

<https://doi.org/10.31146/1682-8658-ecg-244-12-28-39>

Clostridium Difficile Infection and Inflammatory Bowel Diseases: Frequency and Possible Risk Factors

N.M. Alkhalidi¹, M.A. Abdullah^{1,2}, A.A. Mjali³

¹ Baghdad Gastroenterology and Hepatology Teaching Hospital, (Baghdad, Iraq)

² Basrah college of Medicine, (Basrah, Iraq)

³ Al-Kindy Gastroenterology and Hepatology Center, (Baghdad, Iraq)

For citation: Alkhalidi N.M., Abdullah M.A., Mjali A.A. *Clostridium Difficile* Infection and Inflammatory Bowel Diseases: Frequency and Possible Risk Factors. *Experimental and Clinical Gastroenterology*. 2025;(12): 28–39. (In Russ.) doi: 10.31146/1682-8658-ecg-244-12-28-39

✉ *Corresponding author:*

Muntadher Abdulkareem Abdullah

muntaderaltememy984@gmail.com

Nawal Mahdi Alkhalidi, Consultant Gastroenterologist and Hepatologist; ORCID: 0000–0003–1198–7894

Muntadher Abdulkareem Abdullah, Assistant professor, gastroenterologist, and Hepatologist; ORCID: 0000–0002–8893–1920

Abass Abdullah Mjali, Gastroenterologist and hepatologist

Summary

Background and aims: The incidence of CDI among IBD patients is increasing, and has been demonstrated to be associated with increased hospitalization period, costs, morbidity and mortality, the recent guidelines advocate testing all IBD patients who are experiencing disease flare for CDI, this is a cross-sectional study to estimate the incidence and to assess possible risk factors for CDI among IBD patients who are in disease flare up.

Methods: Eighty-seven patients with IBD were studied, who attended the Gastroenterology and Hepatology Teaching Hospital in the Medical City (Baghdad), during the period from January 2019 to April 2020, all with disease flare up.

Patients' demographic and clinical data including factors expected to be a risk factors or have an association with CDI such as age, sex, comorbid conditions, recent hospitalization (within 1 month), drugs including PPI, recent antibiotic exposure (within 1 month) and IBD drugs (Aminosalicylate, steroids, immunomodulators and biological therapy), in addition to the duration, severity and endoscopic extend of IBD, all have been recorded.

Diagnosis of CDI was done by the detection of *clostridium difficile* toxin A and B in a fecal specimen using an enzyme immunoassay (ELISA).

Results: A total of 87 IBD patients were enrolled in this study (62 cases of UC and 25 cases with a diagnosis of CD), female comprised 66% of cases with female to male ratio of 2:1, with a mean age of 33 years, The most frequent IBD disease duration was (2–5) years in 37 patients (42.5%) of cases, followed by > 5 years in 31 (35.6%), The highest proportion of study patients (67.8%) were treated with amino-salicylates (mesalamine and sulfasalazine), while azathioprine, steroids (prednisolone and budesonide), and biological therapy (infliximab and adalimumab), were prescribed for 44 (50.5%), 35 (40.2%), and 19 (21.8%) of cases, respectively. Recent PPI use was recorded in 7 cases (8%) while recent antibiotics exposure was recorded in 9 patients (10.3%). Recent hospitalization was recorded in 5 cases. The most common clinical presentations were bloody diarrhea and abdominal pain, that recorded in 51 (58.6%) and 45 (51.7%) of cases, respectively, followed by watery diarrhea in 34 (39%) and BPR in 9 (10.3%). According to the endoscopy, the most frequent underlying pathology was pancolitis in 34 patients (39%), followed by proctosigmoiditis in 24 (27.5%) and ileitis that seen in 20 patients (22.9%), while each of left sided colitis and proctitis were recorded in 11 (12.6%) and 8 (9.1%) of study patients respectively.

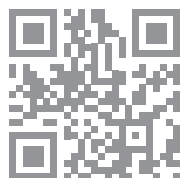
The incidence of CDI among the 87 enrolled IBD patients was 20%, In the study, there was no statistically significant association between the developing of CDI and each of age ($P=0.601$), gender ($P=0.998$), use of PPI ($P=0.131$), recent antibiotic exposure ($P=0.904$), recent hospitalization ($P=0.968$), type of IBD ($P=0.493$), duration ($P=0.272$), severity ($P=0.081$), and endoscopic extend of the colitis ($P=0.713$), on the other hand CDI is significantly associated ($P=0.002$) with administration of multiple IBD drugs, as more than half of patients (53.3%) who treated with multiple drugs including immunosuppressive developed CDI.

Conclusion: The current study showed that IBD patients on multiple immunosuppressive drugs have a higher risk for CDI development, yet no other risk factors have been identified in the current study (age, gender, antibiotic exposure, PPI use and recent hospitalization, in addition to disease duration, severity and endoscopic extend), Further larger study is needed to confirm these findings, to look for other possible risk factors and to evaluate treatment outcome.

Keywords: *clostridium difficile*, inflammatory bowel disease, Risk factors, Pseudomembranous colitis

Conflict of interests. The authors declare no conflict of interest.

EDN: JVASNL





Инфекция *Clostridium Difficile* и воспалительные заболевания кишечника: частота встречаемости и возможные факторы риска

Альхалиди Н.М.¹, Абдулла М.А.^{1,2}, Мджали А.А.³

¹ Багдадская учебная больница гастроэнтерологии и гепатологии, (Багдад, Ирак)

² Басрийский медицинский колледж, (Басра, Ирак)

³ Гастроэнтерологический и гепатологический центр Аль-Кинди, (Багдад, Ирак)

Для цитирования: Альхалиди Н.М., Абдулла М.А., Мджали А.А. Инфекция *Clostridium Difficile* и воспалительные заболевания кишечника: частота встречаемости и возможные факторы риска. Экспериментальная и клиническая гастроэнтерология. 2025;(12): 28–39 doi: 10.31146/1682-8658-ecg-244-12-28-39

✉ Для переписки:

Мунтадер

Абдулкарим

Абдулла

muntaderaltememy984

@gmail.com

Наваль Махди Альхалиди, консультант-гастроэнтеролог и гепатолог

Мунтадхер Абдулкарим Абдулла, доцент, гастроэнтеролог и гепатолог

Абасс Абдулла Мджали, гастроэнтеролог и гепатолог

Резюме

Предыстория и цели: Заболеваемость ИКД среди пациентов с ВЗК растёт, и, как было показано, это связано с увеличением продолжительности госпитализации, расходов, заболеваемости и смертности. В последних рекомендациях рекомендуется проводить тестирование на ИКД всех пациентов с ВЗК с обострением заболевания. Данное поперечное исследование направлено на оценку заболеваемости и выявление возможных факторов риска ИКД среди пациентов с ВЗК с обострением заболевания.

