

Treatment and Prevention of *Clostridium difficile* Infection in the Long-Term Care Setting

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The treatment and prevention of Clostridium difficile infection (CDI) in the long-term care (LTC) setting presents unique challenges. In this review, we offer an overview of CDI treatment along with a brief discussion of infection control strategies in the LTC setting. The approach to recurrent CDI is also addressed.

Key words: *Clostridium difficile*, aging, metronidazole, vancomycin, long-term care

Introduction

In the past decade, *Clostridium difficile* infection (CDI) has increased in frequency and severity and, as a result, has become more difficult to manage and treat. The changing epidemiology of CDI has been closely linked to the emergence of the epidemic B1/NAP1 strain of *C. difficile*, which produces increased levels of toxins A and B, the major virulence determinants of *C. difficile*.^{1,2} The changing epidemiology of CDI is also likely related to the increasing age and comorbidities among hospitalized patients.

Factors associated with increased risk of developing CDI include the following: age greater than 65, prior hospitalization, longer duration of previous hospitalization, use of broad spectrum antibiotics, longer duration of antibiotic use, use of multiple antibiotics, use of acid suppressive therapy, receipt of cancer chemotherapy, renal insufficiency,

hemodialysis, and presence of a nasogastric tube. In general, older adults have been disproportionately affected; advanced age is a risk factor for acquiring CDI, and attributable mortality appears to increase with age.^{3,4} Older adults also experience a higher rate of CDI relapse, as well as more treatment failures on standard therapy.^{5,6}

Clostridium difficile infection has been recognized as the most common cause of nonepidemic diarrheal illness in long-term care (LTC) facilities, where CDI outbreaks can be very difficult to control.⁷ Little published data are specific to older adults, and residence in an LTC facility further complicates treatment and prevention strategies. Finally, the issues of drug-related side effects, drug-drug interactions, and medication cost are especially significant in this patient population.

In this review, we offer an overview of specific agents used to treat CDI and

also briefly discuss the approach to CDI relapse as well as infection control in the LTC setting.

Treatment

General Issues

Treatment for CDI is recommended only for symptomatic patients; asymptomatic carriers of *C. difficile* do not require treatment with antimicrobials.⁷ The mean time for clinical improvement after initiating treatment for CDI is 2–4 days, and, in general, a lack of clinical response after 6 days of treatment is considered a treatment failure.⁸ However, a change in treatment may be indicated much sooner than 6 days depending on the patient's overall clinical condition. In general, a "treatment success" denotes resolution of diarrhea and other symptoms (e.g., abdominal pain, fever), if present.

Whenever possible, the offending antibiotic agent should be stopped as an adjunctive treatment measure.⁸ Antiperistaltic agents such as loperamide should be avoided in patients with CDI as there is a possible association between the use of these drugs and the development of megacolon.⁹

Table 1 presents a summary of the medications used in the treatment of CDI, along with respective dosages and comments.

Metronidazole

Metronidazole remains the first-line agent for the treatment of uncomplicated CDI. Although there is a role for intravenous metronidazole therapy in the setting of severe CDI, these scenarios almost always occur in an acute care setting; in an LTC facility, the oral route is used almost exclusively. Metronidazole is most commonly administered at 250 mg four times per day or 500 mg three times per day for 10–14 days.¹⁰ The three-times-a-day regimen is preferred given the ease of dosing.

Common side effects associated with the use of metronidazole include gastrointestinal complaints and a metallic taste. Many residents of LTC facilities have diminished nutritional reserves and poor oral intake (further exacerbated by

CDI), so the taste disturbance associated with metronidazole can limit its use. Additionally, prolonged use of metronidazole has been associated with peripheral neuropathy. While uncommon, the development of peripheral neuropathy carries a particular significance among members of the LTC population, who frequently have baseline impairments in mobility. Although the neuropathy generally improves after the discontinuation of metronidazole, there are reports of symptoms persisting for up to 2 years after use.¹¹ Prolonged courses of metronidazole should be used with caution, and patients treated for an extended period should be monitored closely for these symptoms.

