Fulminant *Clostridioides difficile* Infection

A Journey into the Unknown!

Jae H. Shin, MD[a], Jasmine Y. Jackson-Akers, DO[b], Sook C. Hoang, MD[c], Brian W. Behm, MD[d], Cirle A. Warren, MD[e,*]

KEYWORDS

- Fulminant *C difficile* infection • Toxic megacolon • *C difficile* therapy
- Severe complicated CDI

KEY POINTS

- Fulminant *Clostridioides difficile* infection (CDI), characterized by hallmarks of critical illness such as hypotension, shock, or megacolon, has been difficult to define and treat.
- Diagnosis of a pre-fulminant state is crucial to identify patients that would benefit from aggressive treatment before a truly fulminant CDI.
- There are many host, bacterial, and microbial factors that contribute to the development of severe outcomes of CDI.
- Treatment options for fulminant CDI are limited and lack solid evidence of efficacy.
- Intestinal microbiota transplantation emerged as an option for fulminant C difficile refractory to medical therapy but well-controlled studies are lacking to determine safety and efficacy.

INTRODUCTION

Clostridioides difficile infection (CDI) is a major health concern in the United States. *C difficile* is 1 of the 5 *urgent* antibiotic resistance threats reported by the Centers for Disease Control and Prevention.[1] *C difficile* is the most common cause of health care-associated infection in the United States[2] and costs the US health care system

[a] Infectious Disease, Hoag Memorial Hospital Presbyterian, 1 Hoag Drive, Newport Beach, CA 92663, USA; [b] Division of Infectious Disease, Carilion Clinic, 1 Riverside Circle, Roanoke, VA 24016, USA; [c] Colorectal Surgery, University of Virginia, 1215 Lee Street, Charlottesville, VA 22903, USA; [d] Division of Gastroenterology, University of Virginia, 1300 Jefferson Park Avenue, Charlottesville, VA 22903, USA; [e] Division of Infectious Diseases and International Health, University of Virginia, 345 Crispell Drive, Charlottesville, VA 22903, USA
* Corresponding author. Division of Infectious Diseases and International Health, University of Virginia, Carter-Harrison Medical Research Building/MR6, 345 Crispell Drive, Charlottesville, VA 22903.
E-mail address: Ca6t@virginia.edu

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Abbreviations	
ACG	American College of Gastroenterology
CDI	*Clostridioides difficile* infection
CT	cycle threshold
IBD	inflammatory bowel disease
IDSA	Infectious Disease Society of America
IMT	intestinal microbiota transplant

between 1 to 4 billion dollars per year.[3] A vital part of the burden of CDI is the high risk of poor outcome, especially in the elderly.[1] One in 11 patients who are 65 and older dies within 1 month.[1]

DEFINITION

Fulminant (or *severe complicated*) CDI in the Infectious Disease Society of America (IDSA) and American College of Gastroenterology (ACG) guidelines is defined by hallmarks of critical illness: hypotension or shock, ileus, or megacolon.[4,5] By the time the fulminant CDI diagnosis is made, the patient is typically already in multiorgan failure with very limited options for treatment. Up to 30% of patients with fulminant disease succumb to CDI.[6,7] Identification of high-risk patients, would facilitate development and initiation of a treatment regimen that would help prevent severe outcome or death from CDI.

PATHOGENESIS

Development of disease in CDI is primarily driven by *C difficile* toxins in the setting of intestinal dysbiosis (**Fig. 1**). The main *C difficile* toxins are toxins A (TcdA) and B (TcdB), with binary toxin (CDT) considered a contributor in increasing disease severity in infection with CDT-positive strains. TcdA and TcdB induce cell death via activation of Rho GTPase leading to disruption of the epithelial barrier and initial localized induction of inflammatory response in the intestinal tissue. Activation of gut inflammatory pathways may progress to a systemic inflammatory response, sepsis, and even death. Unlike other forms of sepsis, fulminant CDI is not caused by systemic dissemination of the bacterium itself, with *C difficile* bacteremia being a rare phenomenon documented only in case reports.[8] However, recent studies in patients have not only shown that the toxins are detectable in the systemic circulation, but that higher levels were associated with more severe disease, suggesting that dissemination of the *C difficile* toxins in the systemic circulation may contribute to the systemic response in CDI.[9,10]