Методы: В исследовании приняли участие 87 пациентов с ВЗК, которые посещали Учебную больницу гастроэнтерологии и гепатологии в Медицинском городе (Багдад) в период с января 2019 года по апрель 2020 года. У всех пациентов наблюдалось обострение заболевания. Регистрировались демографические и клинические данные пациентов, включая факторы, предположительно являющиеся факторами риска или имеющие связь с ИКД, такие как возраст, пол, сопутствующие заболевания, недавняя госпитализация (в течение 1 месяца), принимаемые препараты, включая ИПП, недавнее применение антибиотиков (в течение 1 месяца) и препараты для лечения ВЗК (аминосалицилаты, стероиды, иммуномодуляторы и биологическая терапия), а также длительность, тяжесть и эндоскопическая распространенность ВЗК. Диагностика ИКД проводилась путем обнаружения токсинов А и В *Clostridium difficile* в образцах кала с помощью иммуноферментного анализа (ИФА).

Результаты: В исследование было включено в общей сложности 87 пациентов с ВЗК (62 случая ЯК и 25 случаев с диагнозом КД), женщины составили 66% случаев с соотношением женщин и мужчин 2:1, средний возраст составил 33 года. Наиболее частая продолжительность заболевания ВЗК составила (2–5) лет у 37 пациентов (42,5%) случаев, затем > 5 лет у 31 (35,6%), наибольшая доля пациентов исследования (67,8%) лечилась аminosалицилатами (месаламин и сульфасалазин), в то время как азатиоприн, стероиды (преднизолон и будесонид) и биологическая терапия (инфликсимаб и адалимумаб) были назначены в 44 (50,5%), 35 (40,2%) и 19 (21,8%) случаях соответственно. Недавнее применение ИПП было зарегистрировано у 7 пациентов (8%), а недавнее применение антибиотиков – у 9 пациентов (10,3%). Недавняя госпитализация была зарегистрирована у 5 пациентов. Наиболее частыми клиническими проявлениями были кровавая диарея и боль в животе, зарегистрированные у 51 (58,6%) и 45 (51,7%) пациентов соответственно, за которыми следовали водянистая диарея у 34 (39%) и БПР у 9 (10,3%). По данным эндоскопии, наиболее частой фоновой патологией был панколит у 34 пациентов (39%), за ним следовали проктосигмоидит у 24 (27,5%) и илеит у 20 пациентов (22,9%), при этом левосторонний колит и проктит были зарегистрированы у 11 (12,6%) и 8 (9,1%) пациентов исследования соответственно. Частота возникновения ИКД среди 87 пациентов с ВЗК, включенных в исследование, составила 20%. В ходе исследования не было выявлено статистически значимой связи между развитием ИКД и каждым из следующих факторов: возрастом ($P = 0,601$), полом ($P = 0,998$), применением ИПП ($P = 0,131$), недавним применением антибиотиков ($P = 0,904$), недавней госпитализацией ($P = 0,968$), типом ВЗК ($P = 0,493$), продолжительностью ($P = 0,272$), тяжестью ($P = 0,081$) и эндоскопической распространенностью колита ($P = 0,713$). С другой стороны, ИКД достоверно связана ($P = 0,002$) с приемом нескольких препаратов для лечения ВЗК, поскольку у более чем половины пациентов (53,3%), получавших лечение несколькими препаратами, включая иммуносупрессивные, развивалась ИКД.

Заключение: Настоящее исследование показало, что у пациентов с ВЗК, принимающих несколько иммунодепрессантов, риск развития ИКД выше, однако в настоящем исследовании не выявлено других факторов риска (возраст, пол, прием антибиотиков, применение ИПП и недавняя госпитализация, помимо длительности заболевания, тяжести и эндоскопического распространения). Для подтверждения этих результатов, выявления других возможных факторов риска и оценки результатов лечения необходимы дальнейшие более масштабные исследования.

Ключевые слова: *Clostridium difficile*, воспалительные заболевания кишечника, факторы риска, псевдомембранозный колит

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

Introduction

The idiopathic inflammatory bowel diseases comprise two main types of chronic intestinal disorders: Cohn's disease and ulcerative colitis [1]. Internationally, the incidence of IBD is approximately 0.5–24.5 cases per 100,000 person-years for ulcerative colitis and 0.1–16 cases per 100,000 person-years for Cohn's disease with an Overall prevalence of 396 cases per 100,000 persons annually [2].

Accumulating evidence suggests that IBD results from an inappropriate inflammatory response to intestinal microbes in a genetically susceptible host [3]. UC involves the colonic mucosa, extending proximally from the rectum in an uninterrupted pattern to involve all or part of the colon. In contrast, CD is a transmural process with a special predilection for small-bowel involvement. However, CD can affect any region of the gastrointestinal tract from mouth to anus, manifesting as patchy inflammation with intervening areas of normal mucosa [4].

Characteristic symptoms of IBD include chronic diarrhea and abdominal pain, constitutional symptoms such as fatigue, fever, and weight loss are frequently present. UC typical symptoms include left lower quadrant pain, rectal urgency, tenesmus, mucoid discharge, and bloody diarrhea.

Depending on the segment of bowel involved, patients with CD may present with right lower quadrant pain associated with diarrhea, obstructive symptoms (nausea, vomiting, abdominal pain and distention), fever, and weight loss [5].

The natural history of IBD is characterized by recurring periods of remission and relapse, potential proposed factors that may precipitate IBD flare may include enteric infections, smoking, stress, treatment noncompliance, NSAIDs and antibiotics use [6].

The risk of enteric infections is higher in IBD than non IBD populations [7]. A study showed that 10.5% of IBD relapses were associated with enteric infection [8].

Clostridium difficile is an anaerobic gram-positive, spore-forming, toxin-producing bacillus which is transmitted among humans through the feco-oral route [9]. *C. difficile* colonizes the large intestine and produce two potent toxins, toxin A and toxin B, that cause colitis in susceptible persons. Infection is transmitted by spores that are resistant to heat, acid, and antibiotics. The spores are present in high levels in health care facilities and are found in low levels in the environment and food supply, allowing for both nosocomial and community transmission. Colonization is

prevented by barrier properties of the fecal microbiota; weakening of this resistance by antibiotics is the major risk factor for disease [10]. The organism itself is non-invasive, and infection outside the colon is extremely rare [9].

Clostridium difficile infection (CDI) has increased dramatically worldwide Over the last decade in both incidence and severity [11, 12]. In addition to broad spectrum antibiotic use, other potential risk factors such as advanced age, prolonged hospitalization, immunosuppression, multiple comorbidities, the use of PPI, and the occurrence of a hypervirulent strain of *C. difficile* known as NAP1 (North American pulso-type 1) in some North-American and European areas, have been identified [13, 14, 15].

Patients with IBD are at increased risk of developing CDI, the association may be due to different factors, such as drugs that are used for the treatment of IBD that might alter the intestinal flora and promote colonization (including repeated courses of antibiotics), altered immune and nutritional status, frequent hospitalizations, and even genetic predisposition [16, 17].

Clinical manifestations of CDI can range from asymptomatic carrier to mild or moderate diarrhea to life-threatening pseudomembranous colitis with toxic megacolon [18]. The diarrhea is usually watery; however, in patients with underlying IBD, it may be bloody [19]. It should be noted that on rare occasions diarrhea may be absent in patients with severe CDI which occur when the infection causes paralytic ileus, preventing the passage of stool [19].

