Original Article

Clostridium difficile versus general gastroenteritis: A critical review of a concept

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ABSTRACT

Objective: *Clostridium difficile* is the most important definable cause of healthcare-acquired diarrhea which is mostly associated with inappropriate use of broad-spectrum antibiotics. Recommended treatments for *C. difficile* infection (CDI) are metronidazole, oral vancomycin, and fidaxomicin (a new narrow spectrum macrocyclic antibiotic). The aim of this investigation was to review the chosen management of general gastroenteritis against risks associated with inappropriate therapeutic options such as CDI in the largest teaching medical school in Iran.

Methods: Two thousand medical records and prescriptions were scrutinized, between March 2012 and July 2013 in Phase 1 and September 2014–January 2015 in Phase 2 for patients complaining of diarrhea, colitis, and gastroenteritis. The therapeutic route was investigated in each individual case bearing in mind the medical and medication history as well as other comorbidities. The selection of antibiotic by many medical practitioners for the treatment of mentioned complaints was inappropriate and random.

Results: In most cases, the chosen antibiotic can itself be associated with initiation or worsening of CDI. Although there is no official report on resistance to metronidazole or oral vancomycin at this stage, this unrestricted antibiotic use must be addressed.

Conclusions: The needs for antimicrobial stewardship programs to preserve the effectiveness of current available therapies are strongly recommended. This program must focus on the overall reduction of inappropriate antibiotic prescribing and ultimately on enforcing the adherence to the reputable antibacterial guidelines.

Key words: *Clostridium difficile*, colitis, fidaxomicin, inpatient, outpatient

INTRODUCTION

Clostridium difficile is a Gram-positive spore forming strict anaerobic bacteria which lives in the gut of 3 in every 100 healthy adults and as many as 7 in 10 healthy babies. It is usually found in feces of humans and animals as noninvasive pathogen and produces toxins A and B that cause the disease, ranging from being asymptomatic to mild diarrhea, to colitis, or pseudomembranous colitis mostly associated with the use of broad-spectrum antibiotics in particular with clindamycin and cephalosporins.

Epidemiology and risk factors

C. difficile has been identified as a pathogen in human since 1978, but the incidence of this infection has

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been increasing dramatically since 2000,[1] especially in the elderly patients with recent and recurrent hospitalization or those who are residing in long-term care facilities.

Patients who are admitted as inpatients to the health-care settings can develop serious infections, a group of infections referred to as healthcare-associated infections.[2] The major risk factors are antibiotics exposure, age, duration of hospitalization, patient's contact, gastrointestinal procedures, acquisition of *C. difficile*, immunosuppression, tube feeds, some underlying diseases, antineoplastic chemotherapy, and reduction of gastric acid induced by medicines such as proton pump inhibitor (PPI).[3]

Treatment

Recommended treatments for *C. difficile* infection (CDI) are metronidazole in suggested doses of 500 mg three times daily or 250 mg four times daily, oral vancomycin 125 mg four times daily for 10–14 days and ultimately, fidaxomicin (FDX) 200 mg twice daily for 10 days [Table 1].[2,4]

Bacteriostatic agents such as metronidazole and vancomycin are the first line of therapy for CDI; however, increasing recurrence with CDIs is raising and still a major concern in health-care settings.[3] Therefore, scientists and clinicians are encouraged to find other alternative therapies to challenge this ongoing problem.

When vancomycin is prescribed orally for this type of infection, it inhibits bacterial cell wall synthesis and alters cell membrane permeability and RNA synthesis. It has orally poor absorption, but the low absorption can also cause great enough extent to cause systemic vancomycin reactions, such as red man syndrome and allergic rash.

