

Management of Antibiotic associated diarrhea: Review

Abstract

Each year, there are 47 million unnecessary antibiotic prescriptions written in U.S. doctors' offices and emergency departments. Excessive usage of antibiotics often puts the patients at a risk for reactions to drugs or other problems, including Antibiotic-associated diarrhea. One of the most common and serious causes of antibiotic-associated diarrhea is infection with a bacterium, *Clostridium difficile*. *C. difficile* infections are common, with approximately 500,000 cases per year in the United States. Its occurrence varies from several hours after the commencement of antibiotic therapy to 6-8 weeks after antibiotic therapy is discontinued. A pathognomonic feature of this condition is the formation of pseudomembranes in colonic mucosa. This can result in significant morbidity and mortality if not diagnosed and treated in a timely manner. In 22% of cases of diarrhea related to *C. difficile*, withdrawal of the inciting agent alone will lead to resolution of clinical signs in three days. In some cases, replacement with a suitable antibiotic not known to cause diarrhea may be required. When the presentation is more severe or persistent, which is usually seen in case of *C. difficile* infection, the patient needs to be treated with oral metronidazole or oral vancomycin. Less frequently used agents include bacitracin, teicoplanin or fusidic acid. Numerous probiotics have been tested for the treatment and prevention of antibiotic associated diarrhea. The role of probiotics is controversial in treatment of antibiotic associated diarrhea, particularly when associated with *C. Difficile*. However physicians still continue to use them anecdotally in management of antibiotic associated diarrhea. As an alternative antibiotic in the treatment of *C. difficile* infections, the US FDA approved a new drug Fidaxomicin in May 2011. When the Antibiotic associated diarrhea related to *C. Difficile* is recurrent over multiple times despite treatment, then Faecal Microbiota Transplantation administered to the patients has been proven to be successful.

Introduction & Background

Each year, there are 47 million unnecessary antibiotic prescriptions written in the United States. In 2015 alone, approximately 269 million antibiotic prescriptions were dispensed from outpatient pharmacies in the United States, enough for five out of every six people to receive one antibiotic prescription each year. At least 30 percent of these antibiotic prescriptions were unnecessary. Excessive usage of antibiotics often puts the patients at a risk for reactions to drugs or other problems, including Antibiotic-associated diarrhea [1].

The microflora in the gut are interdependent and generally do not cause disease. When an antibiotic is used antibiotic-sensitive bacteria are killed or suppressed, while drug-resistant bacteria multiply, disrupting the balance in the intestinal flora resulting in Antibiotic-associated diarrhea (AAD). The incidence of AAD is about 5-35% of patients treated with antibiotics and varies due to differences in populations and types of antibiotics used. Its occurrence varies from

40 several hours after the commencement of antibiotic therapy to 6-8 weeks after antibiotic therapy
41 is discontinued [2].

42 AAD is predominantly caused by *Clostridium difficile*, *Klebsiella sp.*, and *Staphylococcus*
43 *aureus*, as well as some fungi and viruses. However, the most common and serious causes of
44 antibiotic-associated diarrhea is infection with a bacterium, *Clostridium difficile*. *C.*
45 *difficile* infections are common, with approximately 500,000 cases per year in the United States.
46 Infection is most common in people who are hospitalized, producing disease in more than 8
47 hospitalized patients per 1000 (0.9 percent) in 2008 in the United States [3]. The main clinical
48 manifestation of this condition is diarrhea with or without mucus, pus, or blood in the stool and
49 is often complicated by increased white blood cell count; fever; abdominal pain; abdominal
50 distension; toxic megacolon; shock and multiple organ dysfunction eventually resulting in death
51 if untreated. In its extreme form, *C. difficile* infection (CDI) results in a condition called
52 Pseudomembranous colitis. It is an acute infectious colitis produced by the unopposed
53 proliferation of *C. difficile* which subsequently produces toxins resulting in colitis. A
54 pathognomonic feature of this condition is the finding of pseudomembranes in colonic mucosa.
55 This often results in significant morbidity and mortality if not diagnosed and treated in a timely
56 manner [4,5].

57 Most of the cases are benign and resolve under symptomatic treatment. In case of *Clostridium*
58 *difficile* infection, symptoms are more severe and can lead to a fulminant, relapsing and
59 occasionally fatal colitis [6]. Initial treatment fails in over 20% of patients with AAD due to *C.*
60 *difficile* infection, and relapse occurs in 40-60% of patients [2]. This may result in increased
61 diagnostic procedures, extended hospital stay and increased medical care costs [6]. This study
62 aimed to review the available treatment and recent advances in the treatment of AAD.