The diagnosis of CDI is based on the presence of diarrhea and other evidence of acute colitis, and demonstration in stools of *C. difficile* toxins or toxinogenic *C. Difficile* [20]. Stool testing for *C. difficile* toxins should be confined to patients with diarrhea. Testing of formed stools is not recommended because only patients with diarrhea require treatment as Treatment of asymptomatic carriers might prolong the carrier state beyond the usual 2 to 6 week [21], a freshly passed stool sample should be submitted immediately to the laboratory in a clean watertight container. because storage at ambient temperatures can result in denaturation of fecal toxin or bacterial DNA; samples should be tested immediately or refrigerated or frozen, pending later testing [22].

A variety of laboratory tests are available to diagnose infection with toxinogenic *C. difficile* either by enzyme immunoassay for toxins in stool or by DNA-based tests

Table 1.
Diagnostic testing
for *C. difficile*

Test	Sensitivity	Specificity	Availability	Utilization
<i>C. difficile</i> culture	low	moderate	limited	No diagnostic use; only toxigenic organisms cause disease
Toxigenic culture	high	high	limited	Reference method Epidemiologic tool Limited diagnostic use
<i>C. difficile</i> cytotoxin neutralization assay	high	high	limited	Reference method Limited diagnostic use
glutamate dehydrogenase	high	low	widely	Diagnostically as a screening test; must be confirmed
Toxin EIA tests	low	high	widely	inferior sensitivity
nucleic acid amplification tests	high	high	widely	false positives of concern

that identify the microbial toxin genes in unformed stool. Stool culture for *C. difficile* requires anaerobic culture which is not widely available. Enzyme immunoassays EIAs to detect toxin antigens in stool currently are used most commonly (Table 1). These tests have the advantages of being relatively inexpensive, quick to perform (2 to 12 hours, and specific; however, their relatively low sensitivity can lead to false-negative results [18]. A systematic review of these tests showed that toxin A + B EIA tests had a sensitivity of 75–95% and a specificity of 83–98% [23]. The lower sensitivity of these tests can be improved by performing the tests on 2 or 3 specimens rather than on 1 specimen, which increases the diagnostic yield by 5%-10% [24]. Assays that test the presence of both toxins are preferable as toxin A-negative, toxin-B positive strains can also cause the disease [25]. The table below summarizes the diagnostic tests for *C. difficile* [23].

Abdominal radiography and CT of the abdomen are useful in severe cases and help in detecting complications such as toxic dilatation and perforation, since intestinal inflammation shows up as mucosal enhancement, CT of the abdomen can also be helpful in the assessment of the extent and severity of pseudomembranous colitis [25].

Endoscopy is helpful when the diagnosis is in doubt or when disease severity demands rapid diagnosis. Sigmoidoscopy may be normal in patients with mild diarrhea or might demonstrate nonspecific colitis in moderate cases, the finding of colonic pseudomembranes is virtually pathognomonic for *C. difficile* colitis [26], which is described in 50% of patients [27], however in patients with underlying IBD, classic endoscopic pseudomembranes are conspicuously absent, making it hard to diagnose CDI in patients with worsening diarrhea [28], yet in IBD endoscopy may be useful to assess disease activity and also to rule out other secondary causes of diarrhea including concurrent cytomegalovirus infection [29].

Because CDI is often a consequence of antimicrobial therapy, the first step in management is to discontinue such drugs [30], antiperistaltic drugs such as narcotics and loperamide should be avoided because of the risk of decreasing toxin clearance and the risk for ileus and/or megacolon [31].

Aims of the Study

The aim of this study is to estimate the frequency and to assess possible risk factors for CDI among IBD patients who are in disease flare up.

Metronidazole and oral vancomycin have been the mainstays of treatment for CDI and despite their use by millions of patients, clinically important resistance has not been reported, fidaxomicin, a poorly absorbed bactericidal antibiotic with activity against specific anaerobic gram-positive bacteria, was approved by the FDA in 2011, it's markedly high cost has limited its use, despite its superiority to vancomycin in reducing the risk of recurrence [9].

IBD outpatients with non-severe CDI can be initially treated with metronidazole, however IBD inpatients regardless of disease severity should receive a vancomycin-containing regimen as first-line therapy [32]. Management of a first recurrence of CDI is identical to the primary episode, long tapering courses of vancomycin or pulsed treatment reduce recurrence and are suggested for treating second episode of recurrence, metronidazole is not used for the treatment of second relapse Because of the risk of often-irreversible neuropathy with long-term use [33].

If there is a third recurrence after a pulsed vancomycin regimen, fecal microbiota transplant (FMT) should be considered [23].

Patients with fulminant colitis require treatment with oral vancomycin at a dose of 500 mg 6 hourly which may be administered with a nasogastric tube in cases of paralytic ileus along with intravenous metronidazole, emergent surgery is required for patients who do not respond to the above medical management and in patients with impending perforation and toxic megacolon. Patients usually undergo a subtotal colectomy and a temporary ileostomy and are associated with a high perioperative mortality rate approaching close to 40% [34].

Outcomes in hospitalized IBD patients with CDI are worse with higher colectomy rates (approaching 20% in some studies [28]) and higher mortality [35].

In the absence of an effective vaccine, CDI control has focused on antibiotic stewardship and prevention of spread in health care facilities [36]. Patients with known or suspected *C. difficile* infection should be isolated in a single room, and health care professionals should wear gloves and gowns and wash hands with soap and water; post discharge disinfection of the room is also recommended [37].

Patients and Methods

This study of a cross-sectional design was conducted on IBD patients (62 cases of UC and 25 cases with a diagnosis of CD), who attended the Gastroenterology and Hepatology Teaching Hospital in the Medical City (Baghdad), during the period from January 2019 to April 2020.

Patients demographic and clinical data including factors expected to be a risk factors or have an association with CDI such as age, sex, comorbid conditions, recent hospitalization (within 1 month), history of PPI, recent antibiotic exposure (within 1 month) and IBD drugs (Aminosalicilate, steroids, immunomodulators and biological therapy), in addition to the duration, severity and endoscopic extend of IBD, all have been recorded on a data sheet from patients with IBD flare.

Statistical Analysis

The data analyzed using Statistical Package for Social Sciences (SPSS) version 25. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. Chi

The diagnosis of IBD was done depending on the clinical, radiological, endoscopic and histopathological characteristics.

Disease severity was assessed according to the mayo score [38] for UC and by the Harvey Bradshaw score [39] for CD.

Blood samples were sent for hemoglobin, white cell count and ESR, in addition to Liver and renal function tests.

Diagnosis of CDI was done by the detection of *Clostridium difficile* toxin A and B in a freshly passed fecal specimens using an enzyme immunoassay (ELISA), which carried out according to the manufacturer package instructions.

square test was used to assess the association between provisional diagnosis and certain information. A level of P – value less than 0.05 was considered significant.

Results

A total of 87 IBD patients were the subjects of this study.