Metronidazole enters bacterial cell and impairs synthesis of DNA and ultimately resulting in cell death. Oral metronidazole is well absorbed from the intestinal tract. Metronidazole has a spectrum of activity that affects most anaerobic bacteria, and the parallel damage to the normal gastrointestinal flora that is considered obligatory for keeping *C. difficile*, the clinical outcomes have been poorer for metronidazole in comparison to vancomycin. Both treatments are suboptimal because of recurrence rates ranging from 20% to 24%.[5]

FDX is a novel narrow spectrum, locally acting macrocyclic antibacterial agent derived from the fermentation of actinomycete dactylosporangium aurantiacum with potent bactericidal activity against *C. difficile* that recently approved by the US Food and Drug Administration (FDA) in adults.[6] In recent clinical trials, FDX was superior to vancomycin in preventing recurrences of CDI.[7]

Classification of *Clostridium difficile* is based on severity

Stage 1 is referred as mild to moderate stage, with white blood cell (WBC) <15K and creatinine (Cr) level <1.5 times of the baseline (i.e., no acute renal failure) with watery diarrhea 3 or more times a day for 2 or more days, mild abdominal cramping, and tenderness as major signs.

Stage 2 is known as severe stage, with WBC >15k and Cr level of >1.5 times of the baseline with watery diarrhea 10–15 times per day and abdominal pain. This presentation can be severe and patients are likely to develop a fever. The presence of blood or pus in the stool, nausea, dehydration, loss of appetite, and weight loss also will be the other major signs. Patients on Stage 3 are those with severe complications such as hypotension shock, ileus, or megacolon.

Recurrent CDI patients are known as Stage 4. Recurrences can be because of both relapses with the same strain or reinfection with another strain. In the United Kingdom, the Bristol Stool Chart (National Institute for Health and Care Excellence) is a medical aid designed to classify the form of human feces based on the shape into seven categories. One of the important diagnostic symptoms in CDI is watery

Table 1: Comparison of antibiotic options with their prices and duration of treatment for *Clostridium difficile* infection

Drugs	Dose (mg)	Route of administration	Regimen	Duration (days)	Cost*/ dose ($)	Cost/10 days regimen ($)	Cost/14 days regimen ($)
Vancomycin	125	PO	125 mg QID	10-14	12.17	486.90	679.98
Metronidazole	250	PO/IV	500 mg TID or 250 mg QID	10-14	0.02	0.6	0.84
Fidaxomicin	200	PO	200 mg BD	10	168.00	1680.00	-

*Cost comparison is only a rough guide and is based on USA dollars. According to Table 1, average cost for 10 days of vancomycin four times a day is $486.90, for metronidazole four times a day is $0.6, and for fidaxomicin twice a day is $1680.00 in Iran. PO=Oral, IV=Intravenous, BD=Two times daily, TID=Three times daily, QID=Four times daily

diarrhea (Type 7 of Bristol Stool Chart: Watery, no solid pieces, and entirely liquid).

As a result of lack of attention to global and local guidelines and inappropriate prescribing habit in Iran, the incidence of antibiotic resistance has lead into complications such as decrease in gastrointestinal flora and increase in the rate of reported *C. difficile*. Despite this problem, most of the Iranian physicians do not pay attention to the diagnosis and detection of the *C. difficile* in inpatients settings or indeed in outpatient clinics. Blind antibiotic therapies are the main chosen route for the treatment of reported diarrhea and in many cases. FDX are referred as a magic agent to treat acute diarrhea which we understand the selections are random and inappropriate. The aim of this investigation was to review the current management of general gastroenteritis, bearing in mind the health risks associated with inappropriate therapeutic options such as CDI.