The immune response, both local and systemic, resulting from CDI appears to be more important in predicting the severity of CDI than the infection burden of *C difficile*. The main response involved in the defense against CDI and in severe disease is predominantly innate immune activation,[11] characterized by a robust neutrophil response. Because the neutrophil response is both a defense against CDI and a manifestation of severe disease, publications have shown detrimental outcomes associated with both unregulated neutrophil response[12] and neutrophil deficiency.[13,14] In addition to neutrophils, another important part of the innate immune response is the proinflammatory cytokines. In prediction models for severe outcome from CDI, elevated levels of systemic proinflammatory markers in combination such as IL-8, procalcitonin, CXCL5, IP-10, IL-2R, HGF,[15] or IL-8, TNF-α/IL-6, CCL5, sST-2, IL-15[16] were shown to be predictive of severe outcomes, suggesting an important role for the inflammatory cytokine pathways.

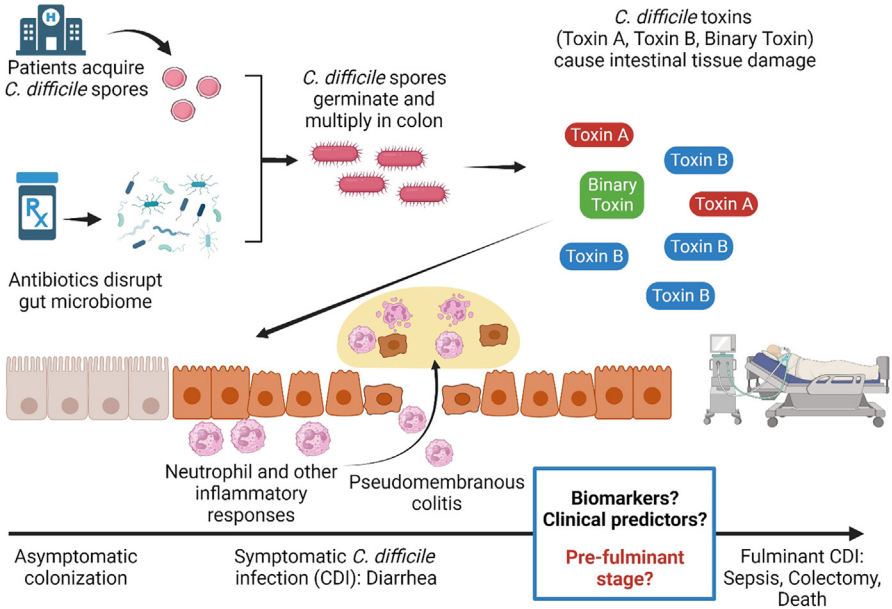

Fig. 1. Pathogenesis of CDI. CDI occurs when the normal intestinal microbiome is disrupted and *C difficile* establishes itself in the host intestinal milieu. The *C difficile* spores may asymptomatically colonize or germinate into vegetative forms and produce toxins and cause symptomatic disease. The infection may stay at a mild or moderate severity or progress to fulminant CDI, leading to sepsis, colectomy, or death. Our limitation in understanding of CDI pathogenesis is in the ability to detect the predictors of progression to fulminant CDI before it is too late. (*Created in* BioRender. Shin, J. (2023) BioRender.com/z22g579.)

FACTORS ASSOCIATED WITH DISEASE SEVERITY

Clinical Prediction Models

Disease severity in CDI is influenced by various factors (**Table 1**). There have been multiple different criteria published for predicting severe outcome from CDI.[17,18] These prediction rules or scoring systems use a combination of comorbidities, symptoms, physical examination findings, laboratory values, and imaging features. The majority of these scoring systems have some validity in predicting death or severe outcome such as colectomy from CDI. Some common themes emerge, such as older age, altered mental status, high or low white blood cell (WBC) count, low albumin, and decreased renal function.