An inhibitor of cytochrome P-450 3A4 (CYP3A4), metronidazole can alter the concentrations of many drugs including amiodarone, phenytoin, fosphenytoin, and carbamazepine. Lithium levels should be closely monitored as metronidazole can increase concentrations. Metronidazole inhibits warfarin metabolism, increasing prothrombin time and international normalized ratios. Finally, metronidazole can produce a disulfiram-like reaction when alcohol is ingested, so alcohol must be avoided during treatment.

Vancomycin

Vancomycin is the only drug approved by the U.S. Food and Drug Administra-

tion (FDA) for the treatment of CDI. Despite older reports of metronidazole's equivalence to vancomycin, oral vancomycin has emerged as the preferred agent in patients with severe CDI.^{12,13} Some proposed markers for severe disease include hypotension, a white blood cell count of $>15,000$ cells/mm³, serum creatinine increased $\geq 50\%$ from baseline, a serum albumin level of <2.5 mg/dL and age >60 years.¹²⁻¹⁵ In addition to promptly initiating treatment, transfer to the acute care setting should be considered in residents of LTC facilities who exhibit these characteristics (if indeed such a transfer is consistent with the individual's overall goals of care).

The oral vancomycin regimen most commonly used for CDI is 125 mg four times per day for 10–14 days,¹⁰ although infectious disease clinicians frequently use higher dosages among patients who do not respond to standard dosages. Oral vancomycin acts locally, and significant systemic absorption is uncommon. For this reason, oral vancomycin is very well tolerated, with few reported adverse events. There are a handful of case reports in the literature suggesting the potential for systemic absorption, but this appears to be a rare finding.¹⁶⁻²²

The cost of oral vancomycin remains a barrier to use. On average, a 10-day course of oral vancomycin costs US\$846 (versus US\$7 for a course of metronidazole). This price differential may be a

major issue in the LTC setting, where the payment structure can require that medication costs be covered by a fixed per diem rate, especially for subacute care. Clinicians should be aware of the higher cost of oral vancomycin and consider the use of metronidazole in mild to moderate CDI among individuals who do not have a contraindication for its use.¹⁴

Other Therapies

Rifamycins (rifampin, rifaximin [not currently available in Canada]) have potent in vitro activity against *C. difficile*; however, the development of resistance is a major concern.²³ At this time, there is no clear role for rifamycins in the treatment of primary CDI; however, rifaximin is sometimes used in combination with vancomycin for recurrent CDI.^{24,25} Rifaximin, like oral vancomycin, is not systemically absorbed and is therefore not typically associated with drug interactions or side effects.

Nitazoxanide is an antiparasitic drug with in vitro activity against *C. difficile* that has shown promising results in clinical trials.^{26,27} The ultimate role of this agent in CDI therapy is unclear, and information on nitazoxanide's drug-drug interactions is limited. Nitazoxanide is not commercially available in Canada.

