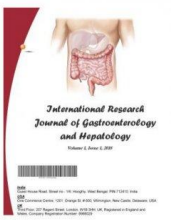

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Management of Antibiotic Associated Diarrhea: Review

Cordelia Markovnikov Reagan[1], Gopikumar Shivaramaiah[2], Prasanna Honnavar[3] and V. N. Prasad[4*]

[1]Xavier University School of Medicine, Aruba.
[2]Department of Physiology, Xavier University School of Medicine, Aruba.
[3]Department of Microbiology, Xavier University School of Medicine, Aruba.
[4]Department of Pharmacology, Xavier University School of Medicine, Aruba.

Authors' contributions

This work was carried out in collaboration among all authors. Author CRM designed the study, performed the literature search and prepared the first draft of the manuscript. Authors GS, PH and VNP prepared the final draft. All authors read and approved the final manuscript.

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ABSTRACT

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*. Its occurrence varies from several hours after the commencement of antibiotic therapy to 6-8 weeks after antibiotic therapy is discontinued. The infection 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

**Corresponding author: E-mail: nvijayashankarmd@xusom.com, narsimprasad@gmail.com;*

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. difficle*. 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. difficle* is recurrent over multiple times despite treatment, then Faecal Microbiota Transplantation administered to the patients has been proven to be successful.

Keywords: Diarrhea; antibiotics; Clostridium difficile; oral metronidazole; oral vancomycin.

1. INTRODUCTION AND 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 several hours after the commencement of antibiotic therapy to 6-8 weeks after antibiotic therapy is discontinued [2].

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

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

2. REVIEW

2.1 Management of Mild to Moderate AAD

Management of AAD depends on the severity at the time of clinical presentation. In cases with mild to moderate diarrhea discontinuation of the offending antibiotic along with adequate rehydration would suffice. 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 an antibiotic which is known to have a low risk of inducing diarrhea, such as quinolones, co-trimoxazole, or aminoglycosides may be required [7]. If a diagnosis of CDI is made then patients with mild-to-moderate symptoms should be treated with metronidazole

500 mg orally three times per day for 10 days. Failure to respond to metronidazole therapy within 5-7 days should prompt consideration of a change in therapy to vancomycin at 125 mg four times daily for 10 days. For mild-to-moderate CDI in patients who are intolerant/allergic to metronidazole and for pregnant/breastfeeding women, vancomycin should be used at standard dosing. Use of anti-diarrheal medications in the setting of CDI must always be accompanied by appropriate antibiotics against *C. difficile* as they may offset or precipitate complicated disease [8].

2.2 Management of Severe Diarrhea

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.

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

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

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

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

The use of antibiotics in treatment of CDI during pregnancy remains controversial. Intravenous vancomycin is categorized as Pregnancy category B, oral formulation of vancomycin is minimally absorbed systemically via the gastrointestinal tract (bioavailability less than 10%) and therefore can be regarded as safe [10]. Metronidazole belongs to Pregnancy category B and has a theoretical potential to cause adverse effects in the fetus. However, several meta-analysis have proven that the use of metronidazole is not associated with increased risk of adverse effects in fetus. In a study published by Piper JM et al, which consisted of a cohort of 1387 women who were exposed to metronidazole between 30 to 120 days after the last menstrual period to a cohort of 1387 women who were not exposed to metronidazole, the pregnancy outcomes were similar in both the cohorts. There was no excess of overall birth defect occurrence in the offspring of exposed women, nor could an excess risk be detected for any category of birth defects. Thus, providing no evidence that prenatal use of metronidazole increases the risk of overall birth defect occurrence [11]. There are also a number of epidemiological studies that show no conclusive evidence that metronidazole causes an increased risk of malformations, stillbirths, or low birth weight infants [12,13].

2.3 Role of Probiotics

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

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

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

2.4 Fidaxomicin

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

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

2.5 Role of Fecal Microbiota Transplant (FMT)

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

The bulk of evidence for FMT exists for multiple recurrent CDI. In this setting, FMT is highly effective for treating multiple recurrent CDIs with a nearly 90% cure rate in many observational studies. In the single randomized control trial for FMT, recurrent CDI was resolved in 81% of patients compared with 31% who received nontapered/nonpulsed vancomycin. FMT performed via lower routes of administration (colonoscopy or enema) appear to be more successful than upper routes (gastroscopy, or nasogastric and nasointestinal tubes). The reason for this difference in effectiveness is

unclear but may be related to FMT dose or inactivation by gastric acid [18].

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

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

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

3. CONCLUSIONS

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

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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