Host Factors

Demographics

Age is a common factor in multiple prediction tools, with various age cutoffs such as age 60, 80, and 90. Age may be used as a scale to stratify the patients most at risk for progression to fulminant CDI as seen in the ATLAS (age [Ag], treatment with systemic antibiotics [Tr], leukocyte count [L], serum albumin [Al] and serum creatinine [S]) scoring system.[17,18] Interestingly, although female sex was associated with an increased risk for CDI[19,20] and recurrence,[19,20] male sex was associated with a higher risk of fulminant CDI and for severe outcome.[6]

Comorbidities

Infection with the human immunodeficiency virus (HIV), solid organ transplantation, and hematopoietic stem cell transplants have been evaluated in regards to risk for

Table 1
Factors that may influence outcome of *Clostridioides difficile* infection

Host	Inflammatory Response	Blood Chemistry	Pathogen	Microbiome
• Age • Sex • Comorbidities • IBD • Immunosuppression	• Leukocyte count • Systemic proinflammatory cytokines • Fecal inflammatory markers • Imaging features • Endoscopic findings	• Albumin • Creatinine	• Pathogen burden • Toxin levels • Clostridial strain	• Degree of dysbiosis

developing CDI as well as for developing severe complicated CDI.[21] Although a potential increase in incidence of CDI was described in many of these conditions, they have major confounding variables, namely antibiotic use and health care exposure, which limit the specificity of these associations. In many of the studies, the risk of severe complicated CDI was not specifically compared between patients with immunosuppression and the general population. However, the mortality rate of CDI did not seem to be increased in these patients with immunosuppression. The degree of immunosuppression does not seem to affect CDI severity in the majority of these studies. One potentially controversial immunocompromising condition is neutropenia. Clinical studies have shown both improved and poor outcomes from CDI associated with neutropenia.

Mental status changes have been shown to be a risk factor for poor outcome. Although not clearly defined, other studies have noted cognitive dysfunction[7,22] or delirium[23] to predict death from CDI.

Inflammatory bowel disease (IBD) increases the risk for developing CDI. The effect of IBD on severe outcomes is not clear. Some studies showed that in patients with CDI and IBD, there were lower risks of recurrences and lower mortality rates due to patients being younger and having less comorbities.[24] Other studies reported that patients with IBD and CDI had higher mortality rates, longer hospitalizations, more recurrences, and a higher rate of complications that included toxic megacolon and colonic perforations[25] while another study has shown an equivalent outcome.[26]

Blood Chemistry

Serum creatinine and albumin have been used as criteria for definition of severe CDI.[4,5] Lactate is a marker used in sepsis and severe sepsis to determine the need for fluid resuscitation but has not been studied in the setting of CDI. In patients undergoing colectomy, elevated lactate was associated with increased mortality. Lactate level of $\geq$5 mmol/L was an independent predictor of 30-day mortality, in addition to leukocytosis of 50 x10^9/L, age $\geq$75 year old, and use of vasopressors.[27]

Inflammatory Response

Systemic

Leukocyte count. WBC count has been one of the consistent factors included in clinical prediction models for severe outcomes from CDI. In the ATLAS scoring system, 1 point is given for WBC count between 16,000 to 25,000 cells/μL and 2 points for higher than 25,000 cells/μL.[17] In others, high WBC count (20,000 cells/μL or higher or 15,000 cells/μL or higher[28]) as well as low WBC count, 1500 cells/μL or lower,[28]

have been used as a factor to predict the risk of severe outcome. Although the WBC count 15,000 cells/μL or higher has been used as one of the factors to define severe CDI in published guidelines,[4,5] a higher cutoff may be appropriate for fulminant CDI in combination with other factors.

Leukemoid reaction is the presence of leukocytosis that resembles leukemia, with WBC exceeding 50,000 cells/μL, in the absence of a primary bone marrow disorder. Leukemoid reaction has been noted to be a poor prognostic factor.[12] Deficiency of eosinophil count may have prognostic value when added to standard measures of CDI severity.[29]

Pro-inflammatory cytokine levels. Levels of interleukin(IL)-8, procalcitonin, chemokine (C-X-C motif) ligand (CXCL)5, interferon-gamma-inducible protein (IP)-10, IL-2R, and hepatocyte growth factor (HGF),[15] or tumor necrosis factor (TNF)-α, IL-6, chemokine ligand (CCL)5, soluble suppression of tumorigenicity 2 (sST-2), IL-8, and IL-15[16] in the systemic circulation have been used to predict mortality or disease-related complications. The inflammatory markers seem to work best when used in combination, but their clinical utility has not been studied in patients at risk of or have fulminant disease.