METHODS

As part of the novel and ongoing antibacterial prescribing assessment, the management of general gastroenteritis was reviewed to highlight the consequences of inappropriate prescribing. A total of 2000 medical records and prescriptions were scrutinized, between March 2012 and July 2013 in Phase 1 and September 2014 to January 2015 in Phase 2 for patients complaining of diarrhea, colitis, and gastroenteritis. The chosen phases of the study exposed the largest number of patients and prescriptions. The chosen teaching hospitals (Islamic Azad University) are the biggest center of medical graduates (approximately 900 medical graduates/year) in the country. Due to the location of these centers, patients who are using the offered medical services in our sample size would be from different background and fulfill all the demographic factors.[8] One thousand two hundred were from inpatients and 800 from outpatient. After considering the exclusion criteria on each arm which were: Patients with final diagnosis except colitis, diarrhea and gastroenteritis, cancerous patients with active or aggressive chemotherapies regimens, patients with active liver disease, end stage life patients in intensive care unit/critical care unit, pregnancy and breast feeding (due to strict policy of Research Ethics Committee), patients with HIV infection, or mycobacterium tuberculosis, patients with contagious disease such as lepromatosis. One hundred and eleven inpatient medical records and 89 outpatient prescriptions with colitis, CDI, and diarrhea were selected. All medical records were investigated to identify the final diagnosis for colitis, diarrhea, and gastroenteritis only. This observation was a retrospective and prospective study, including hospitalized patients, recently discharged the patient and those patients who were treated as an outpatient. In our study, eligible participants were from all ages with CDI defined as diarrhea (with more than three unshaped stools), colitis or detection of *C. difficile* toxin in stools, and colitis. Data collection forms were specific for this study and included patient demographic data such as age, sex, name and number of antibiotics, route of administration, duration for both inpatient and outpatient, confirmation of microbiological tests, other comorbidities, presence or absence of experimental treatment and related changes, and duration of hospitalization (just for inpatient group). Finally, acquired data were compared with reputable global guidelines to evaluate the accuracy of CDI treatment options and their efficacy to establish whether the current therapeutic options are sufficient.

RESULTS

To identify the appropriate patients, we concentrated on selecting those who were diagnosed only with diarrhea, gastroenteritis, or colitis. The selection criteria were specific to identify the exact patient type.

The inpatient data included 49.5% male and 50.5% female and outpatient data included 42.5% male and 57.5% female. The average age in hospitalized patients was 31.4 years. 33.3% of the inpatients were younger than 12 years old, 22.5% were between 12–34% and 44.2% were older than 34 years of age. In comparison, in the outpatient selection, younger than 12, between 12–34 and ultimately older than 34 were 6.7%, 44.9%, and 48.4%, respectively. Population over 34 years olds seem to be the majority of hospitalized and outpatients, in this study [Table 2].

Initiations of antibiotic therapies in hospitals were random with no microbiological test in 80.2% of the patients to diagnose the cause of disease. The most common route of administration for hospitalized patients was intravenous (IV) (73.2%) while in outpatient was oral (100%) as expected [Table 2]. Overall, 40.5% of patients were diagnosed with colitis, 36% diarrhea, and 23.5% gastroenteritis when inpatient and outpatient were considered together [Figure 1].

The majority of selected inpatients were diagnosed with colitis (72.1%), and diarrhea was the least

Table 2: Demographic details for inpatient and outpatient

Variables	Inpatient (%)	Outpatient (%)
Age group (years)		
<12	33.3	6.7
12-34	22.5	44.9
>34	44.2	48.4
Gender		
Male	49.5	42.5
Female	50.5	57.5
Prescribing antibiotic on a day of hospital admission		
Yes	80.2	NA*
No	19.8	NA*
Route of administration		
IV	73.2	0
Oral	26.8	100
Microbiological test		
Yes	82	-
Clostridium difficile test		
Yes	10	-
No	90	-
Antibiogram		
Yes	11	-
No	89	-
No	18	-

*NA=Not applicable. IV=Intravenous

reported diagnosis with 12.6% of the inpatients. Conversely, in the outpatient setting, 62.9% of the patients were diagnosed with diarrhea and very small number (1.1%) with colitis. In terms of further actions for accurate diagnosis, the medical professions did not take any further actions and therefore, all patients (100%) were treated with the antibiotics, albeit in many cases random [Figure 1]. Following the initial diagnosis in the inpatient selection, for 82% of the patient microbiological investigation was requested to confirm the diagnosis where in 18% of the patients no further microbiological investigation was requested. For the next stage, we aimed to establish if the microbiological results were utilized and the choice of selected antibiotics were appropriate. Only 18.7% of those patients with requested microbiological tests did not need the antibiotics and were given supportive therapies. The supportive therapies were defined as any other medical interventions except prescribing antibiotics. 81.3% of those patients with requested microbiology tests were provided with a prescription for antibiotics. In those inpatients with no microbiological investigation (18%), antibiotic prescribing was the only conventional actions taken by the medical professions [Figure 2].