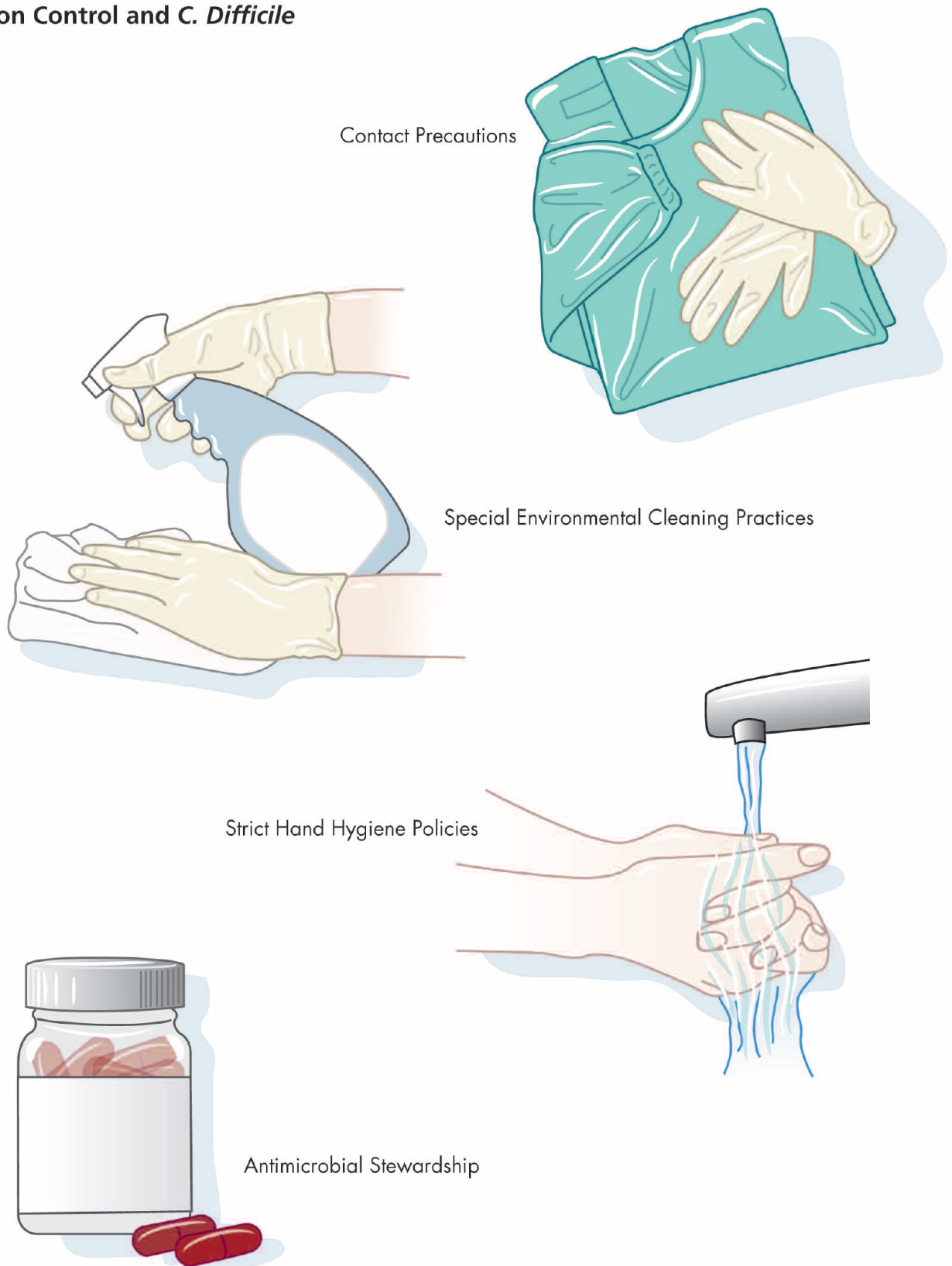
Probiotics *Lactobacillus rhamnosus* and *Saccharomyces boulardii* have both been studied for the treatment of recurrent CDI, although neither have FDA

Table 1: Summary of Medications Used in the Treatment of *Clostridium difficile* Infection

Medication	Typical Dosage	Comments
Metronidazole	500 mg three times per day or 250 mg four times per day	Treatment of mild to moderate CDI Be aware of drug interactions and side effect profile
Vancomycin	125 mg four times per day; higher dosages for fulminant CDI	Treatment of severe CDI More costly than metronidazole
Rifaximin	200 mg three times per day (not currently available in Canada)	Combination therapy for recurrent CDI
Nitazoxanide	500 mg two times per day (not currently available in Canada)	Limited clinical data
Probiotics	Depends on specific agent	Limited clinical data Case reports of fungemia

CDI = *Clostridium difficile* infection.

Figure 1:
Infection Control and *C. Difficile*



Key Points

In the past few years *Clostridium difficile* infection (CDI) has increased in frequency, and older adults have been disproportionately affected.

