Chapter 6

Clostridium difficile in the ICU

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Additional information is available at the end of the chapter

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Abstract

Clostridium difficile has become an increasingly common infectious agent in the healthcare setting. It is generally associated with antibiotic use and causes diarrhea as well as other complications such as pseudomembranous colitis (PMC) and toxic megacolon. This organism poses a serious threat to patients in the intensive care unit (ICU) as it increases hospital length of stay, morbidity, and mortality. Recurrence rates are typically higher in the ICU population as those patients usually have immunocompromised systems, more exposure to antibiotics and proton pump inhibitors, loss of normal nutritional balance, and alterations in their colonic flora. Emergence of more virulent and pathogenic strains has made combating the infection even more difficult. Newer therapies, chemotherapeutic agents, and vaccinations are on the horizon. However, the most effective treatments to date are ceasing the inciting agent, reduction in the use of proton pump inhibitors, and prevention of the disease. In this chapter, we will explore the risk factors, diagnosis, treatment, and prevention of *C. difficile* infections (CDI) in the ICU.

Keywords: *Clostridium difficile*, intensive care unit, pseudomembranous colitis, toxic megacolon, NAP1

1. Introduction

Clostridium difficile is a gram-positive, spore forming anaerobic bacillus that can survive on environmental surfaces for years in the spore (dormant) stage. First cultured in 1935 by Hall and O'Toole, *C. difficile* was a relatively unknown organism until 1978 [1]. It was initially thought to be a mostly harmless colonizer of the human intestinal tract. In 1893, a young woman died after gastric surgery from a "diphtheric colitis" as described by John Finney and Sir William Osler [2]. In 1978, Dr. John G. Bartlett determined that *C. difficile* was associated

with the ailment that had killed the young woman 85 years prior and was now termed pseudomembranous colitis (PMC) [3].

C. difficile is currently the most common cause of antibiotic-associated pseudomembranous colitis in the healthcare setting and caused 20–30% of those with uncomplicated antibiotic-associated diarrhea [4]. According to the Centers for Disease Control, the number of cases of *C. difficile* infections (CDIs) in patients discharged from acute-care facilities doubled from 149,000 to 300,000 between 2001 and 2005 and based on recent trends has reached nearly 500,000 cases per year [5, 6]. There are occasionally other causes of antibiotic associated colitis due to organisms such as *Staphylococcus aureus, Klebsiella oxytoca*, enterotoxin-producing strains of *Clostridium perferingens*, or *Salmonella* [7]. Treatment duration for most microbial infections is usually around 14 days but prolonged exposure to broad-spectrum antibiotics has been associated with increased rates of both initial *C. difficile* infection and recurrence of *C. difficile* infection [8, 9].

The damage caused by *C. difficile* is due to the ability of the microbe to attach to the mucosa of the colon and release of exotoxins into the mucosa. The toxins may cause diarrhea, dilation of the colon (toxic megacolon), (**Figure 1**) sepsis, and death. Transmission is person to person via the fecal-oral route with ingestion of spores that germinate into vegetative bacteria within the small intestine. *C. difficile* produces two toxins—toxins A and B. These are large proteins (308 and 270 kDa, respectively) that cause severe inflammation and necrosis of the mucosal tissue by inactivating Rho, Rac, and Cdc42 targets within the epithelial cells through irreversible glycosylation [10, 11]. Toxin B is thought to be a gene duplication event of toxin A but is 10 times more cytotoxic than toxin A [12, 13].

The bacteria are normally found in up to 25% of hospitalized adults and up to 70% of the hospitalized pediatric population [14]. It does not cause disease until the normal flora is disrupted and *C. difficile* is allowed to proliferate. *C. difficile* infection has a very high economic cost