Demographic characteristics

The distribution of study patients by certain demographic characteristics is shown in figures (3.1 and 3.2). The age of patients was ranging from 17 to 58 years with a mean of 33.56 and standard deviation (SD) of ± 10.34

years. About two thirds of patients (64.4%) were aged between (25 and 45) years. Regarding gender, proportion of females was more than males (66.7% versus 33.3%) with female to male ratio of 2:1.

Figure 1. Distribution of study patients by age

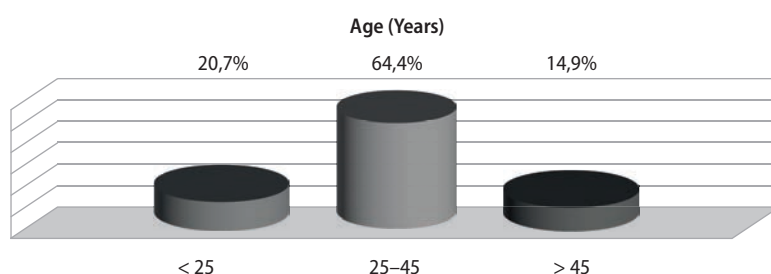
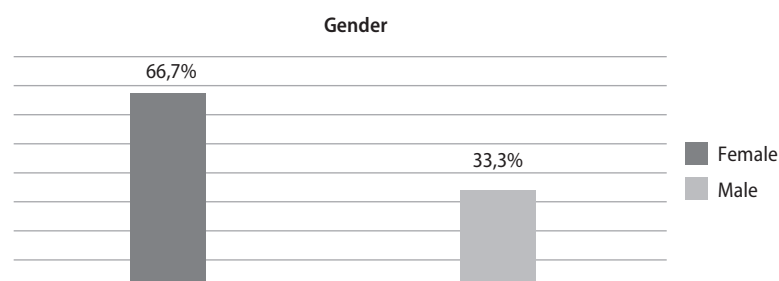


Figure 2. Distribution of study patients by gender



Clinical characteristics of patients

From the 87 recruited IBD patients, 62 (71.3%) were diagnosed with UC, while 25 patients (28.7%) were diagnosed as CD. The most frequent duration of disease was (2–5) years in 37 patients (42.5%) of cases, followed by > 5 years in 31 (35.6%), as shown in table (3.1).

The highest proportion of study patients (67.8%) were treated with amino-salicylates (mesalamine and sulfasalazine), while azathioprine, steroids (prednisolone and budesonide), and biological therapy (infliximab and adalimumab), were prescribed for 44 (50.5%),

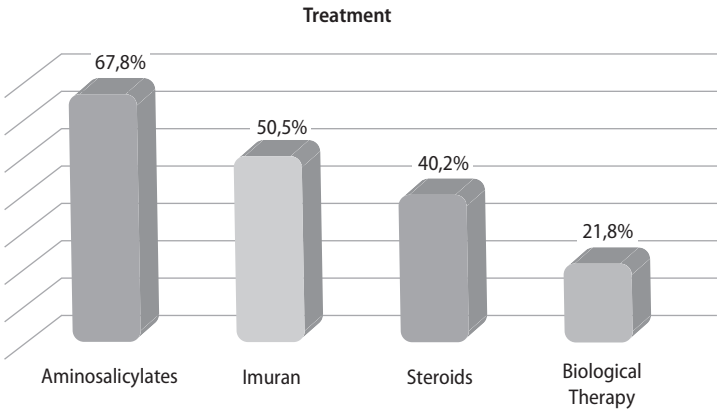
Table 1. Distribution of study patients according to diagnosis and duration of IBD prior to the study

Clinical Features	No. (n= 87)	Percentage (%)
diagnosis		
CD	25	28.7
UC	62	71.3
Duration of Disease (Years)		
< 2	19	21.9
2–5	37	42.5
> 5	31	35.6

Table 2. Distribution of study patients by risk factors for CDI and comorbidities in IBD patients

Risk factors and comorbidities	No. (n= 87)	Percentage (%)
IBD drugs		
Aminosalisylates	59	67.8
Steroids	35	40.2
Azathioprine	44	50.5
Biological therapy	19	21.8
Recent Antibiotics exposure (within 1 month)		
Yes	9	10.3
No	78	89.7
Use of PPI		
Yes	7	8.0
No	80	92.0
Previous hospitalization (within 1 month)		
Yes	5	5.7
NO	82	94.3
Comorbidities		
DM	4	4.6
CLD	2	2.3
No	81	93.1

Figure 3. Distribution of study patients by drug treatment



35 (40.2%), and 19 (21.8%) of cases, respectively (figure 3.3). Recent PPI use was recorded in 7 cases (8%) while recent antibiotics exposure was recorded in 9 patients (10.3%). Recent hospitalization was recorded in 5 cases. In the study, comorbidities were seen in six patients, four patients were diabetics and the other two were with CLD, as shown in table (3.2).

Endoscopic Findings

According to the endoscopy, the most frequent findings were pancolitis in 34 patients (39%), and proctosigmoiditis in 24 (27.5%) and ileitis that seen in 20 patients

The most common clinical presentations were bloody diarrhea and abdominal pain, that recorded in 51 (58.6%) and 45 (51.7%) of cases, respectively, followed by diarrhea in 34 (39%) and BPR in 9 (10.3%). Other symptoms as fever, vomiting, arthralgia, weight loss, fatigue, and perianal fistula were reported separately among 16 patients (18.4%), as shown below in figure (3.4).

(22.9%), while each of left sided colitis and proctitis were recorded in 11 (12.6%) and 8 (9.1%) of study patients, respectively. As shown in figure (3.5).

Incidence of CDI

The incidence of CDI among the 87 enrolled IBD patients was 20.7%, while the other 79.3% of cases had no CDI. As shown in figure (3.6).

