

# 1 ASHP Therapeutic Position Statement on the 2 Management of *Clostridium difficile*-Associated Disease

## 3 4 Statement of Position

5  
6 ASHP supports the use of oral metronidazole as the preferred antimicrobial agent for treating an  
7 initial episode of mild to moderate *Clostridium difficile*-associated disease (CDAD). Oral  
8 metronidazole and oral vancomycin appear to be equally efficacious for the treatment of CDAD  
9 in patients with mild to moderate disease. However, oral vancomycin has shown more favorable  
10 results in patient with severe disease. Routine use of oral vancomycin may contribute to the  
11 emergence of vancomycin-resistant *Enterococcus* (VRE) species, and oral vancomycin is  
12 typically more costly than oral metronidazole. Oral vancomycin should be utilized for severe  
13 cases of CDAD including patients with leukocytosis ( $\geq 15000$ ), for cases that fail to respond to  
14 oral metronidazole, and for patients who are unable to tolerate oral metronidazole or to whom  
15 metronidazole should not be given.

## 16 Background

17  
18 CDAD is an infectious disorder that can develop when toxin producing *C. difficile* is acquired as  
19 a component of the colonic microflora. If an individual harboring the organism is subsequently  
20 exposed to certain antimicrobial agents, *C. difficile* is able to evade eradication by spore  
21 formation, while many of the bacteria that help maintain normal microbial ecology in the colon  
22 are destroyed. This selective advantage for replication can result in the uncontrolled overgrowth

23 of *C. difficile* and production of bacterial exotoxins that cause inflammation and cellular  
24 damage.<sup>1,2</sup> When symptomatic disease ensues, its severity ranges from self-limiting diarrhea to  
25 life-threatening enterocolitis with toxic megacolon.<sup>2,3</sup> CDAD is predominantly, but not  
26 exclusively, a nosocomial disease.<sup>1</sup> Epidemic outbreaks of CDAD may occur within institutions,  
27 with patterns of antimicrobial use contributing to the initiation of an outbreak as well as  
28 compromising the efficacy of infection control measures intended to limit it.<sup>4</sup> The frequency of  
29 community-acquired CDAD is less than one case per 10,000 antimicrobial prescriptions,<sup>5</sup>  
30 compared with as many as one case per 100 hospitalized adult patients treated with an  
31 antimicrobial agent.<sup>2</sup> However, CDAD will likely become more common in the community  
32 setting as outpatient antimicrobial treatment of serious infections increases.

34 The most sensitive test for diagnosis of *Clostridium difficile* infection is stool culture. However,  
35 this test is often not clinically practical secondary to the slow turnaround time for results. As  
36 such, diagnostic testing focuses on detection of *C. difficile* toxin production since this is the  
37 agent responsible for colitis. Toxin B testing required for diagnosis can be rapid, but, is limited  
38 by its sensitivity. Therefore, a two-step process is recommended in which enzyme immunoassay  
39 is used to initially detect glutamate dehydrogenase (GDH) as a surrogate for toxin A or B and is  
40 followed by a confirmatory cell cytotoxicity test or toxigenic culture for GDH-positive samples.  
41 Polymerase chain reaction (PCR) testing appears to be sensitive and specific and would confer  
42 less turnaround time than culture; however, more data is necessary before it can be  
43 recommended for routine use. Minimum criteria for diagnosis of CDAD consist of mild to  
44 moderate diarrhea accompanied either by a positive *C. difficile* cytotoxin (or toxin b) test result  
45 or by endoscopically observed pseudomembranes.<sup>1</sup> Concurrent or recent antimicrobial use is