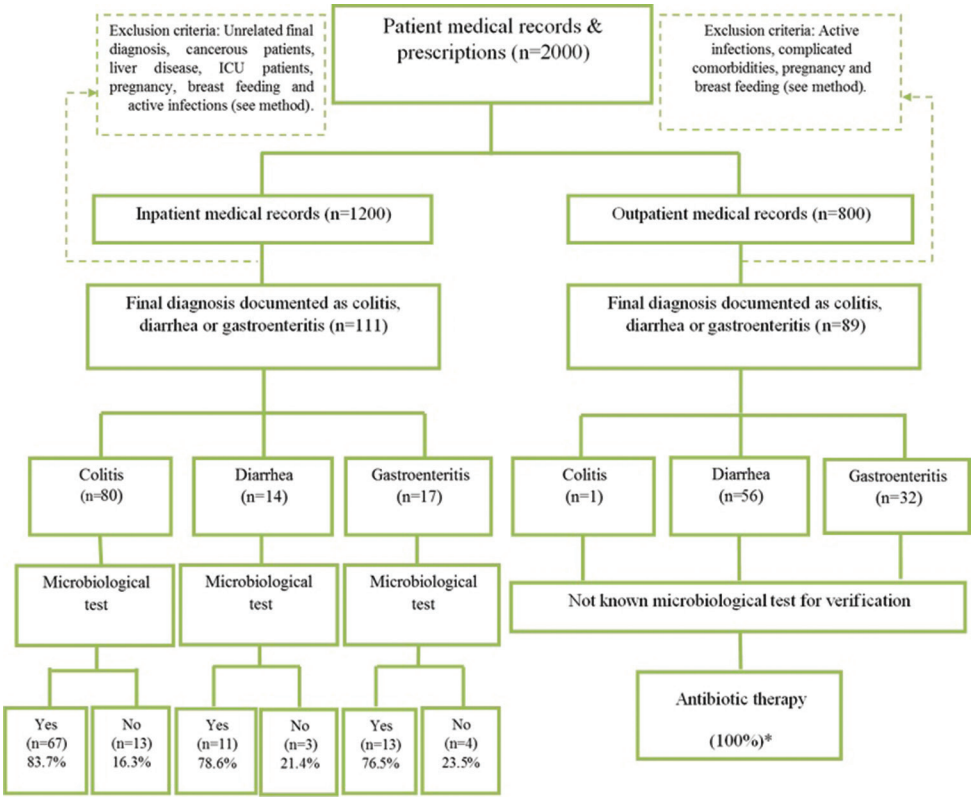

Figure 1: Comparison of common diagnosis and overall management between inpatient and outpatient setting. *The high level of reporting was due to the fact that patients were only given antibiotics

