1. Introduction

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*Clostridium difficile* (C. difficile) is a Gram-positive, strictly anaerobic, spore-forming bacterium that causes a spectrum of presentation ranging from mild, self-limiting diarrhea, to serious diarrhea, pseudomembranous colitis and life-threatening fulminant colitis, which may result in death [1]. It was first isolated in 1935 from feces and meconium of asymptomatic newborn infants, and was originally named *Bacillus difficilis* because of its morphology, and encountered the difficulties in cultivating it [2]. Since then, it was believed to be a commensal organism until the late 1970s, when it was recognized as the etiologic agent of pseudomembranous colitis [3]. It is now known to be the cause of approximately 10%–35% of all cases of antibiotic-associated diarrhea and the most common infectious cause of nosocomial diarrhea, which is associated with substantial morbidity and mortality [4]; besides, it raises the cost for health care systems. For example, in the United States, the disease has an estimated annual cost of $3.2 billion [5].

*Clostridium difficile* infection (CDI) is mainly a healthcare associated illness (80%), but community-acquired *C. difficile* infection (20%) is also of concern. The incidence of *C. difficile* infection is addressed well by many authors in the developed countries, but there is a lack of such information in the developing world, particularly the Gulf countries. The objective of this review is to describe the pathogenesis, changing epidemiology, risk factors and recent advancement in the management of CDI.
2. Pathogenesis

CDI develops when a patient ingests the spores of a toxigenic strain of *C. difficile* via personal contact or environment. Among healthy people, *C. difficile* does not cause problems due to part commensal bowel flora and antibody-mediated immunity; however, in the setting of an abnormal or disrupted colonic mucosa, these spores colonize the bowel and subsequently germinate, and vegetative bacteria start producing two large toxins, an enterotoxin, TcdA, and a cytotoxin, TcdB, which are encoded by *tcdA* and *tcdB*, respectively. The two genes are part of the Pathogenicity Locus (PaLoc) operon, which also contains tcdR, tcdE and tcdC, of which tcdC is a putative negative regulator of tcdA and tcdB[6]. TcdA acts primarily on the intestinal epithelium, causing fluid secretion, inflammation, and tissue necrosis, whereas TcdB with its broad cell tropism acts as a potent cytotoxin. Some *C. difficile* strains known as NAP1/BI/027, contain an additional potential virulence factor (binary toxin) expressed from the cdtA (enzymatic component) and cdtB (binding component) operon. The extent to which this toxin contributes to the pathogenicity of *C. difficile* is unknown; however, *C. difficile* strain in which the binary toxin was first detected caused severe pseudomembranous colitis. Figure 1, describes the pathogenesis of CDI.

![Figure 1. Pathogenesis of CDI.](image)

After binding to appropriate receptors, these toxins are internalized and exert their cellular effects through their glucosyltransferase activity by targeting and disrupting the intracellular signaling pathways regulated by the Rho–family of small GTPases. Altered cellular function caused by TcdA and TcdB disrupts colonic mucosal integrity, activates colonic epithelial cell apoptosis and induces the secretion of a variety of pro–inflammatory cytokines[7,8]. Many of these effects, direct the recruitment of polymorphonuclear neutrophil (PMN) to the site of toxin action. PMN infiltration is the hallmark of a severe form of CDI known as pseudomembranous colitis[7]. There is no correlation between the severity of the disease and fecal toxin levels[9].