46 usually present but is not a criterion for definitive diagnosis.<sup>1</sup> However, hospitalized patients  
47 without antimicrobial exposure during the previous month and either significant diarrhea or  
48 abdominal pain are unlikely to have a positive *C. difficile* cytotoxin test result.<sup>6</sup> Virtually all  
49 antimicrobial agents, proton pump inhibitors, and certain antineoplastic agents with antimicrobial  
50 activity have been implicated in precipitating CDAD,<sup>3</sup> but data suggest that second- and third-  
51 generation cephalosporins play an increasingly important role.<sup>7-9</sup> Amoxicillin and amoxicillin-  
52 clavulanate are among the most frequently implicated antimicrobial agents in community-  
53 acquired CDAD.<sup>10</sup> A previously uncommon strain of *C. difficile* with variations in toxin genes  
54 (NAP1/BI/027) has become more resistant to fluoroquinolones and has emerged as a cause of  
55 geographically dispersed outbreaks of *C. difficile*-associated disease.<sup>41,48-53</sup> The increasing use of  
56 fluoroquinolones around the United States may have provided a selective advantage for this  
57 epidemic strain and promoted its widespread emergence.<sup>41,42</sup>

58  
59 Although the time of onset of CDAD ranges from within one to two days after the initiation of  
60 antimicrobial therapy to as long as 10 weeks after drug discontinuation, most cases occur after  
61 several days of treatment or within the first few weeks after discontinuation of therapy.<sup>2,3</sup>  
62 Asymptomatic colonization by *C. difficile* can occur, especially in healthy neonates and infants.  
63 Long-term carriage of the organism has been documented.<sup>1,2</sup> A well-designed study showed that  
64 treatment of asymptomatic carriers of *C. difficile* with either metronidazole or oral vancomycin is  
65 of no clinical value<sup>11</sup>; more recent data substantiate this.<sup>12</sup> The initial steps in the management of  
66 all cases of CDAD are discontinuation of the precipitating agent, if feasible, and restoration of  
67 fluids and electrolytes, if needed.<sup>2,63</sup> Empiric therapy should be initiated if severe or  
68 complicated disease is suspected.<sup>63</sup>

69

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

71

72 Oral vancomycin was first reported to be effective in the treatment of CDAD in 1978.<sup>13</sup> In 1983,

73 a small but well-designed clinical trial showed oral metronidazole to be equivalent to oral

74 vancomycin for the treatment of CDAD.<sup>14</sup> At that time, oral vancomycin was already established

75 as the drug of choice for CDAD. Early prospective, randomized comparisons showed no

76 significant differences in initial response rates or relapse rates between oral metronidazole and

77 oral vancomycin in the treatment of CDAD.<sup>1,2,14-17</sup> Results of these studies, concerns for the

78 development of vancomycin-resistant enterococci with oral vancomycin use, and a cost-

79 advantage with metronidazole, contributed to oral metronidazole becoming the preferred therapy

80 for most patients with CDAD.<sup>1,3,18,19</sup>

81

82 Treatment recommendations were further revised following a pivotal 2007 trial published by Zar

83 and colleagues which showed superiority of oral vancomycin compared with metronidazole in

84 patients with severe disease.<sup>45</sup> Metronidazole remains the drug of choice for the initial episode

85 of mild to moderate CDAD; however, oral vancomycin is now considered the preferred option in

86 cases of severe CDAD, when oral metronidazole fails, or when oral metronidazole is not

87 tolerated or cannot be used.<sup>3,18,63</sup> Severe CDAD has been characterized in terms of pronounced

88 leukocytosis ( $\geq 15000$ ), and serum creatinine level  $\geq 1.5X$  pre-morbid levels<sup>(2, 3, 14, 45, 46, 63)</sup>. There

89 is little evidence for treatment of initial episodes in patients with complications such as

90 hypotension or shock, ileus, or megacolon. Vancomycin 500 mg four times daily by mouth or

91 by nasogastric tube, plus metronidazole, 500 mg three times daily has been recommended.<sup>46</sup>