63 Review

64 Management of Mild to moderate AAD

65 Management of AAD depends on the severity at the time of clinical presentation. In cases with
66 mild to moderate diarrhea discontinuation of the offending antibiotic along with adequate
67 rehydration would suffice. In 22% of cases of diarrhea related to *C. difficile*, withdrawal of the
68 inciting agent alone will lead to resolution of clinical signs in three days. In some cases,
69 replacement with an antibiotic which is known to have a low risk of inducing diarrhea, such as
70 quinolones, co-trimoxazole, or aminoglycosides may be required [7]. If a diagnosis of CDI is
71 made then patients with mild-to-moderate symptoms should be treated with metronidazole 500
72 mg orally three times per day for 10 days. Failure to respond to metronidazole therapy within 5-7
73 days should prompt consideration of a change in therapy to vancomycin at 125 mg four times
74 daily for 10 days. For mild-to-moderate CDI in patients who are intolerant/allergic to
75 metronidazole and for pregnant/breastfeeding women, vancomycin should be used at standard
76 dosing. Use of anti-diarrheal medications in the setting of CDI must always be accompanied by
77 appropriate antibiotics against *C. difficile* as they may offset or precipitate complicated disease
78 [8].

79

80 Management of Severe diarrhea

81 When the presentation is more severe or persistent, which is usually seen in case of *C. difficile*
82 infection, the patient needs to be treated with oral metronidazole or oral vancomycin. Less
83 frequently used agents include bacitracin, teicoplanin or fusidic acid.

84 The American College of Gastroenterology recommend supportive care to all patients and
85 includes intravenous fluid resuscitation, electrolyte replacement. Vancomycin given orally (125
86 mg four times per day) plus intravenous metronidazole (500 mg three times a day) is the
87 treatment of choice in patients with severe and complicated CDI who have no significant
88 abdominal distention. Vancomycin delivered orally (500 mg four times per day) and per rectum
89 (500 mg in a volume of 500 ml four times a day) plus intravenous metronidazole (500 mg three
90 times a day) is the treatment of choice for patients with complicated CDI with ileus or toxic
91 colon and/or significant abdominal distention. Surgical consult should be obtained in all patients
92 with complicated CDI. Surgical therapy should be considered in patients with any one of the
93 following attributed to CDI: hypotension requiring vasopressor therapy; clinical signs of sepsis
94 and organ dysfunction (renal and pulmonary); mental status changes; white blood cell count
95 $\geq 50,000$ cells/ μ l, lactate ≥ 5 mmol/l; or failure to improve on medical therapy after 5 days [8].

96 Clinical resolution was observed in 80 - 100% of antibiotic treatments. Relapses occurred in 5 -
97 16% of cases treated with metronidazole, 16 - 33% with vancomycin and up to 42% with
98 bacitracin. The lowest rates of relapses were seen with metronidazole which constitutes first line
99 therapy (250 mg, four times daily for 10 days). Vancomycin showed similar efficacy but higher
100 relapse rates [9].

101 It is also important to avoid anti peristaltic agents because of the risk of retention of toxins in the
102 lumen. About 20% of these patient relapse which is due to the germination of persistent *C.*
103 *difficile* spores in the colon after treatment or to reinfection because of reingestion of the
104 pathogen rather than resistant strains, and most of them usually respond to a second course of
105 metronidazole or vancomycin. However, 5% of the patients will experience several relapses (6 or
106 more) and the management of these patients remains controversial [8].

107 The first recurrence of CDI can be treated with the same regimen that was used for the initial
108 episode. If severe, however vancomycin should be used. The second recurrence should be treated
109 with a pulsed vancomycin regimen. If there is a third recurrence after a pulsed vancomycin
110 regimen, fecal microbiota transplant (FMT) should be considered [8].

111 The use of antibiotics in treatment of CDI during pregnancy remains controversial. Intravenous
112 vancomycin is categorized as Pregnancy category B, oral formulation of vancomycin is
113 minimally absorbed systemically via the gastrointestinal tract (bioavailability less than 10%) and
114 therefore can be regarded as safe [10]. Metronidazole belongs to Pregnancy category B and has a
115 theoretical potential to cause adverse effects in the fetus. However, several meta analysis have
116 proven that the use of metronidazole is not associated with increased risk of adverse effects in
117 fetus. In a study published by Piper JM et al, which consisted of a cohort of 1387 women who
118 were exposed to metronidazole between 30 to 120 days after the last menstrual period to a cohort
119 of 1387 women who were not exposed to metronidazole, the pregnancy outcomes were similar in

120 both the cohorts. There was no excess of overall birth defect occurrence in the offspring of
121 exposed women, nor could an excess risk be detected for any category of birth defects. Thus,
122 providing no evidence that prenatal use of metronidazole increases the risk of overall birth defect
123 occurrence [11]. There are also a number of epidemiological studies that show no conclusive
124 evidence that metronidazole causes an increased risk of malformations, stillbirths, or low birth
125 weight infants [12,13].