3. Epidemiology

*C. difficile* is the cause of approximately 10–35% of all cases of antibiotic–associated diarrhea and the most common infectious cause of nosocomial diarrhea, which is associated with substantial morbidity and mortality rates as well as increased health care costs[4]. Data from Canada, Europe and the United States disclose an increase in the incidence and severity of the disease[10,11]. This has been attributed to multiple factors, including changing demographic situation, increased use of broad–spectrum antibiotics and emergence of hypervirulent *C. difficile* strains known as NAP1/BI/027[12,13]. This strain is characterized by increased production of toxins A and B, the presence of an additional potential virulence factor (binary toxin) and resistance to newer fluoroquinolone antibiotics, such as moxifloxacin[14]. Since the late 1990s until 2007, this strain was not reported outside Europe and North America, but a survey of the period 2008–2010 showed global spread had occurred[15]. This can be explained by the movement of people, animals, vectors, and inanimate objects across international borders[13]. The incidence of CDI varies widely in different studies depending on the type of hospital care (acute care *vs*. long term), patient population (elderly *vs*. young) and the presence or absence of nosocomial outbreaks. For example, the incidence of CDI is increased in long term hospitals due to prolonged hospitalization and increased number of elderly patients (patients older than 65 years). Moreover, high incidence of CDI has been reported during outbreaks in many countries such as Canada, Europe and the USA. Generally, the overall incidence of CDI ranges from 2 to 6 cases per 10000 patient days[16–19], and there is no sexual predilection. Increased incidence of CDI is coupled with more serious clinical presentation and, increased
morbidity and mortality. The 30-d mortality ranges from 24.0% to 50.0% [20,21].

4. Risk factors

The chief risk factor for the disease is prior to expose antimicrobials. In the hospital setting, the majority of CDI cases is associated with the use of antibiotics. However, up to 2/3 of cases of community-acquired CDI in a recent study did not have antibiotics in the 90 d prior to the development of symptoms suggesting a different pattern of disease between community-acquired and nosocomial cases [9].

Nearly all antimicrobials have been reported to be associated with CDI. Agents who are active against anaerobic bacteria are considered to present the greatest risk factor, presumably because of their ability to alter intestinal microecology [22]. The risk of developing disease after exposure to antimicrobials is highly variable and depends on host factors (age, diet, immune system function, etc.), the type and dose of antibiotic, and the duration of treatment. Although clindamycin usage was closely linked with the disease historically and still constitutes to be a major risk factor, more cases at the present are attributed to therapy presumably because of their ability to alter intestinal microecology. The incubation period between spore ingestion and the onset of the disease has not been determined. However, most patients develop diarrhea during or shortly after taking antibiotics, or up to 8-10 weeks after its discontinuation [27-29]. CDI has a wide spectrum range of clinical presentations from mild, self-limiting diarrhea, to serious diarrhea, pseudomembranous colitis and life-threatening fulminant colitis, which may result in death. Watery diarrhea is the cardinal symptom of CDI [30]; it varies from mild, moderate to severe. Patients with colitis (with or without pseudomembranous colitis) usually present with watery diarrhea up to 10-15 times daily, abdominal cramping and pain, fever, anorexia and nausea [30]. A leukemoid reaction, hypoalbuminemia and occult colonic bleeding may occur, but visible blood is rare. Approximately, 3% to 8% of CDI patients develop a fulminant disease, defined as patients whose course is complicated by perforation, severe ileus with toxic megacolon, hypotension requiring pressors, or refractory septicemia [31,32]. Although diarrhea may be present, these patients may have little or no diarrhea as a result of toxic megacolon and paralytic ileus.

6. Diagnosis

The diagnosis of CDI is based on the clinical features, confirmation of the presence of either toxin A alone or toxins A and B together in the stool, and sometimes endoscopy to verify pseudomembranous colitis. CDI should be suspected in any hospitalized patient who develops diarrhea or any person in the community who develops diarrhea after a course of antibiotics or in association with immunosuppressive therapy. However, diagnostic tests to confirm CDI are essential. Testing for *C. difficile* or its toxins should be performed only on diarrheal (unformed) stool unless ileus due to *C. difficile* is suspected. Table 2 summarizes the accuracy of various diagnostic tools used for the diagnosis of CDI.