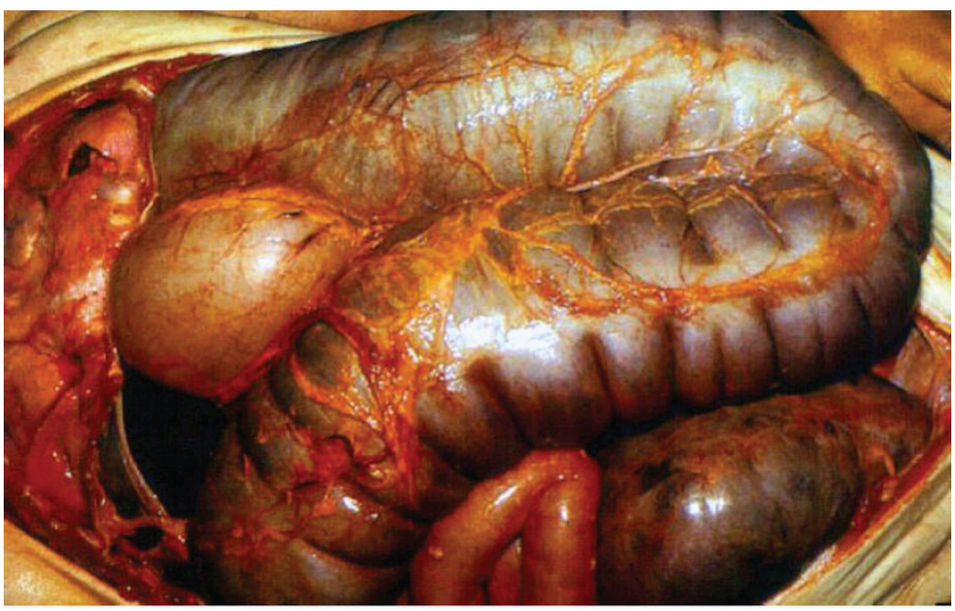

Figure 1. Toxic megacolon related to *Clostridium difficile* infection. Credit: University of Pittsburgh Department of Pathology.

associated with it in the United States and Europe due to high reinfection rates of approximately 30% and risk of relapse of 60% producing over 900,000 cases and an estimated $1.1–$3.2 billion per annum burden [15, 16].

Antibiotic therapy that disrupts the normal flora are usually to blame but proton pump inhibitors and other gastric acid suppression medications are increasingly associated with increases in *C. difficile* overgrowth [17]. Although the cephalosporin class, clindamycin, and the fluoroquinolones are all thought to place a patient at a higher risk of infection, all antibiotics, including oral vancomycin and metronidazole, can induce pseudomembranous colitis due to their ability to eliminate most normal intestinal flora in combination with the increased resistance patterns of more virulent strains of *C. difficile* [3, 14, 18, 19] The NAP1 strain is particularly important as it is associated with fluoroquinolone use and has risen in incidence in Canada, Europe, and the United States with increased virulence, toxin production, mortality, treatment failures, and relapse [20, 21].

The incidence and virulence of this pathogen has been steadily increasing over the last several decades contributing to higher morbidity and mortality. The increasingly older patient population with its higher acuity of medical issues and immunosenescence, the increased use of proton pump inhibitors, and the continued use of antibiotics has all allowed *C. difficile* to leave a greater impact in healthcare settings. In this chapter, we will explore the risk factors, diagnosis, treatment, and prevention of *C. difficile* infections in the intensive care unit (ICU).

2. A historical perspective on *Clostridium difficile*

Pseudomembranous colitis became a common complication of antibiotic use in the 1950s at the beginning of the antibiotic era and was found often in postoperative patients with an incidence of 14–27% [22, 23]. *S. aureus* was the suspected pathogen and standard treatment became oral vancomycin [24].

Tedesco et al. described "clindamycin colitis" in 1974 utilizing culture and endoscopy to diagnose pseudomembranous colitis associated with antibiotic use after 21% of patients given clindamycin developed diarrhea and 10% developed pseudomembranous colitis [25]. Incidentally, *S. aureus* did not grow from stool cultures from any of the patients. This study, more than prior publications, crystallized the connection between antibiotic use and development of pseudomembranous colitis. Green, while studying penicillin-induced death in guinea pigs in 1974 described stool cytopathic changes that he attributed to the activity of a latent virus. In retrospect, this appears to be the first identification of the effects of *C. difficile* cytotoxin [26]. Between 1977 and 1979, using hamster models, multiple teams of researchers identified *C. difficile* as the causative agent of pseudomembranous colitis, including detecting toxin B produced by *C. difficile* [27–30]. "Clindamycin colitis" became known as "antibiotic-induced colitis" and most of the studies done in the 1980s demonstrated that cephalosporins were the most frequently implicated agents followed secondly by broad-spectrum penicillins, including amoxicillin [30–33].

Although there are many causes of pseudomembranous colitis, the majority of cases since the late 1970s have been caused by *C. difficile* infection. Pseudomembranous colitis is limited to the proximal colon in 20–30% of cases and may therefore be missed by sigmoidoscopy, providing more credence to performing a complete colonoscopy to identify anatomic lesions [25, 34]. With the current availability of *C. difficile* toxin assays, colonoscopy is rarely necessary. The first test used to diagnose *C. difficile* involved neutralization of the cytotoxin by *C. sordellii* antitoxin. This remains the most sensitive and specific diagnostic test, but is expensive and requires 24–48 hours for results [35] that has led to the development of latex particle agglutination [36–38], dot immunoblot [39], PCR [40, 41], stool culture on selective media [42, 43], and enzyme immunoassay (EIA) [44, 45]. Because of differences between the hamster model and humans, it was originally believed that toxin A was important in human disease and many early EIA tests only detected toxin A, leading to false negative tests [46, 47].

