INFECTION

Key Points

- Diagnosis of *Clostridium difficile* infection (CDI) should be based on a case definition that includes: (1) the presence of symptoms (usually diarrhea); and (2) either a stool test result positive for toxigenic *C. difficile* or its toxins, or colonoscopic or histopathologic findings demonstrating pseudomembranous colitis.
- Management of CDI should be individualized, based on disease severity and whether illness represents the initial episode or is recurrent. In all instances, discontinuing therapy with the inciting antimicrobial should occur as soon as possible.
- Metronidazole and vancomycin are the mainstays of current therapy, and these agents have been shown to reduce morbidity and mortality associated with CDI.
- Important infection control measures for prevention of CDI include proper hand hygiene (soap and water), contact precautions, use of private rooms or cohorting of infected patients, thorough environmental cleaning and disinfection, and antimicrobial use restrictions.

Clostridium difficile infection (CDI) is a major cause of intestinal disease, especially among hospitalized patients exposed to antibiotics.[1] Recent increases in the incidence and severity of CDI have been reported, possibly related to the emergence of a hypervirulent strain of *C. difficile* that produces higher levels of toxins than historic strains.[1,2] The epidemiology of CDI also appears to be changing, with a greater number of cases seen in populations previously deemed low-risk.[1,2]

Given the changes noted above and the burden of illness associated with CDI – including prolonged hospital stays, excess health care expenditures, and increased morbidity and mortality[1,3] – it is important that pharmacists be aware of current management recommendations to help ensure optimal patient outcomes.

BACTERIOLOGY, PATHOGENESIS & RISK FACTORS

C. difficile is an anaerobic, Gram-positive, toxin-producing bacterium that is prevalent in nature.[1,4] It exists in both vegetative and spore forms; in its spore form, *C. difficile* can survive harsh environments and common sterilization techniques.[2] Spores are also resistant to antibiotics; hence, they can remain in the gastrointestinal tract and may contribute to recurrent disease after treatment and eradication of vegetative *C. difficile*.[2]

The principal mode of bacterial transmission resulting in CDI is person-to-person spread by the fecal-oral route.[3,4] In a hospital setting, patients can be exposed to *C. difficile* through contact with:

- a health care worker with transient hand colonization (likely the primary means of spread during non-outbreak periods);
- contaminated environmental surfaces or fomites (e.g., electronic rectal thermometers, inadequately cleaned commodes or bedpans); or
- a patient with CDI.[3]

After bacterial ingestion and colonization of the large intestine, spores convert to vegetative bacteria that divide and produce the toxins responsible for clinical disease.[2,4]

Important risk factors for the development of CDI are listed in Box 1. Disturbance of the normal, protective flora of the colon is believed to be an essential precursor to infection.[1] In regards to antibiotics, virtually all agents have been associated with CDI.[3] The relative risk associated with a particular antimicrobial is very difficult to quantify accurately, and depends on local bacterial strains and susceptibility patterns.[3] Nonetheless, drugs most frequently associated with disease to date include ampicillin and amoxicillin, cephalosporins (especially second- or third-generation agents), clindamycin, and fluoroquinolones.[4,5]

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Box 1 – Risk factors for *C. difficile* infection[1-3]

- Advanced age*
- Antibiotic exposure†
- Hospitalization‡
- Long-term care facility residence
- Antineoplastic medications
- Gastrointestinal procedures
- Immune suppression
- Severe underlying illness
- Gastric acid suppressants§

* A large population-based analysis showed that the rate of CDI was 10-fold higher in persons >65 years compared with persons <20 years.[2]

† In clinical practice, antimicrobial use is generally part of the operative definition of CDI, and it is considered the most important modifiable risk factor.[3,6] Risk increases with the duration of exposure and the number of antimicrobials received, but even single doses increase a patient's risk.[3] Symptoms usually appear within 14 days of antimicrobial exposure, but may be delayed for as long as two to three months.[1-3]

‡ Risk increases with the duration of hospitalization.[3]

§ For example, proton pump inhibitors and histamine$_2$-receptor antagonists. The role of these agents in CDI is unclear; while some data suggest increased risk (by allowing more viable spores to reach the colon and/or disrupting normal gastrointestinal flora), results of other studies suggest that the association between acid suppression and CDI is the result of confounding with the underlying severity of illness and duration of hospital stay.[3,4,7]

SYMPTOMATOLOGY & DIAGNOSIS

C. difficile infection can vary in manifestation from asymptomatic carriage, to mild or moderate diarrheal illness, to fulminant pseudomembranous colitis.[1,3] The two factors that appear to influence the clinical expression of disease are virulence of the infecting bacterial strain and host immune response.[4]

