Original Article

Management of *Clostridium difficile* in a developing nation

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ABSTRACT

Introduction: *Clostridium difficile* is the most important definable cause of healthcare acquired diarrhea. Recommended treatments for *Clostridium difficile* infection (CDI) are metronidazole, oral vancomycin and fidaxomicin (a new narrow spectrum macrocyclic antibiotic). **Aim:** The aim of this investigation was to review the treatment of CDI in Iran. **Method:** 1600 medical records and prescriptions were scrutinized 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 co-morbidities. **Results:** The selection of antibiotic by many medical practitioners for the treatment of diarrhea, colitis and gastroenteritis were inappropriate and random. In most cases the chosen antibiotic, can itself be associated with initiation or worsening of CDI. **Conclusion:** The needs for antimicrobial stewardship program 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, outpatients

INTRODUCTION

Clostridium difficile is a Gram-positive spore-forming strict anaerobic bacterium, which lives in the gut of 3 in every 100 healthy adults and 7 in 10 healthy babies. It is usually found in the feces of humans and animals as noninvasive pathogen and produces toxins A and B that cause disease ranging from asymptomatic to mild diarrhea, colitis, or pseudomembranous colitis. The disease is mostly associated with the use of broad-spectrum antibiotics, in particular, clindamycin and cephalosporins. The incidence of this infection has been increasing dramatically since 2000, especially among elderly patients with recent and recurrent hospitalization or those who are residing in long-term care facilities.[1]

The recommended treatments for *C. difficile* infection (CDI) include metronidazole 500 mg three times daily or 250 mg four times daily, oral vancomycin 125 mg four times daily for 10 to 14 days, and fidaxomicin (FDX) 200 mg twice daily for 10 days.[2] Bacteriostatic agents such as metronidazole and vancomycin are the first line of therapy for CDI; however, increasing recurrence of CDIs is rising and it is still a major concern in health-care settings.[3]

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Therefore, scientists and clinicians are encouraged to find other alternative therapies to challenge this ongoing problem. Both treatments are suboptimal because recurrence rate ranges from 20% to 24%.[4] FDX has a potent bactericidal activity against *C. difficile* and it was recently approved for use in adults by the US Food and Drug Administration.[5]

Inappropriate antibiotic prescribing leads to unintentional consequences such as antimicrobial resistance and CDI. In Iran, the diagnosis and management of CDI is inappropriate. Blind therapies are the main chosen route for the treatment of reported diarrhea, which we understand the selections are random and inappropriate. The aim of this study is to review the treatment options for CDI in Iran.

METHODS

Study design and location

This is an observational study conducted among hospitalized patients, recently discharged patients, and those patients who were treated as outpatients. The study was conducted at the Islamic Azad University Teaching Hospitals, Iran.

Study population

Medical records and prescriptions of 1600 patients (1000 for inpatients and 600 for outpatients) were scrutinized. After screening for exclusion criteria, 100 inpatients and 80 outpatients with colitis, gastroenteritis, and diarrhea were selected.

Inclusion criteria

Patients of all ages with CDI (defined as diarrhea with more than three unshaped stools), colitis, or detection of *C. difficile* toxin in stools were included in the study.

Exclusion criteria

Cancer patients with active or aggressive chemotherapy regimens, patients with active liver disease, end-stage life patients in the Intensive Care Unit/Critical Care Unit, pregnancy and breastfeeding, patients with HIV infection or *Mycobacterium tuberculosis*, and patients with contagious disease such as lepromatosis were excluded from the study.

Data collection

Data collection form was used to obtain demographic data such as age, sex, name and number of antibiotics, route of administration, duration for both inpatients and outpatients, confirmation of microbiological tests, other comorbidities, 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.

Data analysis

The data were analyzed using SPSS software version 20. All data were reported in terms of frequency and percentage.

RESULTS

The proportion of male and female patients was equal (50% each) in the inpatient group; however, there were more females (57.5%) in the outpatient group. The average age of the hospitalized patients was 33.6 years. Empirical antibiotic therapy was initiated on the day of hospital admission in 95% of the hospitalized patients [Table 1].

Overall, 45% of the patients were diagnosed with colitis, 32.2% with diarrhea, and 22.8% with gastroenteritis, when inpatients and outpatients were considered together. The majority of the selected inpatients were diagnosed with colitis (80%) while diarrhea was the most common diagnosis among outpatients (62.5%) [Table 2].

