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Critical Care Management of the Patient with *Clostridioides difficile*

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Abstract

Objective: To review published clinical evidence on management of *Clostridioides difficile* infection (CDI) in critically ill patients.

Data Sources: We obtained relevant studies from a PubMed literature review and bibliographies of reviewed articles.

Study Selection: We selected English-language studies addressing aspects of CDI relevant to critical care clinicians including epidemiology, risk factors, diagnosis, treatment, and prevention, with a focus on high-quality clinical evidence.

Data Extraction: We reviewed potentially relevant studies and abstracted information on study design, methods, patient selection, and results of relevant studies. This is a synthetic (i.e., not systematic) review.

Data Synthesis: CDI is the most common healthcare-associated infection in the United States. Antibiotics are the most significant CDI risk factor, and among antibiotics, cephalosporins, clindamycin, carbapenems, fluoroquinolones and piperacillin-tazobactam confer the highest risk. Age, diabetes mellitus, inflammatory bowel disease and end-stage renal disease are risk factors for CDI development and mortality. CDI diagnosis is based on testing appropriately selected patients with diarrhea, or on clinical suspicion for patients with ileus. Patients with fulminant disease (CDI

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with hypotension, shock, ileus, or megacolon) should be treated with oral vancomycin and intravenous metronidazole, as well as rectal vancomycin in case of ileus. Patients who do not respond to initial therapy should be considered for fecal microbiota transplant (FMT) or surgery. Proper infection prevention practices decrease CDI risk.

Conclusions: Strong clinical evidence supports limiting antibiotics when possible to decrease CDI risk. For patients with fulminant CDI, oral vancomycin reduces mortality, and adjunctive therapies (including intravenous metronidazole) and interventions (including FMT) may benefit select patients. Several important questions remain regarding fulminant CDI management, including which patients benefit from FMT or surgery.

Keywords

Clostridium difficile infection; intensive care units; healthcare associated infections; fecal microbiota transplantation

INTRODUCTION

Clostridioides (formerly *Clostridium) difficile* infection (CDI) is a potentially lethal illness characterized by colonic inflammation and diarrhea. Pathogenic *C. difficile* strains elaborate cytotoxins; toxin B is especially virulent and associated with severe disease(1). CDI is a significant cause of healthcare-associated infections (HAI)(2), and knowledge of CDI management is crucial for healthcare providers. This review provides a concise evidence-based clinical summary of CDI for the intensive care unit (ICU) clinician.

EPIDEMIOLOGY

CDI is the most common HAI in the United States(2–4). Despite successful efforts to reduce CDI incidence, there are still nearly 250,000 hospital-acquired cases annually(2, 4, 5). The clinical spectrum of CDI ranges from mild diarrhea to fulminant colonic inflammation, ileus, shock, and death. Among patients hospitalized with CDI, 5–15% require ICU admission(6–8), and ICU-onset CDI prevalence is 2–5%(9–12).

ICU admission is associated with poor outcomes for patients with CDI: at least 30% develop septic shock(10, 13) and mortality is 20–40%(9–11, 13, 14). CDI is associated with increased ICU length of stay(9, 10, 14, 15) and cost(14). Among patients who survive, 27% are readmitted within 30 days, mainly due to CDI recurrence(16).

RISK FACTORS

Patient characteristics

Several patient characteristics associated with critical illness are risk factors for CDI (Table 1). Increasing age (≥65 years) is generally regarded as a risk factor for CDI(9), however a meta-analysis of over 14,000 ICU patients did not show an age difference between patients with and without CDI(11). End-stage renal disease (ESRD)(17), inflammatory bowel disease (IBD), malignancy, and diabetes mellitus (DM) are also risk factors(18). Among patients

with CDI, complications (including fulminant colitis, shock and death) are more likely with increasing age and DM, ESRD, acute kidney injury (AKI), and IBD(19, 20).