Intestinal

Fecal inflammatory markers. Fecal inflammatory markers such as lactoferrin or myeloperoxidase are chemicals released by neutrophils. Increase in peripheral WBC and elevated fecal lactoferrin in patients have been shown to be indicators of severe CDI. Fecal calprotectin and fecal lactoferrin can be used to differentiate between CDI and antibiotic-associated diarrhea. Higher levels of fecal calprotectin appear to correlate with more severe CDI, although 1 study also showed that fecal lactoferrin but not fecal calprotectin had an association between levels and CDI severity.[30] Fecal lactoferrin could be used to monitor disease activity in patients with CDI as a response to medical treatment and to predict the occurrence of a relapse.[31] Higher fecal calprotectin levels were observed in patients with ribotype 027 and in patients with a higher clostridium severity score index.[32] Fecal biomarkers, however, have not been specifically studied as predictors of fulminant disease.

Morphologic Changes in Pathology and Radiology

Pseudomembranes are found in 30% to 85% of patients with CDI and are mainly found in those patients with severe infection.[33] It was initially thought that the presence of pseudomembranes indicated a worse prognosis, but recent studies suggest that the prognosis of CDI with pseudomembranous colitis is no different than that without the presence of pseudomembranes.[33] Endoscopically, pseudomembranous colitis appears as elevated yellow-white plaques or nodules on the mucosal surface of the colon.

Radiographic studies have also been used to evaluate severe CDI. Plain radiographs of the abdomen can be used in cases of colonic and small bowel ileus to show *thumbprinting* or haustral thickening. Computed tomography of the abdomen and pelvis can show findings such as thickened colonic wall/colonic dilatation, and ascites, which may predict severe outcomes.[34]

Pathogen Factors

Pathogen burden

With the advent of nuclear acid amplification testing, that is, PCR, quantification of the pathogen burden is usually defined by cycle threshold (CT) value. Few studies have

shown that lower CT values (≤26) can predict severity of outcome and/or presence of toxins.[35] However, these studies have not shown conclusively that CT values can be used in the clinical setting.

Toxin levels

Recent studies have shown that high levels of TcdA and TcdB are associated with severe outcome.[9,10] Not only were the fecal toxin levels higher in patients with severe CDI compared to nonsevere CDI, they were also much higher in the patients who died compared to patients who survived.[9] Toxin levels of 2500 ng/mL or higher was associated with a death rate of 47% within 30 days of diagnosis.[9] Using an ultrasensitive quantitative toxin immunoassay, severe outcomes (death, intensive care unit stay, or colectomy within 40 days) attributable to CDI were highly associated with high levels of toxin, with 100-fold difference in median concentration of stool toxin between patients with primarily-attributed severe outcomes and other patients.[10]

Strain characterization

Ribotype 027 is a binary toxin positive strain that is associated with older age, higher Charlson comorbidity scores, more severe disease, increased recurrences, and high mortality.[36] Compared to ribotype 027, ribotype 014 - 020 is associated with a decreased incidence of severe CDI.[36] Ribotype 078 is also binary toxin positive and known to cause increased mortality and severe diarrhea.[37] Ribotype 014 is among the top 10 most common ribotypes in England and the Netherlands and is also binary toxin positive.[38] Ribotype 014 is associated with elevated neutrophil counts but is not associated with increased mortality.[38] Regardless of ribotype, patients infected with binary toxin strains may have increased disease severity and worse clinical outcomes.