Following the initial diagnosis, confirmatory microbiological investigation was requested in 81% of the inpatients. There were 19.8% of patients with requested microbiological test did not require antibiotics and were given supportive therapies. The supportive therapy is defined as any other medical intervention besides prescribing antibiotics. Antibiotic prescription was given in 80.2% of the inpatients with requested microbiology test. When microbiological investigation was not requested, empirical antibiotics were also given. After laboratory confirmation, only 40.8% of the inpatients were supplied with antibiotics based on microbiological report and sensitivity test. The most common antibiotics used were ceftriaxone (45.5%), metronidazole (22.5%), and ciprofloxacin (15%). Majority of the patients were given antibiotics without any attention to the result of the requested microbiological investigation.

Among hospitalized patients, the most commonly prescribed antibiotics were ceftriaxone (45.1%), metronidazole (21.2%), and ciprofloxacin (16.2%). In the outpatient setting, ciprofloxacin (42%),

Table 1: Demographic details for inpatients and outpatients

Variables	Inpatient (%)	Outpatient (%)
Age group (years)		
<12	21	6.3
12-34	35	46.2
>34	44	47.5
Gender		
Male	50	42.5
Female	50	57.5
Prescribed antibiotic on the day of hospital admission		
Yes	95	NA*
No	5	NA*
Route of administration		
IV	67.1	0
Oral	32.9	100
Microbiological test		
Yes	81	-
Clostridium difficile test		
Yes	2.5	-
No	97.5	-
Antibiogram		
Yes	10	-
No	90	-
No	19	-

*NA=Not applicable, IV=Intravenous

Table 2: Distribution of patients' diagnosis based on setting

Variable	Inpatient, *n* (%)	Outpatient, *n* (%)
Colitis	80 (80)	1 (1.25)
Diarrhea	8 (8)	50 (62.5)
Gastroenteritis	12 (12)	29 (36.25)
Total	100	80

Table 3: Antibiotics prescribed for in both settings

Inpatient (*n*=100)	Percentage	Outpatient (*n*=80)	Percentage
Ceftriaxone	45.1	Ciprofloxacin	42
Metronidazole	21.2	Iodoquinol	29.6
Ciprofloxacin	16.2	Metronidazole	13.7
Imipenem	4.9	Cefixime	9.1
Cefixime	2.8	Amoxicillin	2.3
Vancomycin	2.8	Tetracycline	1.1
Amikacin	1.4	Levofloxacin	1.1
Azithromycin	1.4	Co-trimoxazole	1.1
Others*	4.2		

*Others=Amoxicillin, ampicillin, ceftazidime, cephalexin, doxycycline, and erythromycin, at the ratio of 0.7 for each

iodoquinol (29.6%), and metronidazole (13.7%) were the most prescribed medications. In either patient's setting, most of the patients received inappropriate antibiotics, as ceftriaxone and ciprofloxacin were more commonly used among inpatients and outpatients, respectively. In addition, metronidazole was more commonly used among inpatients as compared to outpatients (21.2% vs. 13.7%). Vancomycin was not used among outpatients; however, only 2.8% of the hospitalized patients were given oral vancomycin [Table 3].

Cephalosporins were the most prescribed antibiotic for both in- and out-patients aged between 0 and 12 years. Cephalosporins and quinolones were the most prescribed antibiotics among patients aged 13–30 years in the in- and out-patient settings, respectively. In-patients aged 0–12 years, 13–30 years, and 51–70 years, cephalosporins and quinolones are the most common prescribed antibiotics, although there were variations between in- and out-patient prescriptions. Metronidazole and quinolones were the most utilized antibiotics for in- and out-patients, respectively, who are aged 31–50 years [Figure 1].