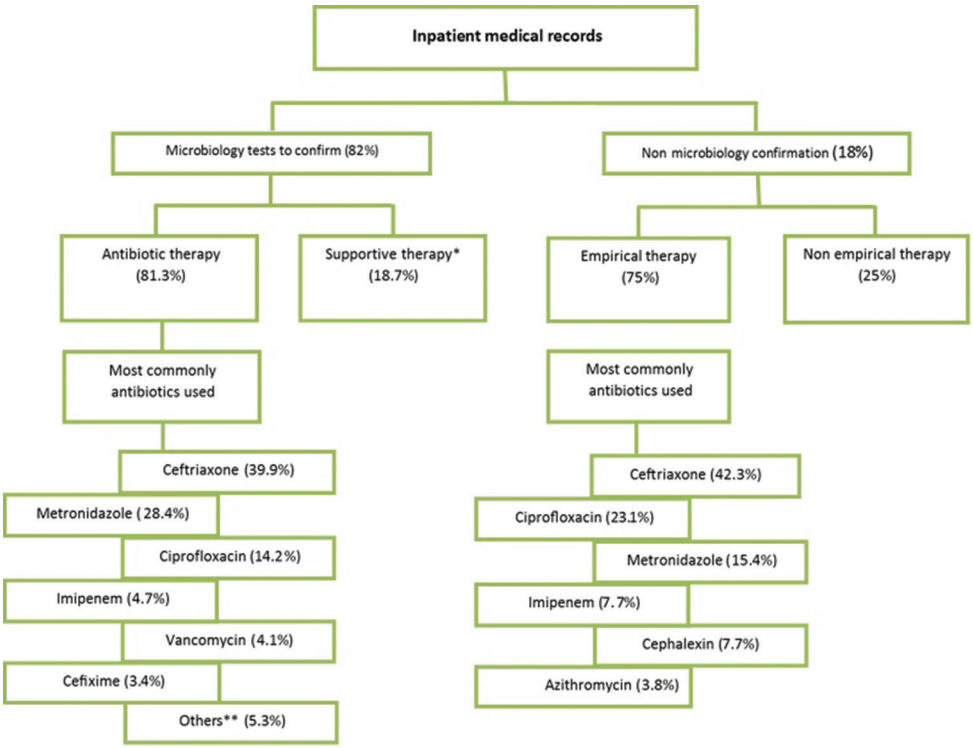

Figure 2: Management of inpatients with the most common used antibiotics. *Supportive therapy is defined as prescribing other drugs to treat the condition without prescribing antibiotics. **Others: Azithromycin, amoxicillin, ampicillin, amikacin ceftazidime, doxycycline and erythromycin

Among inpatients with microbiological tests, 41.7% of the patients were supplied with antibiotics based on the microbiological report and sensitivity tests. The most common antibiotics were ceftriaxone (39.9%), metronidazole (28.4%), and ciprofloxacin (14.2%). The majority of the patients were given antibiotics without any attention to the result of the requested microbiological investigation. Furthermore, the selected antibiotics were not utterly appropriate and included antibiotics such as ceftriaxone (42.3%) and imipenem (7.7%) [Figure 2].

Overall in our inpatient setting (n = 111), the most commonly prescribed antibiotics were ceftriaxone with 40.3% and metronidazole with 26.2% followed with ciprofloxacin in the third line with 15.3%. In the outpatient setting, the top three antibiotics in order were ciprofloxacin (41.8%), iodoquinol (29.6%), and metronidazole (13.3%) [Table 3]. In either patient's setting, the first choice of antibiotic was inappropriate with ceftriaxone in inpatients and ciprofloxacin in our outpatients. Metronidazole in inpatient is more commonly prescribed (26.2%) in comparison to the outpatient (13.3%). Vancomycin was not a therapeutic option in the outpatients; however, 3.4% of the inpatients were given the oral vancomycin [Table 3].

Table 3: Most frequently prescribed antibiotics in both inpatient and outpatient setting

Inpatient (n=111)	Percentage	Outpatient (n=89)	Percentage
Ceftriaxone	40.3	Ciprofloxacin	41.8
Metronidazole	26.2	Iodoquinol	29.6
Ciprofloxacin	15.3	Metronidazole	13.3
Imipenem	5.1	Cefixime	9.2
Vancomycin	3.4	Amoxicillin	3.1
Cefixime	2.8	Tetracycline	1
Azithromycin	1.7	Levofloxacin	1
Amikacin	1.1	Co-trimoxazole	1
Cephalexin	1.1		
Others*	0.6 (equally for each)		

*Others: Amoxicillin, ampicillin, ceftazidime, doxycycline, and erythromycin at the ratio of 0.6 for each

The final part of our investigation aimed to establish if the age of the patients can determine the choice of antibiotics in either setting. In pediatric patients (0–12 years old), the most common prescribed antibiotics were cephalosporins with 81.3% in macrolides 9.4%, and aminoglycosides with 6.2% in our inpatient setting. In the outpatient setting, 83.3% were provided with cephalosporins and 16.7% were given quinolones. In 13–30 years old patients, the most common prescribed antibiotics were cephalosporins in the inpatient setting with 48.4% wherein outpatients, only 5.7% were prescribed with cephalosporins. In

adult patients with the age group of 31–50 years old, the prescribed antibiotics for inpatients in order were metronidazole (38.1%), quinolones (23.8%), cephalosporins (23.8%), penems (7.1%), tetracyclines (2.4%), vancomycin (2.4%), and penicillins (2.4%). In 51–70 years patient's group, cephalosporins, quinolones, metronidazole, penems, and vancomycin with 57.2%, 14.3%, 9.5%, 9.5%, and 9.5%, respectively. In geriatric group patient (equal and more than 71 years), cephalosporins (40%), metronidazole (32.5%), quinolones (15%), penems (7.5%), and vancomycin (5%) were prescribed. In comparison in outpatients, the quinolones are the most common antibiotic prescribed in various age groups across the whole selection [Figure 3].