Microbiome

Dysbiosis

The connection between the degree of dysbiosis and severity of CDI has not been directly demonstrated. However, few case reports and series have shown the effectiveness of intestinal microbiota transplant (IMT) in the treatment of fulminant CDI suggesting contribution of the disruption of the microbiota to the development of fulminant disease. One possible mechanism by which the microbiome can determine severity of CDI is by affecting clostridial growth and production of toxins. Treatment with IMT also have led to changes in the immune response that are associated with improved outcomes in CDI, such as increase in type 2 response with IL-25 and a decrease in T helper (Th)17 response.[39]

TREATMENT OF FULMINANT *CLOSTRIDIOIDES DIFFICILE* INFECTION

Antibiotic Therapy

Vancomycin

Per IDSA and ACG guidelines, oral vancomycin 500 mg 4 times daily or rectal vancomycin 500 mg every 6 hours as retention enema is recommended for fulminant disease although there remains lack of strong evidence to support this recommendation.[5] Previous studies have shown no significant differences in outcome with different doses of vancomycin. The number of patients in these clinical studies was small and not specifically studied in the context of fulminant CDI. Higher oral dose of vancomycin may lead to higher fecal concentration of vancomycin but the levels achieved even by the 125 mg dose was still significantly higher than the MIC.[40] However, when frequency of diarrhea was higher, fecal concentration can fall below the minimum inhibitory concentration (MIC) and thus, higher doses may be warranted in the setting of

severe diarrhea. The ACG guidelines suggest decreasing the dose of vancomycin if patient shows improvement in the first 48 to 72 hours.[4] There is some concern with prolonged exposure, renal failure, or disrupted intestinal epithelium that the serum concentration of vancomycin could be elevated. Higher doses of vancomycin also promote further dysbiosis and thus, may lead to increased recurrence. Intracolonic vancomycin treatment has been used in patients with ileus,[4,5] but this treatment is also based on expert opinion and retrospective studies. A study comparing oral vancomycin alone with oral and rectal vancomycin showed no difference in outcome for fulminant CDI.[41]

Metronidazole

Although not approved by the U.S. Food and Drug Administration for CDI, IDSA and ACG guidelines recommend treatment of fulminant disease with intravenous metronidazole at 500 mg every 8 hours in addition to vancomycin.[4,5] The evidence for this practice is also somewhat limited, but an observational study has shown that in patients who were in the ICU for CDI who received combination therapy had improvement in mortality from 36.4% to 15.9%, although a follow-up retrospective study has shown no difference in outcome.[42] Monotherapy with intravenous (IV) metronidazole has been shown to be associated with higher mortality and thus, not recommended for *C difficile* treatment.[43]

Fidaxomicin

Fidaxomicin is a bactericidal macrolide antibiotic that works by inhibiting the RNA polymerase sigma subunit and results in the inhibition of protein synthesis and bacterial death. Due to the narrow-spectrum of antimicrobial activity,[44] there is a lower risk of potential dysbiosis or induction of antibiotic resistance as could be seen with metronidazole and vancomycin. There have been no large scale studies comparing fidaxomicin to vancomycin for fulminant CDI. A retrospective cohort study in patients with severe CDI found that fidaxomicin had similar rates of recurrence and deaths as vancomycin. However, more patients were switched from fidaxomicin to vancomycin (9%) than from vancomycin to fidaxomicin (1%), suggesting higher clinical failure with fidaxomicin.[45]

Tigecycline

Intravenous tigecycline, a tetracycline derivate antibiotic, has been traditionally used for intra-abdominal infections or antibiotic-resistant organisms, but has fallen out of favor as its use was associated with higher mortality.[46] Tigecycline has *in vitro* activity against *C difficile* and the concentration achieved in the feces in healthy subjects with intravenous tigecycline was shown to be much higher than the MIC.[47] It was used in cases of CDI refractory to conventional antibiotics. Observational studies, with number of patients ranging from 13 to 266, have shown a statistically significant benefit to addition of tigecycline to vancomycin and/or metronidazole.[48] However, there are also studies showing no difference in outcome with use of tigecycline. A retrospective case series analysis and propensity-matched cohort study showed not only that tigecycline did not improve mortality, but also that it was associated with a significantly prolonged hospital stay.[49] Without high quality evidence in the literature for efficacy, the use of tigecycline is not recommended at the present.[4,5] Prospective well-controlled trials are necessary to determine the effectiveness of this intervention.