Figure 4. Distribution of study patients by clinical presentations

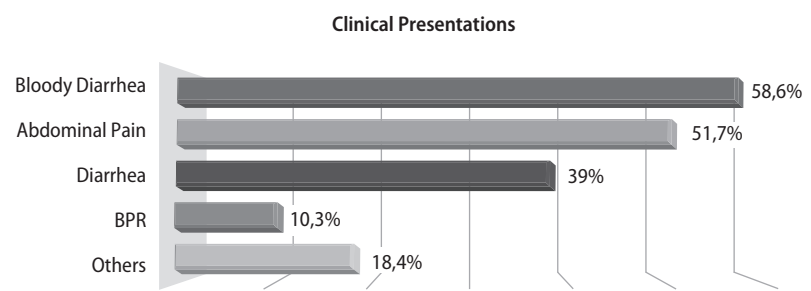


Figure 5. Distribution of study patients by findings of endoscopy

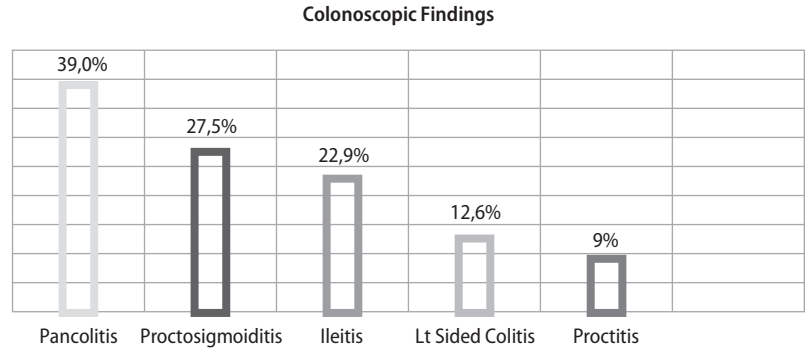


Figure 6. Incidence of CDI among IBD patients

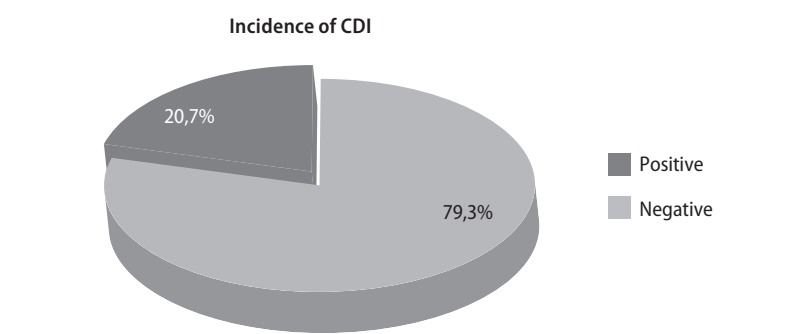


Table 3. Distribution of the study patients with CDI and certain general characteristics

Variable	CDI		Total (%) n= 87	P- Value
	Positive (%) n= 18	negative (%) n= 69		
Age (Years)				
< 25	3 (16.7)	15 (83.3)	18 (20.7)	0.601
25–45	11 (19.6)	45 (80.4)	56 (64.4)	
> 45	4 (30.8)	9 (69.2)	13 (214.9)	
Gender				
Male	6 (20.7)	23 (79.3)	29 (33.3)	0.998
Female	12 (20.7)	46 (79.3)	58 (66.7)	

**Association of CDI
With general characteristics**

In the current study, there was no statistically significant association between the developing of CDI and

each of age (P= 0.601) and gender (P= 0.998) of IBD patients, as shown in table (3.3).

Certain risk factors

The association between CDI and certain risk factors in IBD patients is shown in table (3.4). It has been found that CDI is significantly associated (P= 0.002) with administration of multiple IBD drugs for patients, as

more than half of patients (53.3%) who treated with multiple drugs developed CDI, while the association with use of PPI, recent antibiotic exposure and recent hospitalization was not significant (P > 0.05).

Table 4. Distribution of the study patients by CDI and certain risk factors

Variable	CDI		Total (%) n= 87	P- Value
	Positive (%) n= 18	negative (%) n= 69		
No. of IBD Drugs Used				
One	4 (12.1)	29 (87.9)	33 (37.9)	0.002
Two	6 (15.4)	33 (84.6)	39 (44.8)	
Multiple	8 (53.3)	7 (46.7)	15 (17.3)	
PPI use				
Yes	3 (42.9)	4 (57.1)	7 (8.0)	0.131
No	15 (18.8)	65 (81.2)	80 (92.0)	
Antibiotic Exposure				
Yes	2 (22.2)	7 (77.8)	9 (10.3)	0.904
No	16 (20.5)	62 (79.5)	78 (89.7)	
Recent Hospitalization				
Yes	1 (20.0)	4 (80.0)	5 (5.7)	0.968
No	17 (20.7)	65 (79.3)	82 (94.3)	

With Clinical characteristics and endoscopic findings

Insignificant association was found between the severity (P= 0.081), and endoscopic extend of the colitis CDI and type of IBD (P= 0.493), duration (P= 0.272), (P= 0.713) as shown in table (3.5).

Discussion

CDI incidence has been increasing globally over the last few decades [11, 12, 40, 41] with a much higher increase among IBD patients [42] which may be attributed to different factors, such as drugs that are used for IBD treatment which may alter the intestinal flora and promote colonization (including repeated courses of antibiotics), altered immune and nutritional status, frequent hospitalizations, and even genetic predisposition [16, 17].

In the current study CDI incidence among IBD patients was (20.7%) which was comparable to that reported by Meyer A. et al (20%) [43], higher than that reported by a Chinese (8.9%) [44], British(10%) [8] and a recent Indian study(16%) [45], and lower than that reported by Balamurugan et al(22%) [46] and by Kochhar R. et al(24%) [47], there were no local or

regional published studies about *C. difficile* among IBD patients in the nearby countries to compare with this study.

The predominant clinical symptoms of CDI include watery diarrhea (which may be bloody among IBD patients), abdominal pain and fever, which makes it difficult to be differentiated from IBD flare [19].

The main clinical symptoms in this study were bloody diarrhea and abdominal pain, that recorded in 51 (58.6%) and 45 (51.7%) of cases, respectively, followed by watery diarrhea in 34 (39%) and BPR in 9 (10.3%).

Several risk factors for CDI have been studied extensively in the medical literature with controversial results, With the increasing incidence and complications of CDI in IBD patients [48], evaluation of CDI risk factors is crucial.

Table 5. Distribution of the study patients by CDI and each of certain clinical characteristics of IBD and endoscopic findings

Variable	CDI		Total (%) n= 87	P- Value
	Positive (%) n= 18	negative (%) n= 69		
Diagnosis				
CD	4 (16.0)	21 (84.0)	25 (28.7)	0.493
UC	14 (22.6)	48 (77.4)	62 (71.3)	
Duration of IBD (Years)				
< 2	6 (31.6)	13 (68.4)	19 (21.8)	0.272
2–5	5 (13.5)	32 (86.5)	37 (42.5)	
> 5	7 (22.6)	24 (77.4)	31 (35.6)	
Severity of IBD				
Mild	2 (14.3)	12 (85.7)	14 (16.1)	0.081
Moderate	14 (21.2)	52 (78.8)	66 (75.9)	
Severe	2 (28.6)	5 (71.4)	7 (8.0)	
endoscopic Findings				
Proctitis + Proctosigmoiditis	8 (25.0)	24 (75.0)	32 (36.8)	0.713
Ileitis	2 (10.0)	18 (90.0)	20 (22.9)	
Colitis(left sided and pancolitis)	8 (17.7)	37 (82.3)	45 (51.7)	
Two Parts	0 (0)	10 (100.0)	10 (11.4)	

In the current study no statistically, significant association was found between the developing of CDI and each of age and gender of IBD patients which was consistent with a Netherland study done by Masclee GM et al. [49] in contrast to a study conducted by *Nguyen GC, et al.* [35] in which advanced age was proposed as CDI risk factor in IBD patients.

The CDI association with antibiotics use in the general population is well known, and almost any antibiotics can be associated with CDI development [50] by causing alteration in the normal bowel flora [51], however the exact mechanism for CDI development in IBD patients is not clear [52].

This study showed that antibiotics use is not an independent risk factor for CDI development in IBD patients in which antibiotic exposure was present in (2/18) CDI patients, these findings are similar to that reported by Masclee GM et al [49], Bossuyt P et al. [53] and Regnault H et al. [54], unlike Kariv R et al. [55] who reported increased risk for CDI in patients with antibiotics exposure during the last month prior to the CDI development

Proton pump inhibitors by reducing gastric acidity and altering gut flora was suggested as CDI risk factor [56], however Proton pump inhibitors as a risk factor for CDI is controversial with conflicting results in the published studies.