DISCUSSION

CDI is mainly caused by antibiotic therapy and is usually of acute onset and has the ability to become a chronic condition.[9] It is a particular hazard of ampicillin, amoxicillin, co-amoxiclav, second- and third-generation cephalosporins, clindamycin, and quinolones. It has become an increasingly worse in terms of epidemiology in the past decade with potentials to get unmanageable.[10] CDI prevention program has become a passionate focus for hospitals in the developed countries with some substantiation of success. Never the less, CDI treatment is an ongoing challenges as roughly 20% of the cases fail on current suggested therapies and further 20–30% relapsing after treatment,[11] some repetitively. The primary therapeutic approach is to review the medication history with the view of discontinuing certain medications such as PPIs or drugs such as laxatives and responsible antibiotics

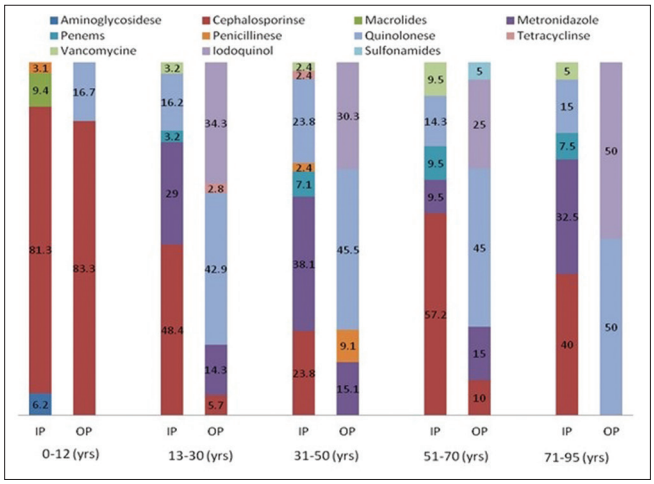

Figure 3: Percentages of the most common antibiotics prescribed for different age groups. *IP: Inpatient, OP: Outpatient, yrs: Years

in these patients. Before the introduction of FDX, the proposed treatments for this infectious disease were oral metronidazole and/or vancomycin as they were suggested by Cochrane, and various reputable guidelines such as Society for Healthcare Epidemiology of America (SHEA), Infectious Diseases Society of America, and Association for Professionals in Infection Control and Epidemiology. However, in many countries and Iran antibiotics are prescribed randomly by many physicians for any general gastrointestinal complaints such as diarrhea or gastroenteritis. In many cases, these patients were not diagnosed properly, and these antibiotics are given as a blind therapy. As well as mentioned antibiotics other antibiotics such as fusidic acid, bacitracin, rifaximin, and nitazoxanide were tried in the past with limited clinical data for the treatment of CDI. Therefore, in developed countries, the need for new agent to treat this challenging disease was a priority. In most countries, the increased incidence of resistance to drugs such as metronidazole and vancomycin has been observed, and new offered agents must be minimally absorbed from the gastrointestinal tract with narrow spectrum of activity to preserve the normal flora of the gut.[12] The new agent known as FDX has a narrow spectrum of antibacterial activity with bactericidal activity in specific against *C. difficile*.[7] Furthermore, it is very minimally absorbed from the gut with low plasma concentration (in ng/ml) after oral dosing when used in patients.[4] There is no inferiority in clinical response when FDX is compared against vancomycin.[12] Never the less, one of the most important factors to consider at this stage for many countries to include this new agent is its safety from nonclinical and clinical studies.

