

ASHP Therapeutic Position Statement on the Preferential Use of Metronidazole for the Treatment of *Clostridium difficile*-Associated Disease

Statement of Position

ASHP supports the use of oral metronidazole as the preferred antimicrobial agent for treating *Clostridium difficile*-associated disease (CDAD). Oral metronidazole and oral vancomycin appear to be equally efficacious for the treatment of CDAD in most situations. However, routine use of oral vancomycin may contribute to the emergence of vancomycin-resistant *Enterococcus* species, and oral vancomycin is more costly than oral metronidazole. Oral vancomycin should be reserved for the most severe, potentially life-threatening forms of the disorder, for cases that fail to respond to oral metronidazole, and for patients who are unable to tolerate oral metronidazole or to whom metronidazole should not be given. Mild cases of CDAD may respond to discontinuation of the inciting agent, making antimicrobial treatment unnecessary and reducing the possibility of CDAD relapse. Asymptomatic carriers of *C. difficile* should not be treated for CDAD.

Background

CDAD is an infectious disorder that can develop when toxin-producing *C. difficile* is acquired as a component of the colonic microflora. If an individual harboring the organism is subsequently exposed to certain antimicrobial agents, *C. difficile* is able to evade eradication by spore formation, while many of the bacteria that help maintain normal microbial ecology in the colon are destroyed. This selective advantage for replication can result in the uncontrolled overgrowth of *C. difficile* and production of bacterial exotoxins that cause inflammation and cellular damage.^{1,2} When symptomatic disease ensues, its severity ranges from self-limiting diarrhea to life-threatening enterocolitis with toxic megacolon.^{2,3}

CDAD is predominantly, but not exclusively, a nosocomial disease.¹ Epidemic outbreaks of CDAD may occur within institutions, with patterns of antimicrobial use contributing to the initiation of an outbreak as well as compromising the efficacy of infection control measures intended to limit it.⁴ The frequency of community-acquired CDAD is less than one case per 10,000 antimicrobial prescriptions,⁵ compared with as many as one case per 100 hospitalized adult patients treated with an antimicrobial agent.² However, CDAD will likely become more common in the community setting as outpatient antimicrobial treatment of serious infections increases.

Minimum criteria for diagnosis of CDAD consist of mild to moderate diarrhea accompanied either by a positive *C. difficile* cytotoxin (or toxin b) test result or by endoscopically observed pseudomembranes.¹ Concurrent or recent antimicrobial use is usually present but is not a criterion for definitive diagnosis.¹ However, a recent study indicated that hospitalized patients without antimicrobial exposure during the previous month and either significant diarrhea or abdominal pain are unlikely to have a positive *C. difficile* cytotoxin test result.⁶

Virtually all antimicrobial agents and certain antineoplastic agents with antimicrobial activity have been implicated in precipitating CDAD,³ but data suggest that second- and third-generation cephalosporins play an increasingly important role.⁷⁻⁹ Amoxicillin and amoxicillin-clavulanate are among the most frequently implicated antimicrobial agents in community-acquired CDAD.¹⁰ Although the time of onset of CDAD ranges from within one to two days after the initiation of therapy to as long as 10 weeks after drug discontinuation, most cases occur after several days of treatment or within the first few weeks after discontinuation of therapy.^{2,3}

Asymptomatic colonization by *C. difficile* can occur, especially in healthy neonates and infants. Long-term carriage of the organism has been documented.^{1,2} A well-designed study showed that treatment of asymptomatic carriers of *C. difficile* with either metronidazole or vancomycin is of no clinical value¹¹; more recent data substantiate this.¹²

The initial steps in the management of all cases of CDAD are discontinuation of the precipitating agent, if feasible, and restoration of fluids and electrolytes, if needed.^{2,3} Antimicrobial treatment should be reserved for cases that fail to respond promptly to this initial therapy and for cases in which discontinuation of the precipitating agent is not a therapeutic option.^{2,3} In mild cases of CDAD (diarrhea accompanied by minimal or no constitutional symptoms), particularly those in individuals who are not elderly or debilitated, the patient should be monitored for symptomatic improvement for 48 hours before oral antimicrobial treatment is instituted. If symptomatic deterioration occurs, appropriate antimicrobial therapy should be started promptly.

Relative Efficacy of Oral Metronidazole and Oral Vancomycin in the Treatment of CDAD

Oral vancomycin was first reported to be effective in the treatment of CDAD in 1978.¹³ In 1983, a small but well-designed clinical trial showed oral metronidazole to be equivalent to oral vancomycin for the treatment of CDAD.¹⁴ By then oral vancomycin was already established as the drug of choice for CDAD.