126 **Role of Probiotics**

127 Probiotics are defined as “living microbial supplement exerting a beneficial effect on the host by
128 improving the intestinal ecosystem”. Most of these probiotics are bacteria or yeasts, and are
129 commercially available as lyophilized forms [9]. Numerous probiotics such as *Lactobacillus*
130 *acidophilus*, *Bifidobacterium bifidum*, *Enterococcus faecium*, *Streptococcus thermophilus*, or
131 *Saccharomyces boulardii* have been tested for the treatment and prevention of antibiotic
132 associated diarrhea.

133 In a study done by Castagliuolo et al. it was demonstrated that *Saccharomyces boulardii* serine
134 protease inhibits the pathogenic effects of toxins A and B in human colonic mucosa. In *C.*
135 *difficile* induced inflammatory diarrhea, the protective effects of *S. boulardii* could be due to the
136 proteolytic digestion of toxin A and B molecules by the secreted protease. Most studies with
137 probiotics have assessed their use in preventing antibiotic associated diarrhea. A meta-analysis
138 done by D'Souza et al suggested that probiotics are useful in prevention however results did not
139 indicate the role of the same in treatment of AAD. The expected advantages of probiotics include
140 ease of administration, cost effectiveness, and relative lack of side effects. However, several
141 cases of bacteraemia with *S. boulardii* have been reported, which should prompt caution in the
142 use of this yeast in immunosuppressed patients or patients with underlying disorders [8,14].

143 In a meta-analysis by Kale-Pradhan PB et al, administration of a *Lactobacillus* single-agent
144 regimen as a prophylactic agent during antibiotic treatment reduced the risk of developing AAD
145 compared with placebo in adults [15]. Probiotic use is a more controversial mode of prevention.
146 *Lactobacilli* have been shown to reduce the incidence of antibiotic-associated diarrhea, but have
147 not been proven to decrease the incidence of *C. difficile*-associated diarrhea. Anecdotally, many
148 physicians report success with *Lactobacilli* and use this preventive measure routinely, especially
149 in patients at higher risk for severe disease [8].

150 **Fidaxomicin**

151 As an alternative antibiotic in the treatment of *C. difficile* infections, the US FDA approved a
152 new drug Fidaxomicin in May 2011. Fidaxomicin is a macrocyclic antibiotic derived from the
153 fermentation product of *Actinomycete*, *Dactylosporangium aurantiacum* and *Actinoplanes*
154 *deccanensis*. Fidaxomicin is a bactericidal drug that was found to have an MIC for *C. difficile* 4
155 times less than that of metronidazole and vancomycin [16]. The drug inhibits the initiation of
156 RNA synthesis very early on in that pathway. To be more precise, it inhibits transcription by
157 binding to the deoxyribonucleic acid (DNA)-template ribonucleic acid (RNA) polymerase sigma
158 subunit and hence, prevents the initial separation of the bacterial DNA strands [17].

159 In a systematic review conducted on 4 studies by Al Momani LA et al., it was shown that the use
160 of fidaxomicin was associated with a statistically significant lower recurrence when used as
161 treatment of first episode of *Clostridium Difficile* infection as compared to vancomycin.
162 However, there was no significant difference with the cure rates when compared with that of
163 vancomycin [17].

164 **Role of Faecal Microbiota Transplant (FMT)**

165 The first documented case of ingested faecal material for medicinal purposes dates back to
166 fourth-century Chinese medicine and was used to treat severe diarrhea. Since 2010, FMT has
167 become increasingly recognized as an effective therapy for multiple recurrent CDI. The principle
168 behind FMT consists of restoring a healthy gut microbiota from an altered gut microbiota state.
169 This restoration is done via transfer of donor faeces from a presumably healthy microbiome to
170 that of a recipient with an altered microbiome. Restoring healthy gut microflora allows
171 competition of normal occurring microflora with that of the toxigenic strain of *C. difficile* and
172 subsequent resolution of infection [18].