3. Clinical signs and symptoms

Watery diarrhea with a distinct odor is usually the hallmark of *C. difficile* infection. Mild disease consists of crampy, watery diarrhea without systemic symptoms. This cohort constitutes 70% of patients with *C. difficile* infection as only about 30% of patients with *C. difficile* infection are febrile and 50% have a leukocytosis [48]. In severe disease, fecal leukocytes are generally high and diagnosis can be confirmed with endoscopy demonstrating pseudomembranous colitis. Other signs and symptoms of severe disease include abdominal pain, leukocytosis, and fever or other systemic symptoms. Leukocytosis is directly correlated with the severity of the disease. The elevation in white blood cell count can be as marginal as 15,000 cells/mL or as high as 50,000 cells/mL. Complications may include paralytic ileus, toxic megacolon, or other life threatening conditions. Postoperative patients and other patients with altered gastrointestinal motility may have pseudomembranous colitis without diarrhea secondary to ileus. Computed tomography is useful with characteristics of colitis readily seen on imaging that may include colonic wall thickening and associated ascites or toxic megacolon [21, 49].

Patients in the ICU tend to demonstrate the same spectrum of disease signs and symptoms as other infected persons. However, due to their illnesses, comorbidities weakened immune system and reduced ability to heal; the progression of the disease may advance more rapidly. Therefore, continual assessment of diarrhea and other symptoms of *C. difficile* infection is necessary as the severity may progress and further impact the already impaired and critical status of the patient in the ICU.

4. Risk factors for *Clostridium difficile* infection

Risk factors for *C. difficile* infection fall under three categories. First category includes disruptions of the endogenous intestinal flora, perturbations of the mucosa, or immunomodulation

by exogenous factors that can occur as a result of medications, procedures, or radiation therapy. Most hospitalized patients with *C. difficile* infection have been exposed to antibiotics within the past 30 days. More recently, it has been noted that medications that suppress gastric acid, including proton-pump inhibitors and H_2-receptor blockers, increase risk of *C. difficile* infection, though study results are not uniform and the mechanism is not known [50–54]. For patients with primary or recurrent *C. difficile* infection, consideration should be given to discontinuation of gastric acid suppressants unless the patient's risk for GI bleeding outweighs the risk of *C. difficile* infection treatment failure. Chemotherapy, medications for autoimmune conditions, transplant medications, and radiation of the bowel increase the risk of *C. difficile* infection by disrupting the normal intestinal mucosal barrier and inhibiting the body's immunodefenses. Nasogastric tubes and enemas, presumably because of alteration of the normal flora and/or pH, increase patients' risk of *C. difficile* infection [55].

The second category of risk factors relates to how patients contract *C. difficile* infection. The most common method is by coming in contact with *C. difficile* spores from the hands of health care workers. Risk of contracting *C. difficile* infection is directly related to length of stay (LOS). Patients with longer LOS have multifactorial risk factors that include more severe illnesses that have a higher likelihood that they will require antibiotics and more prolonged exposure and interactions with health care workers [56, 57]. A patient's risk of contracting *C. difficile* infection is also related to *C. difficile* infection pressure that relates to the number of patients with *C. difficile* infection in a given care area [58]. Certain *C. difficile* strains, including the epidemic BI/NAP1/027 strain, have been isolated from prepared foods, pets, and from livestock [59–61].

The third category of risk factors relates to innate host susceptibility. Age >65 years is related to both an increased risk of primary *C. difficile* infection as well as an increased risk of more severe *C. difficile* infection. It is not known whether this is related to immune senescence, more frequent antibiotic usage, or increased comorbidities. The four comorbidities that place patients at greatest risk are sepsis, pneumonia, urinary tract infections, and skin infections—all of which generally require antibiotics for treatment. Patients hospitalized with higher numbers of conditions are more likely to contract *C. difficile* infection than patients with fewer conditions [48]. More recently, it has been noted that peripartum women and infants also appear to be at increased risk for *C. difficile* infection, including severe *C. difficile* infection related to the epidemic BI/NAP1/027 strain [62, 63]. Patients with inflammatory bowel disease (IBD) are more susceptible to *C. difficile* infection for reasons that are likely multifactorial, including antibiotic exposure, altered gut mucosal integrity, and immunosuppressive therapy. Patients with *C. difficile* infection superimposed on a flare of IBD are at risk for a particularly fulminant course. Because of altered gut physiology, patients with IBD may not develop pseudomembranes and may have a complicated diagnosis. Additionally, administration of glucocorticoids to treat the IBD exacerbation may predispose to *C. difficile* infection progression [64, 65]. Studies have shown that patients with HIV/AIDS or chronic kidney disease requiring hemodialysis are also at increased risk of *C. difficile* infection, possibly due to increased health care worker exposure or less robust immune response [66, 67].