Older patients have more severe disease, more treatment failures, and a higher rate of relapse.

Oral metronidazole and vancomycin remain the key antibiotics used in the treatment of CDI, although other adjunctive treatments may be considered.

For severe or refractory disease, consultation with an infectious diseases specialist is urged, and use of other therapeutic agents can be considered.

Infection control measures remain vital in preventing the spread of *C. difficile* in the LTC setting.

approval for this indication. The most promising data were from a double-blind, placebo-controlled trial that found that treatment with high-dose oral vancomycin plus *S. boulardii* was 67% more effective in preventing CDI recurrences than was high-dose vancomycin alone.²⁸ Although *S. boulardii* is generally well tolerated, there have been reports of fungemia possibly related to probiotic use.²⁹ We suggest that these agents be used with caution in patients with active CDI, particularly among frail and older patients who are likely at increased risk for fungemia. Additional studies are needed to fully define the role for this adjunctive therapy.

Approach to Relapsed Infection

Recurrent CDI is common, especially among older adults. Frail older patients appear to have more relapses of CDI, with reported recurrence rates of almost 30%, although the risk factors for relapse are incompletely understood.^{5,6} Relapsing CDI is typically defined as three or more episodes of CDI.

A second episode of CDI can often be successfully managed with the same agent used for the first episode of CDI.¹⁰ However, metronidazole is used less frequently in relapsing cases due to concerns about neuropathy with extended use (discussed above). An extended tapering course of vancomycin is often used for the treatment of relapsing CDI. Rifaximin added to the tail end of a vancomycin taper appears to be beneficial in

some patients with relapsing CDI.²⁵ The treatment of relapsing CDI is complicated, and there is not a simple paradigm that is appropriate for all patients, especially older adults. We strongly recommend consultation with an infectious disease specialist for guidance in the management of these clinically challenging cases.

Infection Control

Outbreaks of CDI have become a problem in some LTC facilities, where person-to-person spread is often aided by the use of shared bathroom, dining, and rehabilitation facilities.³⁰ Strategies to reduce the exposure of patients to *C. difficile* include the use of contact precautions, special environmental cleaning practices, and strict enforcement of hand hygiene policies (Figure 1). Surveillance for incident cases of CDI among residents is essential to recognize transmission and identify an outbreak.

Individuals with CDI should be placed in private rooms when available in the LTC setting. Contact precautions (the practice of donning a gown and

gloves prior to entering the infected patient's room) should be implemented for patients with CDI. High-risk patients with diarrhea can be placed under contact precautions preemptively, before results of *C. difficile* testing are available. Cohorting of patients with CDI is another approach to consider when private rooms are not available.

Careful attention must be given to cleaning practices especially if transmission is occurring in the LTC facility. Sodium hypochlorite (household bleach) solutions have been shown to kill spores and decrease environmental contamination with *C. difficile* and have been used successfully to control outbreaks of CDI.³¹ Medical directors should work closely with environmental services staff to ensure consistent, effective cleaning procedures.

Strategies to reduce the development of CDI once exposure has occurred centre on antimicrobial stewardship. This is especially important in LTC facilities as antimicrobials are often among the most frequently prescribed medications in the LTC setting.³⁰ Directed efforts should be made to reduce the unnecessary use of high-risk agents, especially fluoroquinolones, cephalosporins, and clindamycin. General infection control practices in LTC facilities are the subject of recently published guidelines.³⁰

Conclusion

As CDI has increased in frequency, older adults have been disproportionately affected. Not only are older patients at higher risk of developing CDI, this population appears to have more severe disease, more treatment failures, and a higher rate of disease relapse. Clinicians should be aware of the side effects and

Clinical Pearls

Oral metronidazole remains the first line of therapy for the treatment of mild CDI.

Oral vancomycin has emerged as the preferred agent in patients with severe CDI.

drug interactions associated with agents used to treat CDI, particularly when prolonged courses of therapy are required. The approach to treatment and infection control in the LTC setting presents unique challenges. Prevention with focused infection control interventions remains critical.



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