173 The bulk of evidence for FMT exists for multiple recurrent CDI. In this setting, FMT is highly
174 effective for treating multiple recurrent CDIs with a nearly 90% cure rate in many observational
175 studies. In the single randomized control trial for FMT, recurrent CDI was resolved in 81% of
176 patients compared with 31% who received nontapered/nonpulsed vancomycin. FMT performed
177 via lower routes of administration (colonoscopy or enema) appear to be more successful than
178 upper routes (gastroscopy, or nasogastric and nasointestinal tubes). The reason for this difference
179 in effectiveness is unclear but may be related to FMT dose or inactivation by gastric acid [18].

180 In meta-analysis done by it Khan MY et al, was concluded that FMT is a promising treatment
181 modality for recurrent CDI compared with medical treatment alone. Different forms and routes
182 of FMT administration seem to be equally efficacious [19].

183 In a RCT done by Dina Kao et al, it was concluded that FMT via oral capsules was not inferior
184 to delivery by colonoscopy for preventing recurrent infection over 12 weeks in among adults
185 with recurrent CDI and that the treatment with oral capsules may be an effective approach to
186 treating recurrent CDI [20].

187 The safety profile is not well elucidated owing to lack of large cohort trials. When FMT is
188 performed via colonoscopy side effects that are attributed to the procedure per say can be
189 expected which are usually transient lasting for few hours. These include abdominal pain,
190 bloating, flatulence with borborygmus, diarrhea, constipation, vomiting, transient fever, and
191 belching. Pathogen exposure is another potential risk and the patients have to be screened for
192 immune status. Another concern in patients with IBD recently reported by Khoruts et al was flare
193 of disease in more than 25% of patients who underwent FMT [20].

194 **Conclusions**

195 The rise in the use of antibiotics has led to rise in the adverse effects of the antibiotic therapy.
196 One of the common adverse effects of antibiotic administration is antibiotic associated diarrhea.

197 Antibiotic associated diarrhea related to *C. Difficile* could be associated with significant
198 complications such as recurrence, Pseudomembraneous colitis and shock. The management of
199 AAD depends on the severity of the diarrhea. Antibiotic associated diarrhea is usually self-
200 limiting and therefore withdrawal of the offending drug could most likely result in resolution of
201 the diarrhea. In case the diarrhea is mild to moderate or persistent then antibiotics such as
202 Metronidazole or Vancomycin are required to be given orally. Metronidazole is the preferred
203 drug and vancomycin being alternative drug in cases where metronidazole is contraindicated.
204 Fidaxomicin is a recently approved drug that is known to have lesser incidence of recurrence
205 when compared to the conventional drugs. The role of Probiotics is controversial in treatment of
206 antibiotic associated diarrhea, particularly when associated with *C. difficile* both in prevention as
207 well as a curative agent. However physicians still continue to use them anecdotally in
208 management of antibiotic associated diarrhea. When the Antibiotic associated diarrhea related to
209 *C. Difficile* is recurrent over multiple times despite treatment, then FMT administered to the
210 patients has been proven to be successful. There are several routes of administration of FMT,
211 however FMT via oral capsules is gaining popularity given the decrease in the risks and adverse
212 effects associated with colonoscopic administration. It has also been proven to be non inferior in
213 efficacy as compared to administration via colonoscopy.