92 Vancomycin per rectum is an option in patients with severe disease with ileus.

93

94 Role of Vancomycin in the Emergence of Vancomycin-Resistant Enterococci

95

96 Many studies have identified prior exposure to vancomycin as a risk factor for colonization and  
97 infection by VRE.<sup>20</sup> Although intravenous rather than oral vancomycin appears to be the most  
98 significant risk factor, oral vancomycin use has also been implicated.<sup>20-23</sup> An apparent  
99 association between CDAD and the acquisition of VRE has also been described.<sup>20,24,25</sup> Two  
100 European studies found that glycopeptide-resistant enterococci could be isolated readily from  
101 stool samples after oral administration of vancomycin to healthy adults.<sup>26,27</sup> Concern over the  
102 probable role of indiscriminate use of vancomycin in the emergence of VRE culminated in the  
103 publication of consensus guidelines for prudent vancomycin use by the Hospital Infection  
104 Control Practices Advisory Committee of the Centers for Disease Control and Prevention.<sup>18</sup> In  
105 addition, several publications question the role metronidazole, in addition to oral vancomycin,  
106 plays in the development of VRE.<sup>64,65</sup> While further data is needed, the combined information  
107 for both oral vancomycin and metronidazole underlies the need to limit unneeded treatment of  
108 CDAD in patients without disease.

109

110 Vancomycin and Metronidazole Dosage Regimens

111

112 Since *C. difficile* usually does not escape the gastrointestinal tract, only antimicrobial levels  
113 within the intestinal lumen are of consequence. When vancomycin is administered orally, high

114 fecal concentrations are obtained because of poor absorption. A regimen of vancomycin 125 mg  
115 (as the hydrochloride salt) four times daily provides the same clinical outcome as 500 mg four  
116 times daily because it yields a mean fecal vancomycin concentration well above the highest  
117 reported minimum inhibitory concentration for *C. difficile*.<sup>28</sup> In contrast to oral vancomycin, oral  
118 metronidazole attains very low fecal concentrations because of nearly complete absorption.  
119 Some unmetabolized metronidazole is eliminated in the feces via biliary excretion, and the drug  
120 appears to cross the intestinal wall into the lumen of the inflamed colon. Total daily dosages of  
121 oral metronidazole in the treatment of CDAD have ranged from 1000 to 2250 mg administered  
122 in three or four divided doses.<sup>2</sup> Of three major studies that found oral metronidazole and oral  
123 vancomycin to be therapeutically equivalent for CDAD, two used a daily metronidazole dosage  
124 of 1000 mg (250 mg four times daily),<sup>7,14</sup> and one used a daily dosage of 1500 mg (500 mg three  
125 times daily).<sup>16</sup> No direct comparisons of metronidazole dosages have been published. Recent  
126 guidelines suggest a dosing regimen of 500 mg three times daily in adult patients.<sup>46</sup> Ten days has  
127 been the usual duration of therapy when either oral agent is used for CDAD<sup>2</sup>, although some  
128 guidelines have suggested 10-14 days.<sup>46</sup> Symptomatic improvement may be apparent within 48  
129 hours, but treatment is most likely to be successful if carried out for the full treatment course.<sup>1</sup>  
130 Recent cephalosporin use, transfer from another institution, and CDAD on admission are all  
131 associated with higher rates of metronidazole failure. A slow or delayed response to therapy  
132 with either metronidazole or vancomycin may occur in patients with a pre-existing intestinal  
133 disorder and associated diarrhea.<sup>62</sup>  
134 Therapeutic failure rates of 2–24% can be anticipated with either oral metronidazole or oral  
135 vancomycin.<sup>7,45</sup> Oral therapy is always preferable for the treatment of CDAD, but the oral route  
136 is not always feasible because of gastrointestinal obstruction or other reasons (e.g., toxic

137 megacolon).<sup>3</sup> Treatment approaches in patients unable to tolerate oral medications are limited  
138 and no comparative studies have been performed.<sup>29</sup> Because treatment failures have been  
139 reported with i.v. metronidazole alone,<sup>30,31</sup> consideration should be given to the concurrent use  
140 of i.v. metronidazole and rectal vancomycin.<sup>3</sup> Several regimens for the rectal administration of  
141 vancomycin have been described, but dosing is typically 0.5-1 g of vancomycin dissolved in 1-2  
142 Liters of isotonic saline, given as a 60-minute retention enema every 4-12 hours.<sup>3,29,47</sup> Because  
143 the available efficacy data are exclusively anecdotal, no definitive recommendations can be  
144 made regarding the treatment of CDAD in the patient who cannot take oral medications.