Prospective, randomized comparisons have shown no significant difference in initial response rates or relapse rates between oral metronidazole and oral vancomycin in the treatment of CDAD.^{1,2,14-17} Therefore, oral metronidazole is now the preferred therapy for most patients with CDAD.^{1,3,18,19} Oral vancomycin is considered appropriate only in cases of severe, potentially life-threatening CDAD, when oral metronidazole fails, or when oral metronidazole is not tolerated or cannot be used.^{3,18}

Severe CDAD is not clearly defined in the literature. It has been generally characterized in terms of pseudomembrane formation, fever exceeding 40 °C (104 °F), marked abdominal tenderness, and pronounced leukocytosis.^{2,3,14} The detection of fecal leukocytes by microscopy also

suggests more severe disease.⁹ Even in these clinical circumstances, there is little objective evidence that oral vancomycin is superior to oral metronidazole.^{14–16} In rare instances, ileus and toxic megacolon develop. These constitute potentially life-threatening conditions in which oral therapy is not feasible, but optimal drug therapy remains undefined.^{2,7}

Role of Vancomycin in the Emergence of Vancomycin-Resistant Enterococci

Many studies have identified prior exposure to vancomycin as a risk factor for colonization and infection by vancomycin-resistant enterococci (VRE).²⁰ Although intravenous rather than oral vancomycin appears to be the most significant risk factor, oral vancomycin use has also been implicated.^{20–23} An apparent association between CDAD and the acquisition of VRE has also been described.^{20,24,25} In two European studies it was found that glycopeptide-resistant enterococci could be isolated readily from stool samples after oral administration of vancomycin to healthy adults.^{26,27}

Concern over the probable role of indiscriminate use of vancomycin in the emergence of VRE culminated in the publication, by the Hospital Infection Control Practices Advisory Committee of the Centers for Disease Control and Prevention, of consensus guidelines for prudent vancomycin use.¹⁸ The guidelines deem oral vancomycin “appropriate or acceptable . . . when antibiotic-associated colitis (AAC) fails to respond to metronidazole therapy or if AAC is severe and potentially life threatening” and state that its use for the “primary treatment of AAC” should be discouraged.

Vancomycin and Metronidazole Dosage Regimens

Since *C. difficile* usually does not escape the gastrointestinal tract, only antimicrobial levels within the intestinal lumen are of consequence. When vancomycin is administered orally, high fecal concentrations are obtained because of poor absorption. A regimen of vancomycin 125 mg (as the hydrochloride salt) four times daily provides the same clinical outcome as 500 mg four times daily because it yields a mean fecal vancomycin concentration well above the highest reported minimum inhibitory concentration for *C. difficile*.²⁸

In contrast to oral vancomycin, oral metronidazole attains very low fecal concentrations because of nearly complete absorption. Although this has resulted in lingering concern about the efficacy of oral metronidazole in the treatment of serious cases of CDAD,¹ such concern seems unwarranted. Some unmetabolized metronidazole is eliminated in the feces via biliary excretion, and the drug appears to cross the intestinal wall into the lumen of the inflamed colon. Furthermore, successful treatment of CDAD with metronidazole is well documented.^{1,14–16} Total daily dosages of oral metronidazole in the treatment of CDAD have ranged from 1000 to 2250 mg administered in three or four divided doses.² Of three major studies that found oral metronidazole and oral vancomycin to be therapeutically equivalent for CDAD, two used a daily metronidazole dosage of 1000 mg (250 mg four times daily),^{7,14} and one used a daily dosage of 1500 mg (500 mg three times daily).¹⁶ No direct comparisons of metronidazole dosages have been published.²

Ten days has been the usual duration of therapy when either oral agent is used for CDAD.² Symptomatic

improvement may be apparent within 48 hours, but treatment is most likely to be successful if carried out for the full 10 days.¹ A slow or delayed response to therapy with either metronidazole or vancomycin may occur in patients with a pre-existing intestinal disorder and associated diarrhea.¹⁷ However, therapeutic failure of metronidazole should not be assumed until a minimum of six days of treatment have been completed without symptomatic improvement.^{7,14,16} Therapeutic failure rates of 2–5% can be anticipated with either oral metronidazole or oral vancomycin.^{7,17}

Oral therapy is always preferable for the treatment of CDAD, but the oral route is not always feasible because of gastrointestinal obstruction or other reasons (e.g., toxic megacolon).³ Treatment approaches in patients unable to tolerate oral medications have included i.v. vancomycin, i.v. metronidazole, and rectal vancomycin alone and in various combinations, but no comparative studies have been performed.²⁹ Because treatment failures have been reported with either i.v. metronidazole or i.v. vancomycin given alone,^{30,31} consideration should be given to the concurrent use of i.v. metronidazole and either i.v. or rectal vancomycin.³ Several regimens for the rectal administration of vancomycin have been described.^{3,29} Because the available efficacy data are exclusively anecdotal, no definitive recommendations can be made regarding the treatment of CDAD in the patient who cannot take oral medications.