DISCUSSION

C. difficile accounts for approximately 30% of the cases of antibiotic-associated diarrhea and it is the number one cause of hospital-associated diarrhea in health-care settings. CDI is mainly caused by antibiotic therapy and it is usually of acute onset and has the ability to become a chronic condition.[6] It is particularly associated with the use of ampicillin, amoxicillin, amoxicillin-clavulanic acid, second- and third-generation cephalosporins, clindamycin, and quinolones. Stool culture is recommended, but seldom used for routine diagnosis because of labor-intensiveness, long turnaround time, and a low specificity.[7]

In our study, microbiological investigation was requested for 81% of the hospitalized patients. For patients treated in the outpatient setting, no microbiological investigation was ordered and antibiotic therapy was initiated in all patients in this category. Empirical antibiotic therapy is recommended after stool collection among patients with severe CDI.[8] Empirical treatment is accepted if the clinical doubt is high, since early initiation of treatment is critical to improving the outcomes. In our study, 73.7% of the patients were started with empirical therapy whereas 19.8% were given supportive therapy (narcotics and loperamide) to decrease intestinal motility. These agents should however be avoided because of the risk of decreasing toxin clearance and the risk for ileus and/or megacolon.[9] Oral metronidazole or

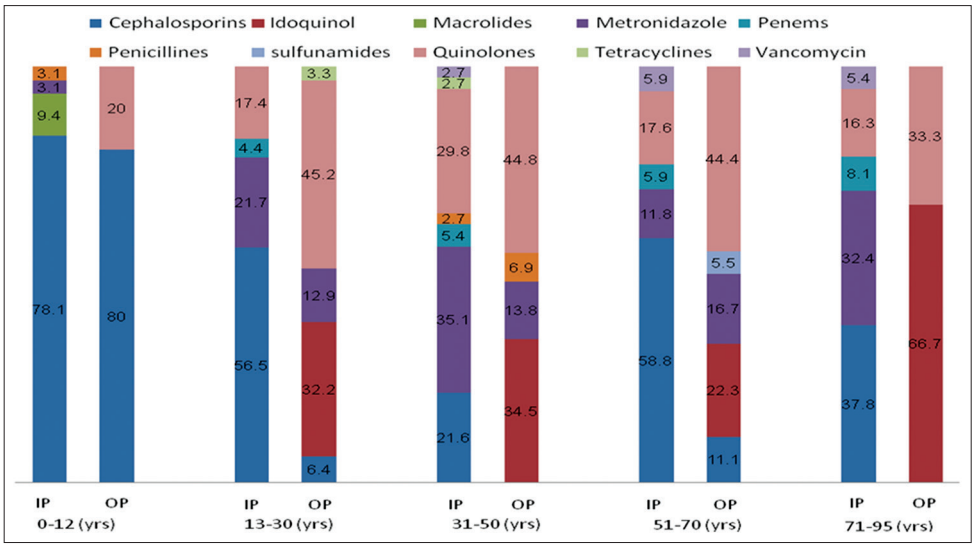

Figure 1: Percentages of the most common antibiotics prescribed for different age groups. IP: Inpatient, OP: Outpatient, yrs: Years

vancomycin is the drug of choice for the management of patients with CDI. Metronidazole can be administered intravenously in patients who are unable to take oral medications.[10] In our study, the choice of antibiotic was inappropriate for most of the hospitalized patients, as ceftriaxone was administered in 45.5% while ciprofloxacin was used in 16.2% of the cases. Among outpatients, however, ciprofloxacin was the most utilized antibiotic representing 42% of the antibiotics used. Metronidazole was used in only 21.2% of the inpatient cases and 13.7% of the outpatient cases. 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 use of broad-spectrum antibiotics.[11] Studies have shown that the most common antibiotics associated with CDI are ampicillin, amoxicillin, cephalosporins, and clindamycin.[8,12-14] In recent years, fluoroquinolones have become a common predisposing factor for CDI.[15-18] This indicates that antibiotic therapy (ceftriaxone and ciprofloxacin) for most patients in our study has the potential to worsen or initiate CDI. The most vulnerable patients are considered to be children (below the age of 12) and elderly patients (above 71 years). Interestingly in both groups, cephalosporins were the most prescribed antibiotics (representing 78.1% in pediatrics and 39.5% in geriatric). Vancomycin in both groups is the least considered option whereas metronidazole was used in 3.1% of children and 32.4% of elderly patients.

CONCLUSION

Management of *C. difficile* colitis in Iran has been inappropriate. Antibiotics prescribed in most cases are associated with initiation or worsening of CDI. There is a need for an antimicrobial stewardship program to reduce the inappropriate use of antibiotics.

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Conflicts of interest

There are no conflicts of interest.

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