5. Diagnosis

In the modern era, multiple tools have been developed to identify and detect *C. difficile* to include cultures, polymerase chain reaction (PCR), and enzyme immunoassays (EIA). Culturing *C. difficile* is difficult due to the strict anaerobic nature of the organism and the oxygen sensitivity that can kill the living organism. Utilizing an anaerobic chamber with a composition of 5% CO_2, 10% H_2, and 85% N_2, along with an air lock, has allowed the culturing, preservation, and storage of the living organism and spores [35, 43]. Once the organism has been cultured, PCR or EIA techniques can be utilized to detect toxin within the culture. These same techniques can be used independently of a culture to detect toxin within the stool sample. PCR has been successfully used since 1985 to amplify the 8.1 kilo base-pairs of the toxin A gene. Using 35 cycles of alternating 95–55°C temperatures and a Southern blot to isolate the 252 base-pair DNA fragment, PCR has become easy and commonplace for identification of the toxins [40, 41]. EIA has similarly been used since the early 80s for detection of both toxin A and B. The early tests were able to detect levels of toxin to 0.1 ng using a double sandwich microtiter plate with specificities of 98.6% and 100% for toxin A and toxin B, respectively [42–45]. More recently, glutamate dehydrogenase-immunoassay has been used as an initial screening tool with a chemiluminescent toxin-immunoassay for confirmation of both toxins A and B. The combined two-step process has a sensitivity and specificity of 100% [68]. The premise of the EIA tests is that antibodies to the toxins are attached to a plate. When the toxins pass over the antibodies, they become bound. A second preparation of antibodies with a marker attached to them is then added and a device to detect the markers allows for quantitative evaluation of the toxins present.

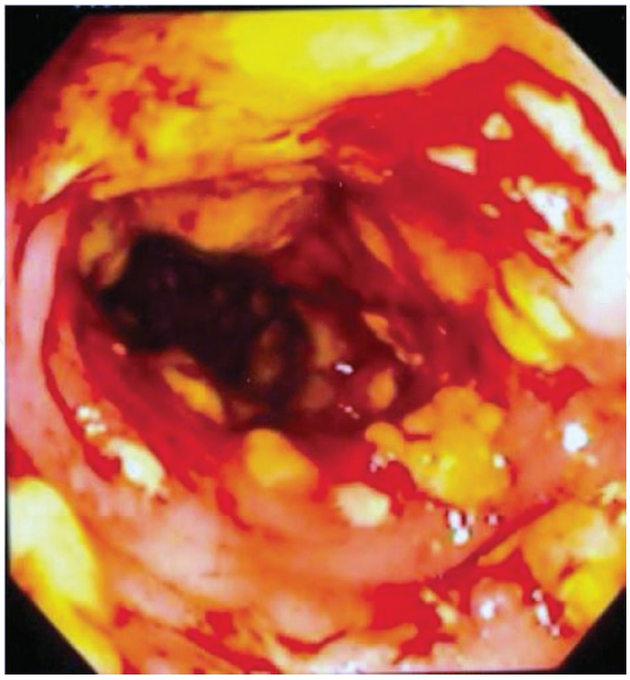

Figure 2. *Clostridium difficile* associated pseudomembranous colitis. Credit: North American Society for Pediatric Gastroenterology, Hepatology and Nutrition.

In addition to laboratory tests, computed tomography is useful to evaluate for toxic megacolon and colitis. When there is high clinical suspicion yet laboratory diagnostic tests have yielded negative results, the definitive test is colonoscopy. The appearance of pseudomembranes in the clinical setting of *C. difficile* infection is confirmatory for the diagnosis (**Figure 2**). **Table 1** displays the various current diagnostic modalities.

Intensivists should be familiar with the tests offered in their institution and be able to interpret the laboratory results in the context of clinical presentation. When clinical suspicion for *C. difficile* infection is high, the intensivist should initiate empiric therapy for *C. difficile* infection regardless of the diagnostic test results [48].