The tissue culture cytotoxicity assay which detects the presence of *C. difficile* cytotoxin (toxin B) in stool filtrate is considered to be the “gold standard” for diagnosis as it can detect as little as 10 pg of toxin in stool and have a high sensitivity (94%-100%) and specificity (99%-100%) shown in Table 2. However, the test has long turn-around time (1-3 d) and high cost and it requires a tissue culture facility [33-35]. Enzyme immunoassay (EIA) for *C. difficile* glutamate dehydrogenase (GDH) antigen is used to detect the presence of the enzyme GDH, which is produced by all strains of *C. difficile* isolates, with toxigenic and non-toxigenic. This test is highly sensitive (75%-90%) and toxicogenic strains. However, it is no more than 50% specific with low positive predictive value, because it does not differentiate toxin-producing from non-toxigenic strains of *C. difficile*. Moreover, antibodies against *C. difficile* GDH in this test may cross-react with the same enzyme in other clostridial species [35,36]. To overcome this problem and to increase the specificity of the test, a 2-step method has been recently suggested by the Infectious Diseases Society of America/Society for Healthcare of America guidelines on diagnostic testing of *C. difficile*. This strategy uses EIA detection of GDH and then uses the cell cytotoxicity assay
EIA for *C. difficile* toxin is used to detect the presence of *C. difficile* toxins A and B in stool. It remains the main diagnostic modality in most clinical settings, because of its rapidity and ease of performance. This test provides results within 2 to 6 h with a specificity of 95%–100%; however, it has reduced sensitivity (65%-85%)[33–38]. A relatively high false-negative rate, could be explained by the fact that 100 to 1000 pg of a toxin must be present for the test to be positive[3].

Diagnostic strategies targeting nucleic acids, including PCR methods and RT–PCR methods have been developed for the detection of the genes encoding TcdA and/or TcdB[39]. Infectious Diseases Society of America/Society for Healthcare of America guidelines on diagnostic testing of *C. difficile* suggest that more data are needed on nucleic acid amplification tests before it can be implemented for wide-scale use[37]. However, RT–PCR methods for the detection of *C. difficile* toxin B gene have recently been employed with high sensitivity (88%-100%) and specificity (96%-100%)[40–42].

*C. difficile* can be isolated by means of anaerobic culture of stool. Although the test is highly sensitive, it is seldom used for clinical diagnosis, as it takes 2–3 d to complete and does not distinguish toxigenic strains from non-toxigenic strains[43]. However, this test is essential for epidemiological studies (i.e., for strain typing in outbreaks of nosocomial infection)[37].

Sigmoidoscopy and colonoscopy are not indicated for patients with classic clinical findings and a positive stool toxin assay and should be avoided in fulminant colitis because of the risk of perforation[44,45]. However, endoscopy is helpful in special situations such as when other diseases need to be ruled out, the diagnosis is in doubt or the clinical situation demands rapid diagnosis, or a stool sample cannot be obtained because ileus develops[44–48].

Radiographic imaging studies can be used to assist the severity of CDI. Abdominal imaging studies may reveal dilated colon, air–fluid levels (mimicking an intestinal obstruction or ischemia), and “thumb printing” (scalloping of the bowel wall) due to an edematous colonic mucosa[43]. Abdominal CT scanning also can help categorize the severity of colitis, and it can diagnose fulminant colitis rapidly. It may show ascites, free air, colon wall thickening, or dilation[25,49].

### 7. Treatment

The first step in treating a patient with documented or suspected CDI includes stopping the inciting agent such as antimicrobials, if possible, and providing appropriate supportive care with hydration and electrolyte replacement.

<table>
<thead>
<tr>
<th>Clinical picture</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non–severe CDI</td>
<td>Metronidazole: 250 mg orally 4 times daily or 500 mg orally every 8 hours daily (given for 10 d; if failed to respond to metronidazole after 5–7 d or patient has contraindications. Vancomycin: 125–250 mg orally 4 times daily for 10 d</td>
</tr>
<tr>
<td>Fulminant disease (severe CDI)</td>
<td>Vancomycin (125 mg p.o. or via nasogastric tube/4 h daily for 10 d) plus intravenous metronidazole (500 mg every 8 h daily for 10 d; if severe paralytic ileus or toxic colon is suspected, treat rectal vancomycin 500 mg in 250 mL normal saline every 6 h daily as a retention enema; if medical therapy fails or perforation develop, patients will be in surgical intervention with colectomy and ileostomy.</td>
</tr>
<tr>
<td>Recurrence of CDI</td>
<td>First recurrence: It can be treated with the same drug as was used during the first episode. Second or subsequent recurrence: 65%–85% 95%–100%</td>
</tr>
<tr>
<td>(Reappearance of diarrhea and other symptoms after successful treatment)</td>
<td>High dose vancomycin: 250–500 mg orally every 6 h for 10 d followed by tapered doses of vancomycin for 21 d or by pulsed–dosing of vancomycin therapy 125 mg every 3 d for 21 d</td>
</tr>
<tr>
<td></td>
<td>Vancomycin with rifampin vancomycin: 125 mg orally 4 times per day and oral rifampin 600 mg 2 times per day for 7–10 d</td>
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<td></td>
<td>Vancomycin with colestipol</td>
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<td></td>
<td>Vancomycin with the probiotic Saccharomyces boulardii</td>
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</tbody>
</table>