In the current study PPI use was seen in 3 patients out of 18 which was statistically insignificant as a CDI risk factor, This is as in a retrospective analysis done by Mazen Issa et al. [57] he found no association between PPIs use and CDI in IBD patients, also this finding was supported by Pepin J, et al. [28] and Lowe DO, et al. [59] yet this in contrast to two retrospective studies which showed an association between PPIs use and CDI [56, 60].

Host immunity was considered to have an important role in the susceptibility and development of CDI [61], by inhibiting activity of the immune system as a part of their intended pharmacological activity, immunosuppressive drugs were supposed to be an independent risk factors for CDI development [62].

Initial studies have not demonstrated an association between CDI development and steroid use [74, 63], however in a large cohort study [64] steroid use in IBD patients was associated with a threefold increased risk for CDI development.

Rodemann JF et al. [65] and Issa M et al. [28] reported an association between immunomodulators use (azathioprine and 6mercaptopurine) and CDI while others like Gellad ZF et al. [66] and Hardt C et al. [67] do not supported immunomodulators as a risk factor for CDI.

The role of the biological agents (infliximab and adalimumab) is less clear with only few studies [68] showing increased risk explaining that by association with opportunistic infections including CDI.

Aminosaliclates use was also suggested as CDI risk factor in some studies [63, 69] by altering normal bowel flora through its antimicrobial sulphonamide component.

In the current study (4/18) of CDI patients were using single IBD drug (from Aminosaliclates, steroids, Azathioprine and biological agents) and each drug was not studied alone because of the small sample size, as (6/18) were using two IBD drugs and (8/18) were using more than two drugs, combining more than two of these medications have been demonstrated to dramatically increasing CDI risk among IBD patients in the current study with a significant P value (0.002), this finding was supported by Toruner M, et al. [62] who reported as much as 14 fold increase in CDI risk in IBD patients combining these drugs.

The majority of CDI cases among IBD patients in this study are community acquired as only (1/18) of CDI patients had a recent hospitalization history, this finding was in keeping with that reported by Libby et al [70], and in contrast to CDI among non IBD patients which is usually hospital acquired [71].

In the current study no significant association was found between CDI development and IBD type, in which 22% of UC patients developed CDI compared with 16% in those with CD, this was consistent with a recent study [72] that found similar incidence of CDI in those with UC and CD, and further supported by a Netherland study⁽⁴⁹⁾ which could not found an association between IBD type and CDI development, however Early studies [28, 73, 74] have reported that patients with UC are more vulnerable to CDI than those with CD, attributing that to more colonic involvement.

This study could not establish an association between the development of CDI and the duration of IBD which may explained by the small sample size, in contrast to Harminder Singh, et al. [72] who reported that the highest risk for CDI in IBD patients will be within the first year of IBD diagnosis, explaining that by increased antibiotics use early in IBD diagnosis and increased dysbiosis of gut flora at the time of IBD diagnosis.

In relation to CDI development, endoscopic disease extension has no impact on CDI acquisition in the current study, unlike to a small study [75] conducted by Powell N et al, which showed that left sided and extensive colitis are associated more with CDI compared with more distal disease.

In this study no significant association was found between CDI development and IBD disease severity, this was in keeping with many other authors [49, 74] who could not establish such a correlation, in contrast Trnka et al [63] have evaluated the impact of IBD disease severity on CDI development, he classified IBD disease severity from mild to severe and found that most of patients (60%) with CDI have severe disease, on the other hand none of those who had mild disease developed CDI.

There are some limitations to the current study. First, the testing method for *C. difficile* was done by Enzyme immunoassay and the majority of patients were tested once only, thus decreasing the sensitivity of the test. Second is the small sample size, which might explain the insignificant association between CDI development and the clinical and endoscopic findings.

Conclusions

The incidence of CDI in IBD patients who are exhibiting disease flare up were 20%, there are no clinical published studies about CDI among IBD patients in Iraq. The IBD patients on multiple immunosuppressive drugs have a higher risk for CDI development, yet no

other risk factors have been identified in the current study (age, gender, antibiotic exposure, PPI use and recent hospitalization, in addition to disease duration, severity and endoscopic extend).

Declarations:

Ethics approval and consent to participate statement

The study was approved by the Ethics Committee of the Arab scientific council of Gastroenterology & Hepatology for researches and committee guidelines, Baghdad, Iraq and Basrah college of medicine ethical committee, verbal

and written informed consent had been taken from the patients enrolled in the study and in order to support privacy and confidentiality, I concealed the unique identifying information of people in the data gathering.

Consent to publication

Written informed consent had been taken from participants

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

Authors have declared that no competing interests exist.

Funding statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Authors' contributions

The three authors contributed to the design and implementation of the research, to the analysis of the results and the writing of the manuscript.

Acknowledgments

The authors are grateful to all patients who agreed to participate in this study.

References

1. Cosnes J., Gower-Rousseau C., Seksik P., et al. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology*. 2011;140:1785.
2. Centers for Disease Control and Prevention. Inflammatory bowel disease (IBD). Available at <http://www.cdc.gov/ibd/#epidIBD>. Accessed: August 6, 2012
3. Clara Abraham and Judy H. Cho. Mechanisms of Disease Inflammatory Bowel Disease. *The new england journal of medicine* 2009; 361(21): 2066–2078.
4. DAVID H. BRUINING. Inflammatory Bowel Disease: Clinical Aspects. Stephen C. Hauser, Amy S. Oxentenko, William Sanchez, (ed). *Mayo Clinic Gastroenterology and Hepatology Board Review*, fifth ed. New York: Oxford University Press; 2015. pp. 155.
5. Jan-Michael A. Klapproth. Inflammatory Bowel Disease. Shanthi Srinivasan, Lawrence S. Friedman (ed). *Sitaraman and Friedman's Essentials of Gastroenterology*, second ed. USA: John Wiley & Sons Ltd; 2018. pp. 116.
6. Linda A Feagins, Ramiz Iqbal, Stuart J Spechler. Case-control study of factors that trigger inflammatory bowel disease flares. *World J Gastroenterol*. 2014; 20(15): 4329–4334.
7. Goodhand JR, Alazawi W, Rampton DS. Systematic review: *Clostridium difficile* and inflammatory bowel disease. *Aliment Pharmacol Ther*. 2011;33:428–41.
8. Mylonaki M, Langmead L, Pantes A, et al. Enteric infection in relapse of inflammatory bowel disease: importance of microbiological examination of stool. *Eur J Gastroenterol Hepatol*. 2004;16:775–8.
9. Daniel A. Leffler and J. Thomas Lamont. *Clostridium difficile* Infection. *The new england journal of medicine* 2015; 372(16): 1539–48.
10. Rupnik M. Is *Clostridium difficile*-associated infection a potentially zoonotic and foodborne disease? *Clin Microbiol Infect*. 2007; 13: 457–9.
11. Khanna S., Pardi D.S. The growing incidence and severity of *Clostridium difficile* infection in inpatient and outpatient settings. *Expert Rev Gastroenterol Hepatol* 2010; 4: 409–416.
12. Ananthakrishnan A.N. *Clostridium difficile* infection: epidemiology, risk factors and management. *Nat Rev Gastroenterol Hepatol*. 2011; 8: 17–26.
13. Kwok C.S., Arthur A.K., Anibueze C.I. et al. Risk of *Clostridium difficile* infection with acid suppressing drugs and antibiotics: meta-analysis. *Am Gastroenterol*. 2012; 107: 1011–1019.
14. Janarthanan S., Ditah I., Adler D.G. et al. *Clostridium difficile*-associated diarrhea and proton pump inhibitor therapy: a meta-analysis. *Am J Gastroenterol*. 2012; 107:1001–1010.
15. McDonald L.C., Killgore G.E., Thompson A. et al. An epidemic, toxin gene-variant strain of *Clostridium difficile*. *N Engl J Med*. 2005; 353: 2433–2441.