Test	Detection	Time	Usefulness
Culture	*Clostridium difficile*	34 days	Nonspecific and not useful for detection of toxins
Culture-toxins	Toxigenic *Clostridium difficile*	3–4 days	Must have initial growth from culture prior to testing for toxins
Cytotoxin	Toxin B	2–3 days	Costly and time-consuming. Results not immediately available
EIA toxin A & B	Toxin A & B	2–3 hours	Very quick but not sensitive. Need 3 specimens for increased sensitivity
EIA GDH	*Clostridium difficile*	2–3 hours	Screening test. Detects presence of bacteria but not specific
Toxin B gene	Toxigenic *Clostridium difficile*	2–3 hours	Very sensitive for detection of toxigenic strains of *Clostridium difficile* using PCR
Colonoscopy	Pseudomembranes	<1 hour	Very specific and sensitive for the detection of pseudomembranes
CT scan	Colitis	<1 hour	Very sensitive for colitis but not specific for *Clostridium difficile* infections

EIA, Enzyme Immunoassay; GDH, glutamine dehydrogenase; PCR, polymerase chain reaction; CT, computed tomography

Table 1. Diagnostic modalities for the identification of *Clostridium difficile* in the ICU.

6. Treatment

Once diagnosed, the first line of treatment is to discontinue implicated antibiotics, gastric acid suppression medications, and antiperistaltic medications, including narcotics and antimotility agents. Reduced peristalsis may prolong toxin exposure to the colonic mucosa [7]. Unfortunately, a large proportion of patients who develop *C. difficile* infection have documented infections that require treatment with antibiotics, and in the ICU setting, this proportion may reach 60% [69]. When it is not possible to stop antibiotic therapy, it is best to tailor coverage to more narrow spectrum agents once cultures and sensitivities are available. It is recommended to transition as soon as possible to β-lactams, macrolides, aminoglycosides, antistaphylococcal drugs, tetracyclines, and other agents that have a lower likelihood of causing *C. difficile* infection [70].

Oral vancomycin is the only agent currently approved for treatment of *C. difficile* infection, although metronidazole in both oral and intravenous forms has been shown to be effective in treating *C. difficile* infection. Intravenous vancomycin has not been shown to be effective. Metronidazole has become the preferred agent for initial treatment of *C. difficile* infection because of lower cost [71, 72] and because of concerns over the possibility of increased development of vancomycin-resistant enterococcus [73, 74]. Metronidazole should be considered first-line therapy for mild to moderate *C. difficile* infection; however, it does have disadvantages compared to oral vancomycin. In a study involving 207 patients with *C. difficile* infection, 22% of patients remained symptomatic after 10 day therapy with metronidazole and 27% developed a relapse [75]. In a separate randomized trial involving 150 patients, the cure rate for metronidazole was only 76% compared with a 97% cure rate after treatment with vancomycin for the treatment of severe *C. difficile* infection [49]. Based on these studies and other data, oral vancomycin should be considered superior in the treatment of severe infections when GI motility is intact (**Table 2**) [49]. The pharmacology of oral vancomycin lends itself to being more effective as it is not absorbed by the GI tract and reaches the colon in high concentrations. The usual dosing regimen of 125 mg achieves levels of vancomycin 500–1000 times the minimal inhibitory concentration (MIC) of 90% of *C. difficile* in stool [48].

If the patient has ileus or severe pseudomembranous colitis and medication cannot be given orally, the use of rectal instillation of vancomycin solutions is supported by case reports [70, 76, 77]. The addition of intravenous metronidazole to either oral or intracolonic vancomycin in severely ill patients with ileus has been described, although this approach has not been adequately studied [78, 79].

Fidaxomicin is the first member in a new class of narrow spectrum macrocyclic antibiotics that are enterally administered and minimally absorbed in the GI tract. Having excellent *in vitro* and *in vivo* activity against *C. difficile*, including NAP1/BI/027 strains, and, while exhibiting limited activity *in vitro* and *in vivo* against components of the normal gut flora, fidaxomicin is an excellent candidate for replacing other agents in the treatment of *C. difficile* infections [80]. In a prospective, multicenter, double-blind, randomized, parallel-group trial involving 596

Severity	Preference	Medications
Mild CDI	1st line Alternate (PO) Alternate (IV)	Metronidazole: 500 mg PO every 8 hours Vancomycin: 125 mg PO every 6 hours or Fidaxomicin: 200 mg PO every 12 hours Metronidazole: 500 mg IV every 8 hours
Severe CDI	1st line Alternate (IV)	Vancomycin: 125 mg PO every 6 hours Metronidazole: 500 mg IV every 8 hours
Life-threatening CDI	1st line	Vancomycin: 500 mg every 6 hours via NGT or by enema plus Metronidazole: 500 mg IV every 8 hours
Relapsed CDI	1st line	Treatment based on severity as above

Table 2. Treatment modalities for *Clostridium difficile* infections.

patients, of which 287 received fidaxomicin and 309 received vancomycin, 88.2% of patients in the fidaxomicin group and 85.8% of those in the vancomycin group met the criteria for clinical cure. In addition, treatment with fidaxomicin was associated with a significantly lower rate of recurrence than was treatment with vancomycin (15.4 vs. 25.3%). More studies are warranted but results are promising [49, 81, 82].