Most patients present with diarrhea, defined as passage of three or more unformed stools in a 24-hour period, and a diagnosis of CDI should be considered in anyone with such symptoms who has risk factors for illness[1,3] (see Box 1). Other common signs and symptoms include abdominal pain, cramping, fever, and peripheral leukocytosis; however, these findings are present in fewer than 50% of patients.[1,3] Diarrhea may be associated with passage of mucus or occult blood, but gross blood in the stools is rare.[1,3] In less than one per cent of cases, patients present with ileus and colonic distention, with minimal or no diarrhea.[3]

Health care providers should be aware that mild disease can progress rapidly.[1] Unfortunately, the factors instigating transition from mild to fulminant disease are unclear.[2] Complications of severe *C. difficile* colitis include dehydration, hypotension, renal failure, toxic megacolon, bowel perforation, systemic inflammatory response syndrome, sepsis, and death.[3]

According to 2010 guidelines from the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA),[3] the diagnosis of CDI should be based on a case definition that includes: (1) the presence of symptoms (usually diarrhea); and (2) either a stool test result positive for toxigenic *C. difficile* or its toxins, or colonoscopic or histopathologic findings demonstrating pseudomembranous colitis. The optimal stool testing strategy remains a subject of controversy.[3]

TREATMENT

Management of CDI should be individualized, based on disease severity and whether illness represents the initial episode or is recurrent. In all instances, discontinuing therapy with the inciting antimicrobial should occur as soon as possible.[1-3] Historically, stopping the offending therapy alone has resulted in cure for some patients; however, active therapy is now recommended for all due to the presence of more virulent strains of *C. difficile*.[2]

The 2010 SHEA-IDSA recommendations for specific drug treatment of CDI in adults are summarized in Table 1. Metronidazole and vancomycin are the mainstays of current therapy, and these agents have been shown to reduce morbidity and mortality associated with CDI.[3,4] Other treatments have been used or investigated, although their role in therapy is presently not well defined (see Table 2).

If a diagnosis of severe or complicated disease is suspected, treatment should be initiated promptly. Nevertheless, empirical therapy without diagnosis is considered inappropriate (if diagnostic tests are available), since only about 30% of hospitalized patients with antibiotic-associated diarrhea will have CDI.[3]

Antiperistaltic medications (e.g., antidiarrheal agents) and opioids should be avoided where possible, as they may mask symptoms and precipitate toxic megacolon.[3,4] When continued antimicrobial therapy is required for treatment of a different infection, switching to an agent with a narrower spectrum of activity has been suggested.[2] While this approach seems logical, the efficacy of such an intervention has not been confirmed.[2]

Unfortunately, up to 25–30% of patients have a relapse in symptoms after successful initial therapy, most commonly in the first few weeks after treatment completion.[1,3,4] Some patients go on to develop repeated recurrences of CDI over a period of months to years.[1] Although the approach to therapy is relatively well defined for those with a first or second recurrence (see Table 1), selecting the best treatment for individuals with multiple recurrences is challenging because robust data on such patients are not available.[1,3] Nonetheless, vancomycin therapy using a tapered and/or pulse regimen (see Table 1) appears to be the preferred strategy in such instances.[3,4]

INFECTION CONTROL & PREVENTION

Infection control measures recommended for prevention of *C. difficile* transmission and infection are summarized in Box 2. At present, administration of probiotics is not recommended to prevent primary CDI.[3]

For patients requiring antimicrobials during or shortly after the end of CDI therapy, no specific recommendations can be made regarding prevention of recurrent CDI. A common approach in such cases is to prolong the duration of CDI treatment until after the other antimicrobials have been stopped; however, the benefits of doing so are unknown. Oral vancomycin is the preferred agent if this strategy is employed.[3]

Box 2 – Infection control measures for prevention of *C. difficile* transmission and infection[1,3,4,6]

Hand hygiene
- Wash hands with soap and water after caring for or contacting patients with CDI*

Contact precautions
- Use gloves and gowns on entry to a room of a patient with CDI
- Maintain contact precautions for the duration of diarrhea

Use of private rooms or cohorting
- Place patients with CDI in single rooms; if single rooms are not available, cohort patients and provide each with a dedicated commode

Environmental cleaning and disinfection
- Use chlorine-containing cleaning agents† or other sporicidal agents for disinfection of patient rooms, environmental surfaces, and equipment
- Identify and remove environmental sources of *C. difficile* (e.g., electronic rectal thermometers)

Antimicrobial use restrictions
- Minimize antimicrobial therapy (frequency, duration, and the number of agents prescribed)
- Use antibiotics with a spectrum no broader than necessary and switch to agents with a narrower spectrum once results of cultures and/or susceptibility tests are known
- Implement an antimicrobial stewardship program, targeting agents based on local epidemiology and the *C. difficile* strains present