16. Freeman H.J. Recent developments on the role of *Clostridium difficile* in inflammatory bowel disease. *World J Gastroenterol.* 2008; 14: 2794–2796.
17. Ananthakrishnan A.N., Oxford E.C., Nguyen D.D. et al. Genetic risk factors for *Clostridium difficile* infection in ulcerative colitis. *Aliment Pharmacol Ther.* 2013; 38: 522–530.
18. Ciaran P., Kelly and J. Thomas Lamont. Antibiotic-Associated Diarrhea and *Clostridium difficile* Infection. Mark Feldman, Lawrence S. Friedman and Lawrence J. Brandt. *Sleisenger and Fordtrans gastrointestinal and liver disease*, 10th ed. Philadelphia: Elsevier Saunders; 2016. pp. 1946–1947.
19. Bartlett JG, Gerding DN. Clinical recognition and diagnosis of *Clostridium difficile* infection. *Clin Infect Dis* 2008; 46Suppl 1: S12–S18.
20. Kyne L., Warny M., Qamar A., Kelly C.P. Asymptomatic carriage of *Clostridium difficile* and serum levels of IgG antibody against toxin A. *N Engl J Med.* 2000; 342:390–7.
21. Sethi A.K., Al-Nassir W.N., Nerandzic M.M. et al. Persistence of skin contamination and environmental shedding of *Clostridium difficile* during and after treatment of *C. difficile* infection. *Infect Control Hosp Epidemiol.* 2010; 31: 21–7.
22. Crobach MJ, Dekkers OM, Wilcox MH, et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID): Data review and recommendations for diagnosing *Clostridium difficile* infection (CDI). *Clin Microbiol Infect.* 2009; 15:1053–66.
23. Christina M. Surawicz, Lawrence J. Brandt, David G. Binion, et al. Guidelines for Diagnosis, Treatment, and Prevention of *Clostridium difficile* Infections. *Am J Gastroenterol.* 2013; 108: 478–498.
24. Manabe YC, Vinetz JM, Moore RD, et al. *Clostridium difficile* colitis: an efficient clinical approach to diagnosis. *Ann Intern Med.* 1995; 123: 835–840.
25. Tanya M. Monaghan and Yashwant R. Mahida. Pseudomembranous colitis. C.J. Hawkey, Jaime Bosch, Joel E. Richter, et al. (eds). *Textbook of Clinical Gastroenterology and Hepatology*, 2nd ed. UK: Blackwell Publishing Ltd; 2012. pp. 413–414.
26. Ciaran P., Kelly and J. Thomas Lamont. Antibiotic-Associated Diarrhea and *Clostridium difficile* Infection. Mark Feldman, Lawrence S. Friedman and Lawrence J. Brandt (ed). *Sleisenger and Fordtrans gastrointestinal and liver disease*, 10th ed. Philadelphia: Elsevier Saunders; 2016. pp. 1948.
27. Fekety R., Shah A.B. Diagnosis and treatment of *Clostridium difficile* colitis. *JAMA* 1993; 269: 71–75.
28. Issa M., Vijayapal A., Graham M.B. et al. Impact of *Clostridium difficile* on inflammatory bowel disease. *Clin Gastroenterol Hepatol.* 2007; 5: 345–351.
29. Ananthakrishnan A.N., Issa M., Binion D.G. *Clostridium difficile* and inflammatory bowel disease. *Med Clin North Am.* 2010; 94: 135–153.
30. Aslam S., Musher D.M. An update on diagnosis, treatment, and prevention of *Clostridium difficile*-associated disease. *Gastroenterol Clin North Am.* 2006;35:315.
31. Walley T., Milson D. Loperamide related toxic megacolon in *Clostridium difficile* colitis. *Postgrad Med J.* 1990; 66: 582.
32. Horton H.A., Dezfoli S., Berel D. et al. Antibiotics for Treatment of *Clostridium difficile* Infection in Hospitalized Patients with Inflammatory Bowel Disease. *Antimicrob Agents Chemother.* 2014;58: 5054–5059.
33. Maroo S., Lamont J.T. Recurrent *Clostridium difficile*. *Gastroenterology.* 2006; 130: 1311–1316.
34. Synnott K., Mealy K., Merry C. et al. Timing of surgery for fulminating pseudomembranous colitis. *Br J Surg.* 1998; 85: 229–231.
35. Nguyen G.C., Kaplan G.G., Harris M.L. et al. A national survey of the prevalence and impact of *Clostridium difficile* infection among hospitalized inflammatory bowel disease patients. *Am J Gastroenterol.* 2008;103:1443–50.
36. Vonberg R.P., Kuijper E.J., Wilcox M.H. et al. Infection control measures to limit the spread of *Clostridium difficile*. *Clin Microbiol Infect.* 2008; 14: Suppl 5: 2–20.
37. Muto C.A., Blank M.K., Marsh J.W. et al. Control of an outbreak of infection with the hypervirulent *Clostridium difficile* BI strain in a university hospital using a comprehensive “bundle” approach. *Clin Infect Dis.* 2007; 45: 1266–73.
38. Christopher Andrew Lamb, Nicholas A Kennedy, Tim Raine et al, British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut.* 2019; 0: 1–106.
39. Harvey R.F., Bradshaw J.M. A simple index of Crohn’s-disease activity. *Lancet.* 1980;1:514.
40. McDonald L., Owings M., Jemigan D. *Clostridium difficile* infection in patients discharged from US short-stay hospitals, 1996–2003. *Emerg Infect Dis.* 2006;34:346–53.
41. Pépin J., Valiquette L., Alary M.E. *Clostridium difficile*-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. *CMAJ.* 2004;171:466–72.
42. Murthy S.K., Steinhart A.H., Tinmouth J. et al. Impact of *Clostridium difficile* colitis on 5-year health outcomes in patients with ulcerative colitis. *Alimentary pharmacology & therapeutics.* 2012;36:1032–9.
43. Meyer A., Nizar R., Loftus E. et al. The diagnostic yield of stool pathogen studies during relapses of inflammatory bowel disease. *J Clin Gastroenterol.* 2004;38(9):772–775.
44. Hui Xu, Hao Tang, Tao Xu et al. Retrospective analysis of *Clostridium difficile* infection in patients with ulcerative colitis in a tertiary hospital in China. *BMC Gastroenterology.* 2019; 19(3): 1–8.
45. Chetana Vaishnavi, Rakesh Kochhar. Inflammatory Bowel Disease and *Clostridium difficile* Infection: A Report from a Tertiary Care Center of North India. *Journal of General Practice.* 2017; 5(3): 1–6.
46. Balamurugan R., Balaji V., Ramakrishna B.S. Estimation of faecal carriage of *Clostridium difficile* in patients with ulcerative colitis using real time polymerase chain reaction. *Indian J Med Res.* 2008; 127: 472–7.
47. Kochhar R., Ayyagari A., Goenka M.K. et al. Role of infectious agents in exacerbation of ulcerative colitis in India: a study of *Clostridium difficile*. *J Clin Gastroenterol.* 1993;16(1):26–30.
48. Negrón M.E., Barkema H.W., Rioux K. et al. *Clostridium difficile* infection worsens the prognosis of ulcerative colitis. *Can J Gastroenterol Hepatol.* 2014;28:373–80.
49. Masclee G.M., Penders J., Jonkers D.M., Wolffs P.F., Pierik M.J. Is *Clostridium difficile* associated with relapse of inflammatory bowel disease? Results from a retrospective and prospective cohort study in the Netherlands. *Inflammatory bowel diseases.* 2013;19:2125–31.
50. Bartlett J.G., Chang T.W., Gurwith M. et al. Antibiotic-associated pseudomembranous colitis due to toxin-producing clostridia. *New England J Med.* 1978;298:531–4.