Regardless of the type of medication, early treatment has been supported as the most effective pharmacologic treatment. A study by Zahar et al. conducted in three French ICUs has demonstrated that early treatment of ICU-acquired *C. difficile* infection results in mortality rates consistent with a control population of other ICU patients that have developed diarrhea that is not *C. difficile* infection associated. Treatment was initiated within 24 hours of onset and consisted of either metronidazole or oral vancomycin. The study involved 5,260 patients with an incidence of ICU-acquired diarrhea of 9.7%. All those with diarrhea were tested for *C. difficile* infection and 13.5% of those tested had confirmed toxin A or B by EIA and further confirmation by culture. None of the positive cultures produced any of the hypervirulent NAP1/027 strains seen in North American outbreaks. Overall mortality of ICU-acquired *C. difficile* infection was not independently associated with higher mortality rates compared to other patients with diarrhea in the ICU when matched for severity of illness, comorbidities, or complications occurring in the ICU. However, both the overall hospital stay and ICU stay was prolonged in the ICU-acquired *C. difficile* infection patients when compared to ICU patients as a whole (median 4 vs. 20 days) and ICU patients with diarrhea not associated with *C. difficile* infection (median 17 vs. 20 days). Despite these prolonged median stays, analysis did not demonstrate a statistically significant difference in length of stay with an estimated increase in overall ICU stay of 6.3 days ± 4.3, $p = 0.14$ compared to other ICU patients with diarrhea [83].

Microbial therapy with fecal transplantation can be accomplished with instillation of liquid preparations of stool from healthy donors. This method has proven successful for treating recurrent *C. difficile* infection in 70–100% of cases [84]. Probiotics may prevent attachment of *C. difficile* to epithelial cells and can reduce the incidence of *C. difficile* infection. *Saccharomyces boulardii* in particular has proven to be effective [49] whereas the use of *Lactobacillus* with conventional antibiotic therapy has shown mixed results including some studies showing no benefit in the treatment of *C. difficile* infection in several randomized controlled trials [85–88].

Use of anion exchange resins, such as cholestyramine and colestipol, with the hope of binding *C. difficile* cytotoxins in the treatment of *C. difficile* infection, has not only been shown to be effective [89, 90], but also carries the theoretical risk of binding intraluminal vancomycin, thus resulting in subtherapeutic vancomycin levels [91]. Intravenous immunoglobulins have been suggested for treatment of *C. difficile* infection but due to an insufficient evidence base and conflicting data, its use cannot be generally recommended until further studies have been conducted [92, 93]. Subtotal colectomy should be considered if there is no response to medical therapy within 3–4 days or if the patient remains seriously ill to avoid complications such as colonic perforation and sepsis [7].

7. Treatment failure and relapse

Patient characteristics that predispose to metronidazole failure include low serum albumin, continued exposure to the inciting antibiotic, and residence in the ICU [94, 95]. Particularly worrisome and concerning is the finding that relapsing or recurrent infections occur in up to 30% of patients treated for *C. difficile* infection whether the initial treatment was metronidazole or vancomycin [96]. This could be due to reinfection with the same endogenous strain or from a different strain acquired exogenously. Patients that had an initial infection followed by reinfection have a 50–65% chance of further repeated episodes. A metaanalysis by Garey et al. found that reexposure to antimicrobials, gastric acid suppression, and older age are all associated with an increased risk of recurrent *C. difficile* infection [97]. Patients that have three or more episodes of *C. difficile* infection, considered to be multiple *C. difficile* infection recurrence, are best treated with a tapered regimen of oral vancomycin. The initial dose of vancomycin administered is at the usual 125 mg by mouth four times a day for 10–14 days but then one dose per day is removed one week at a time until the patient is taking one dose every 2–3 days. The rationale for this regimen is that as the doses are spaced out, the colonic flora has time to regenerate [48].

8. Generating optimal colonic flora for risk reduction

There is an urgent need for alternative means of preventing and treating *C. difficile* infection in high-risk individuals. Metagenomics have improved our understanding of the "colonization resistance barrier" and how this could be optimized. The "colonization resistance barrier" in the normal healthy colon consists of high microbial diversity, substrate/area competition, immune response modulation and short-chain fatty acid (SCFA) production [16, 98]. These factors are often missing in the elderly. Decreased pH, oxidation-reduction potentials, and higher concentrations of short-chain fatty acids have been suggested to inhibit *C. difficile* growth and toxin production throughout *in vitro* and *in vivo* studies. There is, therefore, evidence in support of a colonization resistance barrier against *C. difficile* infection [16, 98].