#### 145 146 Treatment of Recurrence

147  
148 Approximately 15–35% of patients treated for CDAD with either oral metronidazole or oral  
149 vancomycin relapse within two months after completing initial therapy.<sup>3</sup> Most patients relapse  
150 only once, although multiple relapses may occur in a small subset of patients.<sup>2,17</sup> Relapse  
151 frequency is unrelated to the antimicrobial selected for initial treatment of CDAD,<sup>3,17</sup> but  
152 additional exposure to antimicrobials given to treat other types of infection appears to be a  
153 significant risk factor for recurrence of CDAD, and the frequency of recurrence increases with  
154 the number of antimicrobials administered.<sup>17</sup> A multitude of protocols for treating CDAD relapse  
155 are described in the literature, but no comparative studies have been conducted.<sup>2,3,17</sup>

156 More than 90% of patients with CDAD who relapse respond to a single repeated course  
157 of oral medication, either metronidazole or vancomycin.<sup>7</sup> Since relapse is usually unrelated to  
158 antimicrobial resistance, the same agent used to treat CDAD initially can be used to treat the  
159 relapse.<sup>2,3</sup> Thus, patients with a first relapse of CDAD who were treated with oral metronidazole

160 initially should receive a second course of metronidazole if their white blood count remains  $\leq$   
161 15,000 cells/ $\mu$ L.<sup>1</sup> Treatment with metronidazole beyond the first recurrence or for long-term  
162 chronic therapy is not recommended due to neurotoxicity.<sup>46</sup> Some studies suggest using a pulsed  
163 or tapered dose of vancomycin for relapse of CDAD, given over an extended period of time  
164 (usually 3 weeks) to allow gradual weeding out of *C. difficile* spores from the intestinal  
165 reservoir.<sup>43</sup> Head-to-head trials in this area are lacking. No definitive therapeutic  
166 recommendation can be made for a patient with multiple relapses. Therapeutic options are  
167 discussed in detail elsewhere.<sup>2,3,17</sup>

168 A phase III, noninferiority trial compared, fidaxomicin, versus oral vancomycin for the  
169 treatment of *C. difficile* infection. Six hundred twenty nine patients were enrolled with 548 of  
170 those who were stratified according to whether the current *C. difficile* infection was the first or  
171 second episode and randomized within their stratified group to receive fidaxomicin 200mg po  
172 bid or vancomycin 125mg po q6h. Noninferiority criteria were met in both the modified  
173 intention-to-treat and the per-protocol treatment populations. Further, those in the fidaxomicin  
174 treatment arm had a significantly lower rate of recurrence by 9.9% ( $p=0.005$ ) when compared to  
175 vancomycin in both the modified intention-to-treat and the per-protocol treatment populations.  
176 However, these positive results were only demonstrated in those patients who were not infected  
177 with the BI/NAP1/027 strain of *Clostridium difficile*.<sup>58</sup> Fidaxomin was approved by the US  
178 Food and Drug Administration in 2011 for the treatment of CDAD. The role of this agent in  
179 comparison with metronidazole and oral vancomycin has yet to be defined; however, the  
180 significant acquisition cost of fidaxomicin compared with metronidazole or compounded oral  
181 vancomycin is a likely point of consideration for prescribers and health-care decision makers.

182

183 Treatment of refractory *Clostridium difficile* infection

184 No clear guidelines are available for the treatment of *Clostridium difficile* infection that is  
185 refractory to treatment with metronidazole or vancomycin. The vast majority of alternative  
186 therapies studied are applicable to relapsed infection. Rifaximin, an oral structural analog of  
187 rifampin, is often mentioned as a treatment alternative for refractory disease. An *in vitro* study  
188 suggests rifaximin has high activity against 359 different *Clostridium difficile* isolates.<sup>54</sup> Further,  
189 one clinical case report chronicles a case in which a 56 year old male with refractory *Clostridium*  
190 *difficile* infection was successfully treated using a vancomycin taper dose schedule concurrently  
191 with rifaximin 400mg TID and then a subsequent treatment with a vancomycin taper dose  
192 schedule concurrently with rifaximin 400mg QID. During each treatment the patient also  
193 received daily probiotic therapy.<sup>55</sup>