**Table 1**

Treatment of CDI.

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
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<tbody>
<tr>
<td>Tissue culture cytotoxicity assay</td>
<td>94–100</td>
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</tr>
<tr>
<td>Glutamate dehydrogenase enzyme immunoassay</td>
<td>75–90</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Enzyme immunoassay for <em>C. difficile</em> toxin</td>
<td>65–85</td>
<td>95–100</td>
</tr>
<tr>
<td>RT–PCR</td>
<td>88–100</td>
<td>96–100</td>
</tr>
<tr>
<td>Anaerobic culture of stool</td>
<td>89–100</td>
<td>48–68</td>
</tr>
</tbody>
</table>

**Table 2**

Sensitivity and specificity of test used for the diagnosis of CDI. &.

<table>
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<tr>
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as needed\textsuperscript{37}. Anti-diarrheal medications should be avoided as they may obscure symptoms and precipitate toxic megacolon.

Metronidazole and vancomycin are the mainstays of antimicrobial therapy for CDI. Although both drugs are effective for treatment of this disease, they are matters of much ongoing debate, as none of them is clearly superior to the initial cure of this infection\textsuperscript{26,50,51}. Therefore, local guidelines, which are based on local epidemiology of CDI, should be developed in each country to solve this debate, as the majority of treatment guidelines are formulated in the developed countries. Treatment modalities of CDI are summarized in Table 1.

8. Metronidazole

The preference of metronidazole as a first-line treatment is supported by its low-cost and avoidance of selection for vancomycin-resistant enterococci, even though subsequent data have suggested that the risk of bowel, vancomycin-resistant enterococci colonization is equivalent with these two drugs\textsuperscript{52}. Metronidazole also has the advantage of allowing intravenous administration in patients who are unable to take oral medications. Oral or intravenous metronidazole therapy (250 mg four times daily or 500 mg every 8 h daily) given for 10 d is recommended as the initial treatment of choice.

9. Vancomycin

Vancomycin can be used as initial therapy for patients with contraindications or intolerance to metronidazole or for those who have severe CDI or who are living in areas with local prevalence of the NAP1/027\textsuperscript{53}. Moreover, vancomycin should be reserved for patients who fail to respond to metronidazole after 5–7 d. Vancomycin (125–250 mg orally four times daily for 10 d) is the recommended second line therapy.

In the recommended doses, metronidazole and vancomycin have similar efficacy, with response rates 90%–97%. The therapeutic response usually involves the resolution of fever and of diarrhea on the fourth or fifth day.

Patients with fulminant disease should be treated with both oral vancomycin and intravenous metronidazole despite a lack of evidence from clinical trials about combination therapy. When severe paralytic ileus is suspected, intraluminal vancomycin via a long catheter in the small intestine or retention enema should be considered\textsuperscript{49}.

In patients with suspected CDI who received empiric antimicrobial therapy, if the stool toxin assay result is negative, the decision to stop, or to continue treatment must be individualized\textsuperscript{49}.