Antitoxin Treatment

Studies have shown that levels of antibody against *C difficile* TcdA correlated with protection against recurrent CDI[50] and patients that did not respond to treatment had

lower levels of antibodies against TcdA.[51] In case reports and case series, patients who did not respond to treatment with metronidazole or vancomycin showed improvement when treated with intravenous immunoglobulin (IVIG). However, an observational study comparing patients who were treated with IVIG and patients who were treated with conventional therapy did not show significant benefit with IVIG.[52] The major society guidelines do not recommend use of IVIG for treatment of CDI.[4,5]

Bezlotoxumab, a monoclonal antibody against TcdB, has been shown to have a modest effect on preventing recurrence in at-risk patients mostly treated with a standard short course of either metronidazole or vancomycin.[53] There is no strong evidence that treatment with bezlotoxumab influences outcome of severe disease and thus, it is currently not recommended for fulminant CDI.

Surgical Therapy

Surgical management of *C difficile* colitis should be reserved for patients with severe colitis that is refractory to medical therapy or concern for toxic megacolon and perforation. There is no clear algorithm for when surgery should be pursued; however, patients with significant lactic acidosis, sepsis, or multiorgan failure should be given serious consideration. When surgery is performed, the recommended procedure is a subtotal colectomy with end ileostomy and rectal stump. Although previous studies have compared and found that partial and subtotal colectomy for the surgical management of severe, complicated CDI to be equivocal with regards to overall 30 day mortality and overall complication rates, a subtotal colectomy with end ileostomy remains the most commonly performed procedure.[54] The overall mortality rate following surgery for fulminant CDI is significant at greater than 50%, prompting the need for earlier surgical intervention, which can be associated with improved survival.

Long term outcomes after colectomy for fulminant CDI is poor with a median survival of 3.2 months. Additionally only 20% of patients who undergo surgery will proceed to stoma reversal.[55] When first introduced, loop ileostomy with antegrade colonic lavage provided a viable alternative to subtotal colectomy for patients with medically refractory fulminant CDI with mortality rates as low as 19% in the ileostomy group.[56] A majority of these patients remained colectomy free (93%) and subsequently underwent stoma reversal surgery (79%). Unfortunately, the survival benefits of loop ileostomy with colonic lavage over subtotal colectomy were not reproduced in subsequent small and large scale studies.[57] Despite this discrepancy, loop ileostomy with colonic lavage remains an attractive surgical option as the rate of restoration of intestinal continuity remains high across all studies.

Intestinal (or Fecal) Microbiota Transplantation

IMT introduces colonic microbial communities from a healthy individual into a patient by colonoscopy, enema, nasoenteric tube, or oral capsules. At present, it is the most effective therapeutic option to prevent recurrence. There has been an interest to expand the indication for IMT to fulminant CDI. Initial case reports suggested that IMT was safe and effective in this patient population. Additional studies suggested that more than one IMT may be required to achieve cure.[58] Several observational studies have shown that IMT is associated with reduced rates of colectomy and mortality in patients with severe and fulminant CDI with low rates of complications.[59] These studies have used mostly lower endoscopy administered fecal suspension and not the commercially available oral or rectal IMT formulations.

The ACG published practice guidelines suggest IMT be considered for patients with fulminant CDI particularly when patients are deemed to be poor surgical candidates.[4] It is recommended that IMT be considered in patients with fulminant CDI who have not