For instance, *in vitro, Bifidobacterium longum* and *Bifidobacterium breve* have been show to significantly reduce the growth of the toxigenic strain *C. difficile* LMG21717 [99]. In a randomized, placebo-controlled, double-blind trial at a long-term elderly care facility, the effectiveness of a *Lactobacillus casei* strain Shirota (LcS) infused beverage was demonstrated by altering *Clostridium* infection rates among the residents. Daily consumption of the beverage resulted in a significantly lower incidence of fever and improved bowel movements. When compared to a resident control group drinking a placebo beverage, stool studies from the experimental LcS group showed significantly higher number of both *Bifidobacterium* and *Lactobacillus* ($p < 0.01$), significantly lower number of destructive bacteria such as *C. difficile* ($p < 0.05$), and a higher fecal acetic acid concentration. This study was also conducted among the facility's staff and a significant difference in the intestinal microbiota, fecal acetic acid, and pH was also observed between the LcS and placebo groups [100].

There is some evidence to support that plant based diets may reduce the number of pathobionts such as *C. difficile* and increase the number of protective species such as Lactobacillus [100–103]. Altered flora with resulting altered bile metabolism within the gut by flora favored by plant-based diets have implications in colonocyte protection [102]. Intestinal microbiota are able to produce short chain fatty acids (SCFA), such as acetate, propionate, and butyrate, through metabolism of dietary fiber. These SCFA have been shown to be colonocyte protective. A strong positive correlation has been found between *Faecalibacterium prausnitzii* and butyrate production in the gastrointestinal tract, suggesting that this species may be associated with higher fiber intake and reduced risk, not only for *C. difficile* infection, but also for other common comorbidities in the elderly including cardiovascular disease, colon cancer, diabetes, and obesity [104]. A move toward a diet that decreases risk for contracting *C. difficile* infection should be encouraged, not only in the elderly, but also generally, because of the broad implications.

9. Prevention of hospital spread

Disinfectant products based on quaternary ammonium compounds, commonly used to clean patient rooms, are not sporicidal. Therefore, using sporicidal hypochlorite-based disinfectants on surfaces is recommended. However, use of antisporicidal agents outside an outbreak is not associated with lower rates of *C. difficile* infection [105, 106].

Hand hygiene is the most important preventive measure to reduce transmission of *C. difficile* spores. Soap and water has been demonstrated to be superior to alcohol based hand rubs and other forms of hand sanitation with regard to transmission by healthcare workers [21, 107]. Hospital hygiene hand protocols should be followed assiduously at all times. Other precautions that should be utilized include isolation of the patient, barrier precautions, and use of chlorine based chemical wipes [107]. These precautions should not be lifted based on stool studies as there are no diagnostic methods to determine response to treatment. Rather, the decision should be made on clinical signs and symptoms with resolution of diarrhea, fevers, and leukocytosis. A strong antibiotic stewardship program is essential to limit the use of antibiotics that may cause *C. difficile* infection and is generally a good principle to follow. It has been demonstrated that up to 25% of antibiotic administration is not indicated, even in the ICU [108].

10. *Clostridium difficile* infection in the intensive care unit

Diarrhea is a common problem in the ICU affecting up to 40% of patients admitted. Severely burned patients may have an incidence of greater than 90% [109, 110]. Enteral tube feeding is the most common cause of diarrhea in the ICU; other causes include hypoalbuminemia, intestinal ischemia, and medications. *C. difficile* infection is the most common infectious cause of diarrhea in the ICU [111, 112]. The severity of *C. difficile* infection is increasing which is possibly related to the emergence of more virulent strains such as the BI/NAP1/027 strain, prompting more admissions to the ICU for management of *C. difficile* infection related complications [113].

In a systematic review and metaanalysis of 22 published studies from 1983 to 2015 that included 80,835 ICU patients, the effects of *C. difficile* infection on morbidity and mortality were investigated. Karanika et al. found that prevalence of *C. difficile* infection among ICU patients was 2% but 5-fold greater in those patients with diarrhea (11%). Those patients that were diagnosed with *C. difficile* infection had a 25% incidence of the severe form of the disease and diagnosed with pseudomembranous colitis. ICU mortality was not significantly different between the group with *C. difficile* infection and the non*C. difficile* infection group based on seven studies that enrolled a combined 12,165 patients. However, the overall hospital mortality between those same groups was significantly increased in the *C. difficile* infection group with 32% mortality compared to 24% ($p = 0.03$). Similarly, length of ICU and hospital stay among *C. difficile* infection patients was longer when compared to non*C. difficile* infection patients. Based on five studies with over 10,000 patients, *C. difficile* infection patients had an average ICU stay of 24 days and overall hospital stay of 50 days compared to 19 days and 30 days, respectively, for the non*C. difficile* infection group ($p = 0.001$) [114].