Other antibiotics that may be considered as alternative therapy for CDI in the unusual events (e.g., allergy or intolerance to both first-line agents) include fidaxomicin, bacitracin, teicoplanin, fusidic acid and nitazoxanide, rifaximin and rifampin. Most of the active comparator studies found no statistically significant difference in efficacy between vancomycin and these agents for initial therapy of CDI except teicoplanin and fidaxomicin. Teicoplanin appears to be better than vancomycin for bacteriologic cure and has borderline superior effectiveness in terms of symptomatic cure\textsuperscript{54}, while fidaxomicin appears superior to vancomycin in terms of lower recurrence rates and global clinical cure rates (i.e., clinical cure rates combined with recurrence rates)\textsuperscript{10}.

None antimicrobial therapies such as intravenous immunoglobulin, specific monoclonal antibodies therapy, toxin-binding agents (e.g., cholestyramine, tolevamer), probiotics [e.g., Saccharomyces boulardii (S. boulardii)] and faecal therapy have been studied for use as stand-alone treatments or in combination with standard therapy for CDI.

Surgical intervention (colectomy) is indicated in patients with toxic megacolon who are not responding to medical treatment, in patients with ongoing severe sepsis despite antibiotic treatment, and/or when colonic perforation is clinically suspected\textsuperscript{55}.

After effective treatment of CDI, about 10%–30% of patients with CDI experienced recurrence\textsuperscript{56}. These recurrences can correspond to either a relapse of the original infection or a reinfection with a different strain. Risk factors for recurrent CDI include advanced age, administration of additional antibiotics, prolonged hospital stay, concomitant use of antacid medications, and long-term dialysis\textsuperscript{57,58}. First recurrences can be treated using the same drug as was used during their first episode\textsuperscript{49}. For patients with multiple recurrences of CDI or with CDI that is not responsive to standard treatments, there is a lack of randomized, large prospective, controlled clinical trials to suggest the optimal approach to these patients. However, higher doses of orally administered vancomycin (250–500 mg every 6 h for 10 d) followed by tapered or pulsed doses of vancomycin have been used\textsuperscript{49,59,60}. In addition, a tapered regimen of vancomycin consisted of 500 mg/d during Week 1, 250 mg/d during Week 2, 125 mg/d during Week 3, and a pulsed dose of 125 mg every 3 d during
Weeks 4–6 has been found to be effective. Failure of these treatment strategies may prompt administration of donor stool from a healthy individual. This treatment modality is called fecal microbiota transplant. The infusion of a fecal suspension from a healthy individual into the gastrointestinal tract of a patient with CDI can be achieved by colonoscopy, retention enema, nasogastric/nasoduodenal tube, self–administered enema or by esophagogastroduodenoscopy. In 317 patients with recurrent CDI and pseudomembranous colitis treated across 27 case series and reports, fecal microbiota transplant was highly effective, showing disease resolution in 92% of cases. Other therapeutic options include treatment with vancomycin in combination with rifampin or with anion–binding resins such as colestipol, or treatment with vancomycin followed by course of rifaximin. Small randomized clinical trials support the use of vancomycin with the probiotic S. bouardiwi. A meta–analysis of six RCTs of different probiotics, including S. bouardiwi showed that probiotics had a significant efficacy to prevent subsequent recurrences of CDI. Therapeutic options of recurrent CDI are summarized in Table 1.

10. Prevention

Prevention of CDI is challenging health authorities. However, preventive measures are taken such as implementation of infection–control measures (contact isolation and following good hand–washing by everyone). In addition, the cornerstone to controlling this infection is the control of antimicrobial prescribing. A multidisciplinary antibiotic management program to restrict the inappropriate use of antibiotics can lead to a significant decrease in nosocomial infections caused by C. difficile.

In conclusion, CDI is the cause of approximately 10%–35% of all cases of antibiotic–associated diarrhea and is the most common infectious cause of nosocomial diarrhea, which is associated with substantial morbidity, mortality and increased healthcare costs. Spectrum of presentation of CDI ranges from mild, self–limiting diarrhea, to serious diarrhea, pseudomembranous colitis and life–threatening fulminant colitis, which may result in death. Prompt identification of patients with symptomatic CDI is essential as majority of patients respond quickly to antimicrobial therapy. Prevention is best accomplished by implementation of infection–control measures and by judicious use of antimicrobial agents.

Conflict of interest statement

We declare that we have no conflict of interest.

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