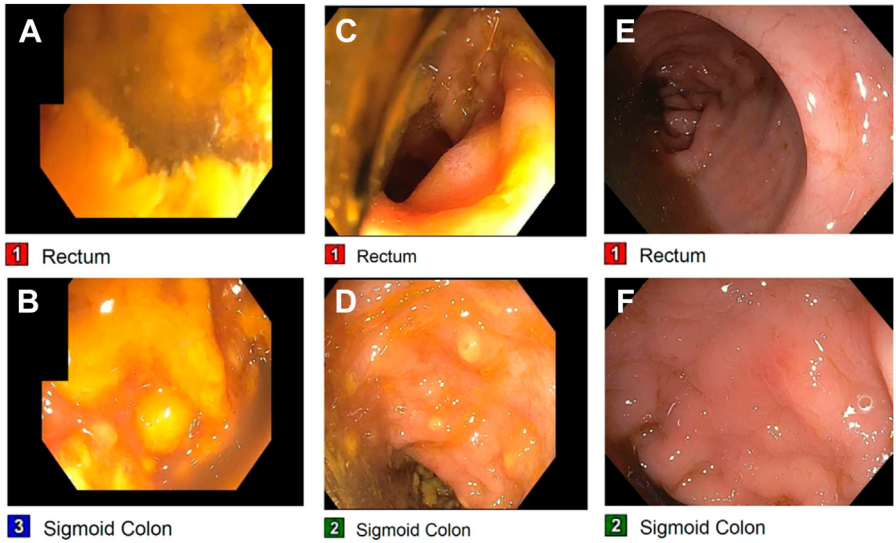

Fig. 2. Changes in colonoscopy findings during successive fecal microbiota transplantation (FMT) in hospitalized patients with refractory or fulminant CDI and pseudomembranes. Colonoscopic findings from one patient shows yellow pseudomembranes covering both the rectum (*A*) and the sigmoid colon (*B*) during the first FMT. There is some improvement on the second FMT in the rectum (*C*) and the sigmoid colon (*D*). On the patient's third FMT, both the rectum (*E*) and the sigmoid colon (*F*) exhibited resolution of pseudomembranes and healthy intestinal epithelium. (Jae Hyun Shin et al., Hospitalized Older Patients with Clostridioides difficile Infection Refractory to Conventional Antibiotic Therapy Benefit from Fecal Microbiota Transplant. Adv Geriatr Med Res. 2021;3(2):e210012. https://doi.org/10.20900/agmr20210012.)

responded adequately after 48 to 72 hours of maximum medical therapy, and is performed using a sequential pseudomembrane-based strategy. If pseudomembranes are present, colonoscopy with IMT is repeated every 3 to 5 days until the resolution of pseudomembranes (**Fig. 2**A-F). Concomitant administration of oral vancomycin or fidaxomycin is continued as long as pseudomembranes are present. When pseudomembranes have resolved a final IMT is completed and antibiotics are held. This sequential IMT strategy has been associated with high rates of cure in hospitalized patients, although it has not been compared with single IMT in a well-controlled study.

Translocation of potentially pathogenic microorganisms and transmission of infectious agents are practical concerns with IMT. The integrity of the intestinal epithelium is decreased with inflammation, and this may be more of a concern in patients with sepsis and fulminant disease. However, 1 study showed that bacterial translocation may be lower with IMT.[60] Few observational studies in patients with complicated CDI have shown good treatment outcomes with IMT.[61,62] Randomized clinical trials would be ideal to assess effectiveness and safety of IMT, whether from universal donor stool system or defined microbial formulations (or live biotherapeutic products) to treat fulminant CDI.

SUMMARY

Fulminant CDI leads to the high mortality of CDI, a significant burden on the health care system, especially among the aging population. There are 2 major challenges in the

management of CDI: identification of patients likely to develop fulminant CDI and early institution of effective treatment.

While the current IDSA criteria for *severe CDI* is nonspecific and is too broad, the criteria for fulminant CDI represent an advanced stage of CDI, which may be too late for effective intervention. Finding diagnostic criteria or clinical prediction rules, which would identify patients at risk for advancing to fulminant CDI, yet are not quite so ill, would present an effective tool in managing CDI.

As of now, the available treatment options for fulminant CDI are limited and lack strong evidence for efficacy. Further research is needed to optimize diagnosis and to develop treatment strategies to improve outcomes in patients with fulminant CDI.

CLINICS CARE POINTS

- Fulminant *Clostridioides difficile* infection (CDI) is associated with very high mortality, especially in the elderly.
- Identification of patients at risk of fulminant CDI is critical for early intervention to prevent progression of disease.
- Current guidelines recommend enteral high dose vancomycin and IV metronidazole for fulminant CDI although without solid evidence from the literature.
- Prompt multidisciplinary evaluation for potential need for intestinal microbiota transplantation or surgical intervention is needed for patients with fulminant CDI in case of inadequate response to antibiotic therapy.

DISCLOSURES

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