194 There is limited evidence that tigecycline, a structural analog of minocycline, may be  
195 effective as adjunctive or alternative therapy for severe, refractory CDAD. One case series  
196 illustrates 4 cases in which the patient's CDAD did not respond to metronidazole, oral  
197 vancomycin or combination therapy were successfully treated with tigecycline with or without  
198 concomitant oral vancomycin.<sup>66</sup> Another case report documents successful treatment with  
199 tigecycline 100mg daily along with metronidazole after treatment failure with both  
200 metronidazole and oral vancomycin.<sup>67</sup> Finally, studies exist suggesting refractory *Clostridium*  
201 *difficile* infection can be successfully treated by donated stool transplanted via colonoscopy.<sup>68</sup>

202

203 Special Populations

204

205 Asymptomatic carriage of toxin-producing *C. difficile* is common in newborn infants and in  
206 children less than two years of age, but CDAD is rare. It is also rare in older children.  
207 However, certain subpopulations, such as children with gastrointestinal motility disorders like  
208 Hirschsprung's disease (congenital megacolon) and severely neutropenic children with leukemia,  
209 are at increased risk.<sup>32</sup> Comparative studies of oral metronidazole and oral vancomycin for the  
210 treatment of CDAD have not been conducted in the pediatric population. Commercial oral  
211 vancomycin solution may prove more palatable than an extemporaneously prepared  
212 metronidazole suspension for children who are unable to swallow metronidazole tablets or for  
213 whom the available tablet formulation is not appropriate.<sup>33</sup> Recommended dosages for the  
214 treatment of CDAD in children are oral metronidazole 30 mg/kg/day given in divided doses  
215 every six hours or oral vancomycin 40 mg/kg/day given in divided doses every six to eight  
216 hours.<sup>19</sup> The maximum dosage in pediatric patients should not exceed the adult dosage. The risk  
217 of metronidazole therapy during the first trimester of pregnancy is uncertain, and metronidazole  
218 use during that trimester is controversial.<sup>34</sup> Metronidazole is excreted into breast milk. Oral  
219 vancomycin may therefore be the preferred agent for the treatment of CDAD during the first  
220 trimester and in nursing mothers.<sup>3</sup>

221

## 222 Therapeutic Alternatives

223 The use of an anion-exchange resin such as cholestyramine, with or without metronidazole or  
224 vancomycin therapy, offers no demonstrable benefit and should be discouraged.<sup>2,3</sup>

225 Concomitant use of cholestyramine and oral vancomycin is particularly undesirable because of  
226 binding of vancomycin by cholestyramine, which may decrease vancomycin efficacy.

227 Antiperistaltic agents can cause retention of *C. difficile* toxins in the colon and should be

228 avoided.<sup>2,3</sup> Oral bacitracin, which is expensive and less efficacious than metronidazole or  
229 vancomycin,<sup>2</sup> should generally not be used. Recent studies suggest a lower incidence of CDAD  
230 for probiotic treatment groups compared to placebo groups.<sup>44</sup> These studies suggest value with  
231 preventative probiotic therapy especially in older patients and for patients on prolonged  
232 antibiotic administration.<sup>44</sup> Definitive dosing and utility of probiotics cannot be recommended at  
233 this time, as further studies are necessary. Further, regulatory oversight of probiotics, considered  
234 to be a dietary supplement, differs greatly when compared with a drug and generally do not  
235 maintain similar standards in terms of safety and efficacy. Additionally, reports of fungemia  
236 associated with use of probiotics have been observed. Infection control risks have also been  
237 identified in in vitro testing whereby opening a capsule conferred contamination of the air  
238 and surfaces for as long as 2 hours. The hands of the person opening the capsule were noted to be  
239 persistently contaminated despite several handwashing attempts.<sup>61</sup>

#### 241 Infection Prevention and Control

242  
243 Strict infection-control measures, including contact precautions, should be instituted for all  
244 patients with CDAD.<sup>41</sup> Specifically, health care workers and visitors should wear gloves and  
245 gowns upon entry to a patient's room. Patients should ideally be placed in their own room,  
246 however if single rooms are unavailable, patient-care equipment either should be used only for  
247 the patient or should be cleaned before it is used for another patient. Enhanced environmental  
248 cleaning with chlorine containing cleaning agents or other sporicidal agents should be used to  
249 eliminate *C. difficile* spores. Because alcohol is ineffective in killing *C. difficile* spores, it is

250 essential for health care workers to wash their hands with soap and water, rather than with  
251 alcohol-based waterless hand sanitizer.