Even though only 3% of patients with *C. difficile* infection require subtotal colectomy for fulminant *C. difficile* colitis, 20% of ICU patients with severe *C. difficile* infection will still require partial colectomy or diversion [115, 116]. Colectomy in this setting is associated with a 50% mortality [90]. Mortality rates are lower when surgical intervention is undertaken within 48 hours of lack of response to medical therapy [117]. During NAP1/027 outbreaks, patients with age >65 years, leukocytosis and elevated lactate appear to benefit the most from early colectomy [118].

In a series of 29 patients with severe or severe/complicated *C. difficile* infection refractory to oral vancomycin ± rectal vancomycin and intravenous metronidazole therapy who underwent fecal microbiota transplantation (FMT) plus continued vancomycin, overall treatment response was 93% (27/29), including 100% (10/10) for severe *C. difficile* infection and 89% (17/19) for severe/complicated *C. difficile* infection. A single FMT was performed in 62%, two FMTs were performed in 31%, and three FMTs in 7% of patients. Continued use of non *C. difficile* infection antibiotics predicted repeat FMT. Thirty-day all-cause mortality after FMT was 7%. Of the two patients who died within 30 days, one underwent colectomy and succumbed to sepsis; the other died from septic shock related to *C. difficile* infection [84]. Further research into the use of FMT combined with continued vancomycin is needed.

11. Modern outbreaks

In 2003, a major outbreak of *C. difficile* occurred in Quebec, Canada and was identified as ribotype 027, strain BI/NAP1. This strain has been identified in >50% of all isolates from hospitals in Europe and North America [4, 10, 20]. Prior to the 2003 outbreak, this strain only accounted for 14 of over 6000 (<0.02%) typed strains collected from U.S. cases during the period of 1984 to 1993. Following the 2003 outbreak in Canada, 96 of 187 (51%) strains tested positive for 027 in eight U.S. outbreaks [119].

The BI/NAP1/027 strain belongs to a hypervirulent group of strains along with types 001, 017, and 078. In particular, the binary toxin produced by 027 was not seen previously. It is

thought to be synergistic with the production of toxin A and B. Strain BI/NAP1/027 was found to be highly resistant to fluoroquinolone classes of antibiotics and was also found to produce 16-fold higher concentrations of toxin A and 23-fold higher concentrations of toxin B than less virulent toxinotype 0 strains. The binary toxin has been associated with more severe diarrhea when combined with toxin A and B. When produced alone, binary toxin does not appear to produce disease [3, 10] but does appear to be a marker of both *C. difficile* infection severity and recurrence [120]. The emergence is generally believed to be related to fluoroquinolone exposure though not to the particular type of fluoroquinolone [121, 122].

12. Conclusions

C. difficile is a very diverse group of toxin producing organisms. Newer technologies have allowed the identification of numerous toxinotypes and ribotypes with varying virulence factors and toxin production. Multiple lineages contain hypervirulent strains. The large degree of horizontal gene transfer through transposons, bacteriophages, and homologous recombination has dispersed genetic material and pathogenic properties among different strains.

The increased prevalence of ribotypes 027, 017, and 078 may be solely due to population expansion over the last decade or due to a nosocomial enrichment of the proper environment and conditions for the expansion and transference of these virulent strains. The sudden rise may also be related to the delay in purifying selection pressures seen in the more recently diverging lineages. However, a more likely explanation for increasing incidence is the right combination of elderly patients in a contaminated environment with antibiotic and acid suppression medications. Given the high incidence of colonized guts in the hospitalized pediatric population (70%), the hospitalized adult population (25%), the animal kingdom (40%), and the natural environment (50%), reducing exposure is near impossible [14].

The high virulence, along with a highly mobile genome capable of antibiotic resistance, has prompted further research in the development of vaccinations. Sanofi-Aventis is currently undergoing trials with a vaccine containing formalin-inactivated toxins A and B. To date, 100 healthy subjects have been exposed to the vaccine without any serious side effects [123].

The hardiness of *C. difficile* spores and the ease with which this bacterium alters its genome has allowed it to flourish and survive among a variety of hosts and reservoirs. More virulent strains are a real possibility given the mobility of code sequencing regions within the genome. As the population continues to age and makes an increasingly stronger presence throughout the healthcare system, especially in the ICU, *C. difficile* will continue to plague patients and healthcare providers until further measures are discovered to control transmission. The increased burden will stress the current resources and facilities financially, geographically, and the pool of available care takers. To date, the best treatment modalities include eliminating the implicated antibiotics, early initiation of oral vancomycin and metronidazole, and strict infection-control engineering to prevent the initial infection.

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