* Alcohol-based hand-sanitizing agents are not sporicidal, and should not be used as the sole agent for hand hygiene when caring for patients with CDI.[1]
† The concentration of available chlorine should be at least 1,000 ppm (5,000 ppm may be ideal).[3]

Table 1 – SHEA-IDSA recommendations for treatment of *C. difficile* infection[3]

Clinical scenario (defining severity criteria*)	Recommended treatment
Initial episode, mild or moderate (leukocytosis with a WBC count ≤15,000 cells/µL AND a serum creatinine level <1.5 times the premorbid level)	Metronidazole 500 mg 3 times per day by mouth for 10–14 days
Initial episode, severe (leukocytosis with a WBC count ≥15,000 cells/µL OR a serum creatinine level ≥1.5 times the premorbid level)	Vancomycin 125 mg 4 times per day by mouth for 10–14 days
Initial episode, severe, complicated† (hypotension or shock, ileus, megacolon)	Vancomycin 500 mg 4 times per day‡ by mouth or nasogastric tube,§ PLUS metronidazole 500 mg every 8 hours intravenously; if complete ileus is present, consider adding rectal vancomycin‖
First recurrence (NA)	Same as for initial episode¶
Second recurrence (NA)	Vancomycin in a tapered and/or pulsed regimen**

IDSA = Infectious Diseases Society of America; NA = not applicable; SHEA = Society for Healthcare Epidemiology of America; WBC = white blood cell
* The SHEA-IDSA guidelines explicitly state that the criteria proposed for defining severe or complicated CDI are based on expert opinion and may need to be reviewed in the future, when data regarding prospectively validated severity scores for patients with CDI are available.[3]
† Colectomy (subtotal colectomy with preservation of the rectum) should be considered for severely ill patients; when possible, it should be performed earlier rather than later (postoperative mortality is greatly increased with serum lactate levels ≥5 mmol/L and white blood cell counts ≥50,000 cells/µL).[3]
‡ In patients with renal failure receiving long courses of vancomycin 2 g/day, monitoring serum trough concentrations would be appropriate.[3]
§ Intravenous vancomycin should not be prescribed for CDI; it is not secreted into the colonic lumen and is therefore ineffective.[1,2,4]
‖ The rectal vancomycin dosage is 500 mg (in ~100 mL normal saline) every 6 hours as a retention enema.[3] In those with ileus, such therapy is hypothesized to enhance vancomycin delivery to the site of infection.[2]
¶ Treatment of the first recurrence of CDI is usually with the same regimen as for the initial episode, but should be stratified by disease severity (e.g., a patient whose initial episode was mild and treated with metronidazole would be treated with vancomycin for their first recurrence if it met the criteria for severe disease).[3]
** Various regimens have been used (e.g., 125 mg 4 times per day for 10–14 days, then 125 mg 2 times per day for 1 week, then 125 mg once per day for 1 week, and then 125 mg every 2 or 3 days for 2–8 weeks).[3] Pulsed doses may allow spores to germinate into antibiotic-sensitive vegetative forms and may also allow restoration of normal colonic flora.[4]

Table 2 – Selected non-standard therapies for *C. difficile* infection[1-3,6]

Therapy	Comments
Bacitracin	• Comparative studies showed a trend toward higher frequency of recurrence or lower efficacy compared with metronidazole and/or vancomycin • Oral formulation not commercially available in Canada
Cholestyramine, colestipol	• There is insufficient evidence to recommend use • Binds to vancomycin and should not be administered concurrently
"Fecal transplant"*	• Has been used in treatment of recurrent CDI with a high degree of success in several uncontrolled case series, but evidence from controlled trials is lacking • May be considered in refractory cases
Fusidic acid	• Comparative studies showed a trend toward higher frequency of recurrence or lower efficacy compared with metronidazole and/or vancomycin • Oral formulation not commercially available in Canada
Immunoglobulins	• Have been used for some patients not responding to other therapies, but no controlled trials have been performed • May be considered in refractory cases
Nitazoxanide	• Shown to be statistically similar to metronidazole in a small prospective trial, but non-inferiority to vancomycin could not be shown in another trial due to lack of power (although results were numerically similar) • Not commercially available in Canada
Probiotics	• There is insufficient evidence to recommend the addition of probiotics to antibiotics • Administration of *Saccharomyces boulardii* has been associated with fungemia in immunocompromised patients and in patients with central venous lines
Teicoplanin	• Treatment probably not inferior to metronidazole or vancomycin • Not commercially available in Canada

* Also referred to as "stool infusion therapy"; involves nasogastric/rectal instillation of stool from a healthy donor in an attempt to restore normal fecal flora.[1,3]

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