252

### 253 Antimicrobial Stewardship

254

255 Since antimicrobial exposure is a significant risk factor for the development of CDAD,  
256 optimizing antimicrobial therapy becomes an essential strategy to confront and limit the disease.  
257 Antimicrobial stewardship programs have emerged as an important tool to facilitate appropriate  
258 antimicrobial use within health-systems while minimizing the unintended consequences of  
259 antimicrobial use such as CDAD.<sup>59,60</sup> Strategies which limit inappropriate antimicrobial use,  
260 decrease therapy durations, and reduce the number of antimicrobial agents prescribed are  
261 recommended.<sup>46</sup> Direct correlation data between reducing specific antimicrobial classes and the  
262 incidence of CDAD is minimal; however, specific strategies limiting the use of second and third-  
263 generation cephalosporins, clindamycin, and fluoroquinolones should be considered. Strategies  
264 which have combined successful infection prevention and control procedures with antimicrobial  
265 stewardship, commonly known as a bundled approach, have shown success in significantly  
266 limiting the incidence of CDAD.<sup>56-57</sup>

267

### 268 The Pharmacist's Role

269

270 Pharmacists should strive to optimize the treatment of CDAD by encouraging the appropriate use  
271 of metronidazole or oral vancomycin, depending on the clinical status of the patient, when  
272 antimicrobial therapy is warranted. Currently, excessive use of oral vancomycin for CDAD is

273 largely an institutional problem because CDAD is primarily a nosocomial disease. However, as  
274 CDAD becomes more common in the community setting, ambulatory care pharmacists too will  
275 have a responsibility for ensuring optimal treatment of this disease. The availability of guidelines  
276 for the treatment of CDAD alone may not result in major changes in prescribing behavior.<sup>33,36-39</sup>  
277 Additional strategies for influencing prescribing may include tailored educational efforts and  
278 interventions that encourage physicians to prescribe the recommended agent for the treatment of  
279 CDAD when antimicrobial therapy is indicated. In addition, pharmacists should become  
280 involved in implementing comprehensive antimicrobial stewardship programs.<sup>38</sup> Pharmacists are  
281 encouraged to develop and collaborate on research to improve the effectiveness of screening and  
282 treatment of CDAD. This includes projects designed to clarify the relationship between oral  
283 vancomycin use and the acquisition of vancomycin-resistant bacteria the impact of stewardship  
284 efforts (i.e. decreasing antimicrobial utilization and improving overall antimicrobial use),  
285 infection prevention and control measures, and the comparative effectiveness and adverse events  
286 associated with different antimicrobial treatments. Pharmacists should also participate in  
287 surveillance for vancomycin-resistant organisms, and contribute to infection-prevention and  
288 control and antimicrobial stewardship measures directed against vancomycin-resistant  
289 pathogens.<sup>40</sup> Finally, pharmacists can play a key role in communicating to patients and  
290 prescribers the risks of resistance associated with the indiscriminate use of antimicrobial agents  
291 and the potential adverse effects of therapy. Improved patient understanding of these risks should  
292 result in better adherence to therapy.

293

294 Summary

295

296 ASHP supports the pharmacist's role in ensuring the proper selection of antimicrobial for  
297 treating CDAD when antimicrobial therapy is indicated. Oral vancomycin should be reserved for  
298 severe CDAD or when oral metronidazole is not a treatment option. Oral metronidazole is as safe  
299 and effective as oral vancomycin in the treatment of mild disease and is considerably less costly.  
300 Pharmacists should work to foster appropriate prescribing of antimicrobials through  
301 antimicrobial stewardship and infection prevention and control efforts. Pharmacists should also  
302 actively seek opportunities to educate health care providers and patients about the risks  
303 associated with the indiscriminate and unwarranted use of antimicrobial agents.

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483 *Commission on Therapeutics and by the Board of Directors and was*  
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