51. Larentis D.Z., Rosa R.G., Dos Santos R.P. et al. Outcomes and risk factors associated with *Clostridium difficile* diarrhea in hospitalized adult patients. *Gastroenterol Res Practice*. 2015;2015:346341.
52. Udayakumar Navaneethan, Preethi G.K. Venkatesh, Bo Shen. *Clostridium difficile* infection and inflammatory bowel disease: Understanding the evolving relationship. *World J Gastroenterol*. 2010; 16(39): 4892–4904.
53. Bossuyt P., Verhaegen J., Van Assche G., Rutgeerts P., Vermeire S. Increasing incidence of *Clostridium difficile*-associated diarrhea in inflammatory bowel disease. *J Crohns Colitis*. 2009;3(1):4–7.
54. Regnault H., Bourrier A., Lalande V., Nion-Larmurier I., Sokol H., Seksik P. et al. Prevalence and risk factors of *Clostridium difficile* infection in patients hospitalized for flare of inflammatory bowel disease: a retrospective assessment. *Dig Liver Dis*. 2014;46(12):1086–92.
55. Kariv R., Navaneethan U., Lopez R., Shen B. Impact of *Clostridium difficile* infection in patients with Ulcerative colitis. *J Crohns Colitis*. 2011;5:34–40.
56. Babey K., Kelton S., Milne W.K. et al. *Clostridium difficile* infection in rural Ontario: a retrospective multisite population-based study. *Can J Rural Med*. 2015;20:117–20.
57. Mazen Issa, Ashwin N. Ananthakrishnan, and David G. Binion. *Clostridium difficile* and Inflammatory Bowel Disease. *Inflamm Bowel Dis*. 2008; 14(10): 1432–1442.
58. Pepin J., Nathalie Saheb, Marie-Andree Coulombe et al. Emergence of fluoroquinolones as the predominant risk factor for *Clostridium difficile*-associated diarrhea: a cohort study during an epidemic in Quebec. *Clin Infect Dis*. 2005;41:1254–1260.
59. Lowe D.O., Muhammad M. Mamdani, Alexander Kopp et al. Proton pump inhibitors and hospitalization for *Clostridium difficile*-associated disease: a population-based study. *Clin Infect Dis*. 2006;43:1272–1276.
60. Reddy S.S., Brandt L.J. *Clostridium difficile* infection and inflammatory bowel disease. *J Clin Gastroenterol*. 2013;47:666–71.
61. Kyne L. et al. Association between antibody response to toxin A and protection against recurrent *Clostridium difficile* diarrhoea. *Lancet*. 2001;357:189–193.
62. Toruner M., Loftus E.V., Harmsen W.S. et al. Risk factors for opportunistic infections in inflammatory bowel diseases. *Gastroenterology*. 2008; 134: 929–36.
63. Trnka Y.M., LaMont J.T. Association of *Clostridium difficile* toxin with symptomatic relapse of chronic inflammatory bowel disease. *Gastroenterology*. 1981;80(4):693–696.
64. Schneeweiss S., Korzenik J., Solomon D.H., Canning C., Lee J., Bressler B. Infliximab and other immunomodulating drugs in patients with inflammatory bowel disease and the risk of serious bacterial infections. *Aliment Pharmacol Ther*. 2009; 30:253–264.
65. Rodemann J.F., Dubberke E.R., Reske K.A., Seo da H., Stone C.D. Incidence of *Clostridium difficile* infection in inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2007; 5: 339–344.
66. Gellad Z.F., Alexander B.D., Liu J.K. et al. Severity of *Clostridium difficile*-associated diarrhea in solid organ transplant patients. *Transpl Infect Dis*. 2007; 9: 276–280.
67. Hardt C., Berns T., Treder W., Dumoulin F.L. Univariate and multivariate analysis of risk factors for severe *Clostridium difficile*-associated diarrhoea: importance of co-morbidity and serum C-reactive protein. *World J Gastroenterol*. 2008; 14: 4338–4341.
68. Bhairavi Balrama, Robert Battatb, Alex Al-Khourya et al. Risk Factors Associated with *Clostridium difficile* Infection in Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. *Journal of Crohn's and Colitis*. 2018: 27–38.
69. Greenfield C., Aguilar Ramirez J.R., Pounder R.E. et al. *Clostridium difficile* and inflammatory bowel disease. *Gut*. 1983;24(8):713–717.
70. Libby D.B., Bearman G. Bacteremia due to *Clostridium difficile* review of the literature. *Int J Infect Dis*. 2009;13: e305–e309.
71. Kelsen J.R., Kim J., Latta D. et al. Recurrence rate of *Clostridium difficile* infection in hospitalized pediatric patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2011;17: 50–55.
72. Harminder Singh, Zoann Nugent B., Nancy Yu. et al. Higher Incidence of *Clostridium difficile* Infection Among Individuals With Inflammatory Bowel Disease. *Gastroenterology*. 2017; 153(2): 430–438.
73. Bolton R.P., Sherriff R.J., Read A.E. *Clostridium difficile* associated diarrhea a role in inflammatory bowel disease? *Lancet*. 1980;1:383–384.
74. Meyers S., Mayer L., Bottone E. et al. Occurrence of *Clostridium difficile* toxin during the course of inflammatory bowel disease. *Gastroenterology*. 1981;80: 697–670.
75. Powell N., Jung S.E., Krishnan B. *Clostridium difficile* infection and inflammatory bowel disease: a marker for disease extent? *Gut*. 2008;57:1183–4.