214

215 References

- 216 1. CDC: [Antibiotic Use in the United States, 2017: Progress and Opportunities](#). US Department of
217 Health and Human Services, CDC, Atlanta, GA; 2017 .
- 218 2. Litao G, Jingjing S, Yu L, et al.: [Risk Factors for Antibiotic-Associated Diarrhea in Critically Ill](#)
219 [Patients](#). Med Sci Monit. 2018, 24:5000-5007. [10.12659/MSM.911308](#)
- 220 3. Leffler DA, Lamont JT: [Clostridium difficile infection](#). N Engl J Med. 2015, 372:1539-1548.
221 [10.1056/NEJMra1403772](#)
- 222 4. Bartlett JG, Chang TW, Taylor NS, Onderdonk AB: [Colitis Induced by Clostridium Difficile](#).
223 Reviews of Infectious Diseases. 1979, 1 (2):370-378. [10.1093/clinids/1.2.370](#)
- 224 5. Kawamoto S, Horton KM, Fishman EK: [Pseudomembraneous Colitis: Spectrum of Imaging Findings](#)
225 [with Clinical and Pathologic Correlation](#). Radiographics. 1999 Jul-Aug, 19(4):887-897.
226 [10.1148/radiographics.19.4.g99j107887](#)
- 227 6. Elseviers MM, Van Camp Y, Nayaert S, et al.: [Prevalence and management of antibiotic](#)
228 [associated diarrhea in general hospitals](#). BMC Infect Dis. 2015 Mar 17, 15:129. [10.1186/s12879-](#)
229 [015-0869-0](#)
- 230 7. Barbut F, Meynard JL: [Managing antibiotic associated diarrhea](#). BMJ. 2002, 324:1345.
231 [10.1136/bmj.324.7350.1345](#)
- 232 8. Surawicz CM, Brandt LJ, Binion DG, et al.: [Guidelines for Diagnosis, Treatment, and Prevention of](#)
233 [Clostridium difficile Infections](#). Am J Gastroenterol. 2013 Apr, 108(4):478-498.
234 [10.1038/ajg.2013.4](#)
- 235 9. Bergogne-Bérézin E: [Treatment and prevention of antibiotic associated diarrhea](#). Int J
236 Antimicrob Agents. 2000 Dec, 16(4):521-526. [10.1016/S0924-8579\(00\)00293-4](#)
- 237 10. Patel S, Preuss CV, Bernice F: [Vancomycin](#). In: StatPearls [Internet]. StatPearls Publishing,
238 Treasure Island (FL); 2019 Jan.
- 239 11. Piper JM, Mitchell EF, Ray WA: [Prenatal use of metronidazole and birth defects: no association](#).
240 Obstet Gynecol. 1993 Sep, 82(3):348-352.

- 241 12. Burtin P, Taddio A, Ariburnu O, Einarson TR, Koren G: [Safety of metronidazole in pregnancy: a](#)
242 [meta-analysis](#). Am J Obstet Gynecol. 1995 Feb, 172(2 Pt 1):525-529. [10.1016/0002-](#)
243 [9378\(95\)90567-7](#)
- 244 13. Sheehy O, Santos F, Ferreira E, Berard A: [The use of metronidazole during pregnancy: A review](#)
245 [of evidence](#). Curr Drug Saf. 2015, 10(2):170-179. [10.2174/157488631002150515124548](#)
- 246 14. Castagliuolo I, Riegler MF, Valenick L, LaMont JT, Pothoulakis C: [Saccharomyces boulardii](#)
247 [protease inhibits the effects of Clostridium difficile toxins A and B in human colonic mucosa](#).
248 Infect Immun. 1999 Jan, 67(1):302-307.
- 249 15. Kale-Pradhan PB, Jassal HK, Wilhelm SM: [Role of Lactobacillus in the prevention of antibiotic-](#)
250 [associated diarrhea: a meta-analysis](#). Pharmacotherapy. 2010 Feb, 30(2):119-126.
251 [10.1592/phco.30.2.119](#)
- 252 16. Vaishnavi C: [Fidaxomicin--the new drug for Clostridium difficile infection](#). Indian J Med Res.
253 2015, 141(4):398-407. [10.4103/0971-5916.159251](#)
- 254 17. Al Momani LA, Abughanimeh O, Boonpheng B, Gabriel JG, Young M: [Fidaxomicin vs Vancomycin](#)
255 [for the Treatment of a First Episode of Clostridium Difficile Infection: A Meta-analysis and](#)
256 [Systematic Review](#). Cureus. 2018 Jun, 10(6):e2778. [10.7759/cureus.2778](#)
- 257 18. Liubakka A, Vaughn BP: [Clostridium difficile Infection and Fecal Microbiota Transplant](#). AACN
258 Adv Crit Care. 2016 Jul-Sep, 27(3):324-337. [10.4037/aacnacc2016703](#)
- 259 19. Khan MY, Dirweesh A, Khurshid T, Siddiqui WJ: [Comparing fecal microbiota transplantation to](#)
260 [standard-of-care treatment for recurrent Clostridium difficile infection: a systematic review and](#)
261 [meta-analysis](#). Eur J Gastroenterol Hepatol. 2018 Nov, 30(11):1309-1317.
262 [10.1097/MEG.0000000000001243](#)
- 263 20. Kao D, Roach B, Silva M, et al.: [Effect of Oral Capsule- vs Colonoscopy-Delivered Fecal](#)
264 [Microbiota Transplantation on Recurrent Clostridium difficile Infection: A Randomized Clinical](#)
265 [Trial](#). JAMA. 2017 Nov, 318(20):1985-1993. [10.1001/jama.2017.17077](#)

266