The nonclinical safety studies for FDX included the safety pharmacology, reproductive toxicity, and genotoxicity. This agent has shown no toxicity to the bone marrow, liver, kidney, or other target organ. However, the long-term carcinogenicity of this agent has not been fully evaluated.[13] The clinical safety profiles in clinical trials have been also investigated. In these clinical studies, the safety profile of FDX was compared with vancomycin and no significant dose-related adverse events were observed, and no death is believed to be due to the toxicity of this drug. The most known frequent adverse effect leading to the discontinuation of this agent was reported to be vomiting which is more or less identical when compared to vancomycin.[14] No serious gastrointestinal adverse event such as

increased in bleeding was reported in these clinical trials. When hematological safety, cardiac safety, hepatic safety as well as use in renal impaired patients were investigated in comparison to the vancomycin, there was no clinical difference between the two agents. Furthermore, there was no difference in the incidence of deaths or serious adverse effects when compared with vancomycin which could confirm the clinical safety of this new agent.

The other important factor to consider is the cost of metronidazole which is lower in comparison to the vancomycin as shown in Table 1. The clinical effect is similar in mild to moderate CDI patients which will favor the use of metronidazole in these patients. However, the absorption of oral Metronidazole is high and can lead to systemic adverse effects such as peripheral and optic neuropathy which could be a serious deciding factor when compared against safer options such as vancomycin.[8] *C. difficile* is a growing concern in frail and elderly patients who are presumably on various medications such as warfarin or other anticoagulants and antipsychotics such as Lithium, which will interact with metronidazole with severe consequences as a result of these drug-drug interactions. Metronidazole is not approved by the FDA for the treatment of CDI. This agent is widely used in hospital settings across Europe, in particular, the United Kingdom. Vancomycin and metronidazole are used as specific treatment for CDI, where vancomycin is more preferred in sick patients and metronidazole by IV infusion is considered when oral treatment is inappropriate and ultimately FDX in recurrent CDI patients [Table 4].

C. difficile accounts for approximately 30% of cases of antibiotic-associated diarrhea and is the number one cause of hospital-associated diarrhea in health-care settings. A stool culture is seldom used for routine diagnosis because of labor intensiveness, long turnaround time, and a low specificity.[15] However, in hospitalized patients diagnosed with colitis, diarrhea, or gastroenteritis the microbiological investigation was requested. For instance, in patients with colitis, 83.7% were requested for microbiological investigation against 16.3% who were not requested for such microbiological investigations. This pattern of variation was roughly the same when patients were diagnosed with diarrhea or gastroenteritis [Figure 1]. *C. difficile* has been reported to be a cause of community-acquired infection among a wider age range of patients, including children.[10] For patients treated in the outpatient setting, no microbiological investigation was ordered, and all patients in this category were initiated with antibiotics [Figure 1].

Table 4: Appropriate treatment for various grades of colitis

Severity	Treatment	Dose	Duration (days)
Mild	Metronidazole	500 mg orally TID	10-14
Moderate	Metronidazole	500 mg orally TID	10-14
Severe	Vancomycin metronidazole	125 mg orally QID 500 mg IV TID	10-14
Recurrent CDI	Fidaxomicin	200 mg BD	10

CDI=*Clostridium difficile* infection, TID=Three times daily, IV=Intravenous, BD=Two times daily, QID=Four times daily

The SHEA recommends initiation of empirical therapy for CDI at once after stool procurement for patients with severe CDI.[16] Empirical treatment is acceptable if the clinical doubt is high without waiting for the results as early initiation of treatment is critical in improving the outcome. 80.2% of the patients in our study were initiated with the empirical therapy, and 19.8% were prescribed with supportive therapy where some of the agents could decrease intestinal motility, such as narcotics and loperamide. These agents should be avoided because of the risk of decreasing toxin clearance and the risk for ileus and/or megacolon [Figure 2].[17]

Specific antibiotic therapy should be initiated as soon as possible. Oral metronidazole or vancomycin is the drug of choice in patients with CDI. Metronidazole can be administered IV in patients who are unable to take oral agents.[18] In our inpatient setting, once the microbiological investigation was requested, 81.3% of the patients were given antibiotics, albeit in some cases inappropriate. Ceftriaxone was one in particular with 39.9% or ciprofloxacin was in 14.2% of the cases. On the other hand, metronidazole was an option with 28.4% of those with microbiological results and in 15.4% of those without microbiological investigation [Figure 2].