Treatment of Relapse

Approximately 15–35% of patients treated for CDAD with either oral metronidazole or oral vancomycin relapse within two months after completing initial therapy.³ Relapse is defined as a return of symptoms and positive diagnostic test results after discontinuation of successful antimicrobial therapy for CDAD.³ Most patients relapse only once, although multiple relapses occur in a small subset of patients.^{2,17} Relapse frequency is unrelated to the antimicrobial selected for initial treatment of CDAD,^{3,17} but additional exposure to antimicrobials given to treat other types of infection appears to be a significant risk factor for recurrence of CDAD, and the frequency of recurrence increases with the number of antimicrobials administered.¹⁷

A multitude of protocols for treating CDAD relapse are described in the literature, but no comparative studies have been conducted.^{2,3,17} More than 90% of patients with CDAD who relapse respond to a single repeated course of oral medication, either metronidazole or vancomycin.⁷ Since relapse is usually unrelated to antimicrobial resistance, the same agent used to treat CDAD initially can be used to treat the relapse.^{2,3} Thus, patients with a first relapse of CDAD who were treated with oral metronidazole initially should receive a second 10-day course of metronidazole.¹ No definitive therapeutic recommendation can be made for a patient with multiple relapses. Therapeutic options are discussed in detail elsewhere.^{2,3,17}

Special Populations

Asymptomatic carriage of toxin-producing *C. difficile* is common in newborn infants and in children less than two years of age, but CDAD is rare. It is also rare in older children. However, certain subpopulations, such as children with gastrointestinal motility disorders like Hirschsprung’s disease (congenital megacolon) and severely neutropenic children with leukemia, are at increased risk.³² Comparative studies

of oral metronidazole and oral vancomycin for the treatment of CDAD have not been conducted in the pediatric population. Since the pharmacokinetic profile of oral metronidazole in children is similar to that in adults, there is no reason to consider oral metronidazole inferior to oral vancomycin for CDAD in pediatric patients. However, commercial oral vancomycin solution may prove more palatable than an extemporaneously prepared metronidazole suspension for children who are unable to swallow metronidazole tablets or for whom the available tablet formulation is not appropriate.³³

Recommended dosages for the treatment of CDAD in children are oral metronidazole 30 mg/kg/day given in divided doses every six hours or oral vancomycin 40 mg/kg/day given in divided doses every six to eight hours.¹⁹ The maximum dosage in pediatric patients should not exceed the adult dosage.

The risk of metronidazole therapy during the first trimester of pregnancy is uncertain, and metronidazole use during that trimester is controversial.³⁴ Metronidazole is excreted into breast milk. Oral vancomycin may therefore be the preferred agent for the treatment of CDAD during the first trimester and in nursing mothers.³

Therapeutic Alternatives

The use of an anion-exchange resin such as cholestyramine, with or without metronidazole or vancomycin therapy, offers no demonstrable benefit and should be discouraged.^{2,3} Concomitant use of cholestyramine and oral vancomycin is particularly undesirable because of binding of vancomycin by cholestyramine. Antiperistaltic agents can cause retention of *C. difficile* toxins in the colon and should be avoided.^{2,3} Oral bacitracin, which is expensive and less efficacious than metronidazole or vancomycin,² should generally not be used. Biotherapy, such as supplementation of the normal colonic microflora with *Saccharomyces boulardii*, may be a future approach to the prevention and treatment of CDAD.³⁵

The Pharmacist's Role

Pharmacists should strive to optimize the treatment of CDAD by encouraging the preferential use of metronidazole when antimicrobial therapy is warranted. Currently, excessive use of oral vancomycin for CDAD is largely an institutional problem because CDAD is primarily a nosocomial disease. However, as CDAD becomes more common in the community setting, ambulatory care pharmacists too will have a responsibility for ensuring optimal treatment of this disease.

The availability of guidelines for vancomycin use alone may not result in major changes in prescribing behavior.^{33,36-39} Additional strategies for influencing vancomycin prescribing may include tailored educational efforts and interventions that encourage physicians to prescribe oral metronidazole preferentially for the treatment of CDAD when antimicrobial therapy is indicated. In addition, pharmacists should become involved in implementing comprehensive antimicrobial management programs that can both help to prevent the development of bacterial resistance and reduce overall expenditures.³⁸

Pharmacists should collaborate on studies designed to clarify the relationship between oral vancomycin use and the acquisition of vancomycin-resistant bacteria, participate in surveillance for vancomycin-resistant organisms, and contribute to infection-control measures directed against vancomycin-resistant pathogens.⁴⁰

Finally, pharmacists can play a key role in communicating to patients the risks of resistance associated with the indiscriminate use of antimicrobial agents and the potential adverse effects of therapy. Improved patient understanding of these risks should result in better adherence to therapy.

Summary

ASHP supports preferential use of oral metronidazole for treating CDAD when antimicrobial therapy is indicated. Oral vancomycin should be reserved for severe, potentially life-threatening cases or when oral metronidazole cannot be used. Oral metronidazole is as safe and effective as oral vancomycin and is considerably less costly. In addition, preliminary data suggest that routine use of oral vancomycin for CDAD may contribute to the spread of VRE—emerging nosocomial pathogens that can be extraordinarily difficult to treat. Pharmacists should work to foster preferential prescribing of oral metronidazole for the treatment of CDAD. Pharmacists should also actively seek opportunities to educate health care providers and counsel patients about the risks associated with the indiscriminate use of vancomycin and other antimicrobial agents.

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This therapeutic position statement was reviewed in 2002 by the Commission on Therapeutics and by the Board of Directors and was found to still be appropriate.

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