The most common antibiotics associated with CDI so far were ampicillin, amoxicillin, cephalosporins, and clindamycin.[16,19-21] However, with widespread use, fluoroquinolones have become one of the common predisposing factors for CDI.[22-25]

This type of selections is purely random and without any attention to the microbiological or sensitivity reports or indeed any reputable guidelines. In any case, these choices of antibiotics are irrational, knowing the fact that these antibiotics are very much associated with worsening or initiating the *C. difficile*.

In Iran, as yet, resistance to metronidazole and vancomycin has not been reported in these groups of patients. Based on our findings, the majority of patients in our clinical settings been prescribed inappropriate antibiotics as 44.8% of inpatients were given cephalosporins in particular ceftriaxone (40.3%) in this group and ciprofloxacin with 41.8% of the outpatients as shown in Table 3. Metronidazoles in both groups are given as second and third options, respectively in any patient with colitis, diarrhea, and gastroenteritis.

Antibiotic-associated diarrhea can be a common complication of antibiotic use in hospitals as well as outpatient settings. One of the major risks for this problem is the aggressive prescribing of broad-spectrum antibiotic which happens in many developing countries.[9] Hospitalized patients exposed to broad spectrum antibiotics may also be at risk of developing CDI. Despite this well-known facts, many patients are still been prescribed cephalosporins and quinolones such as ciprofloxacin [Table 3]. Equally, the inappropriate antibiotic prescribing in outpatient is followed in the same pattern where ciprofloxacin and iodoquinol were prescribed in 41.8% and 29.6% respectively. Overall, the patients are exposed to antibiotics, and this exposure, especially to cephalosporins and fluoroquinolones predispose the patients to CDI.[9]

In our investigation, the uses of antibiotics were evaluated in different age groups. The most venerable patients are considered to be pediatrics (between the age of 0 and 12 years old) and geriatric patients (above the age of 71 years old). Interestingly in both groups cephalosporins are the most common antibiotic prescribed with 81.4% in the pediatric group and 36.4% in the geriatric patients. Vancomycin in both groups is the least considered option with metronidazole in geriatric patients with diarrhea, colitis, and gastroenteritis [Figure 3]. This low level of vancomycin and metronidazole prescribing in all group of patients were observed, and this may justify the reason for low level of vancomycin/metronidazole resistance reporting in our health-care setting. Although this inappropriate antibiotic prescribing has had some good news associated with it, there is no doubt that over and aggressive antibiotic prescribing of high-risk antibiotics such as cephalosporins will expose the large number of patients to CDI. In similar study, it was suggested that 26% of the hospitalized children with CDI were infants younger than 1 year old, and 5% were neonates.[26] Although metronidazole is currently the drug of choice for the initial treatment of children with mild to moderate CDI, it should not be used for the treatment of the second recurrence as there is possible risk of neurotoxicity.[26] On the other hand, the use of vancomycin in these groups of patients are lacking evidence and extrapolating these facts, treatment of infants, and children is difficult and more data are required.

As mentioned in Iran and presumably countries with the same approach for the management of CDI, resistance to metronidazole and vancomycin has not been reported. The concern is whether this is purely the case of under-reporting or if in actual fact the level of resistance is very low, if latter, by modifying the current system of improving the diagnosis, the overall management of CDI will be tackled by the current therapeutic options and therefore there is no need for the introduction of FDX into the current line of therapy. However, if the problem is associated with underreporting; then, the mentioned countries need to act immediately to modify the whole pattern of management of CDI all the way from prevention by appropriate use of antibiotics.

In the future, the defining severity of CDI and the role of metronidazole will be essential. No antibiotic is likely to be superior to oral vancomycin for the treatment of acute infections; however, an agent that shows decreased recurrence rates of CDI would be a major advance in the treatment of the disease.[27] The drugs that show most promise to be considered as therapeutically options based on clinical trials to date will include nitazoxanide, rifaximin, and FDX.

The author does believe that at this stage, a thorough investigation of antibiotic consumption needs to be carried out, and the unrestricted antibiotic use must be addressed with emphasis for the need of antimicrobial stewardship programs to preserve the effectiveness of currently available therapies. This program must focus on the overall reduction of the total doses of antibiotics as well as number and days of antibiotic exposure and ultimately on enforcing the adherence to the guidelines.

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Conflicts of interest
There are no conflicts of interest.

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