Antibiotics

Antibiotics are the strongest CDI risk factor. Antibiotics disrupt the gut microbiome allowing for *C. difficile* colonization and infection. While clindamycin and fluoroquinolones are assumed to confer the highest risk of CDI, these associations were shown in meta-analyses of community-acquired CDI(21, 22); different antibiotics appear to confer more risk in hospitalized patients. A 2013 meta-analysis of hospital-acquired CDI (HA-CDI) in nearly 16,000 patients identified 3rd-generation cephalosporins (e.g. ceftriaxone) as highest risk, followed by clindamycin, 4th-generation cephalosporins (e.g. cefepime), carbapenems, fluoroquinolones and penicillin combinations (e.g. piperacillin-tazobactam) (Table 1)(23).

Risk for CDI is not only affected by antibiotic class: antibiotic dose, duration, and number of antibiotics have dose-response relationships with HA-CDI(24–26). Even perioperative prophylactic antibiotics increase risk, which may be important in post-operative ICU patients(27, 28). Among patients who require antibiotics, de-escalation based on culture results is crucial for prevention. For example, in one study patients with Enterobacteriaceae bloodstream infection (most commonly *Escherichia coli* and *Klebsiella* species) who received anti-pseudomonal antibiotics (including carbapenems, piperacillin-tazobactam, and cefepime) for >48 hours had higher CDI risk than patients who received these antibiotics for ≤48 hours and were de-escalated to an appropriate definitive regimen (hazard ratio 3.6, 95% confidence interval [CI] 1.5–9.9)(29). For all patients, clinicians should discontinue or de-escalate antibiotics as appropriate to prevent CDI.

Gastric acid suppression

Proton-pump inhibitors (PPIs) are commonly prescribed in the ICU for gastrointestinal bleeding prophylaxis(30). Several early non-ICU observational studies demonstrated an association between PPIs and CDI, and the U.S. Food & Drug Administration issued a warning for omeprazole in 2012(31, 32). Similarly, early ICU-specific literature, including two 2014 single-center observational studies, demonstrated an association with PPIs(33, 34). However, several recent high-quality studies, including a 2020 meta-analysis of randomized controlled trials with almost 4000 ICU patients(35), did not show an association between PPIs and CDI(30, 35–37). Although long-term PPI use may be associated with CDI, CDI risk should likely not be a significant factor when deciding whether to prescribe PPIs in the ICU.

DIAGNOSIS

CDI diagnosis in the ICU is challenging, as many CDI signs and symptoms (including fever, diarrhea, and leukocytosis) are common among critically ill patients with and without CDI. For example, diarrhea is present in 5–15% of ICU patients(11, 38–41), and CDI is causative in only 10–25% with diarrhea(11, 39–41). Nevertheless, ICU clinicians should maintain a high degree of suspicion for CDI. The most common diagnostic tests are nucleic acid amplification tests (NAAT) for toxin-encoding genes, and enzyme immunoassays (EIA) for

C. difficile toxins A and B or glutamate dehydrogenase (GDH), an enzyme produced by *C. difficile*.

Up to 10% of hospitalized patients are colonized with *C. difficile*(42–44), and distinguishing between infection and colonization (for which treatment is not indicated) is crucial. For example, a positive NAAT for *tcdB,* the gene encoding for toxin B, does not indicate toxin production, which is required for disease. A positive toxin EIA establishes infection, however toxin EIAs are insensitive(45, 46), and false positives can rarely occur.

Two testing strategies help to distinguish infection from colonization. First, only patients with ≥3 loose stools in 24 hours (and compatible clinical signs) should be tested. Although NAAT detects both infection and colonization, NAAT is sensitive and specific in patients who meet the stool number criteria(47, 48). Second, diagnostic algorithms with multiple tests can increase positive predictive value(47). The 2017 IDSA/SHEA Clinical Practice Guidelines for CDI recommend using NAAT+toxin EIA or GDH+toxin EIA(47); positive results of both tests in an algorithm confirms CDI. Patients with a positive NAAT or GDH EIA and negative toxin EIA should be treated based on clinical suspicion, as they may have either infection or colonization.

Patients with fulminant CDI may have ileus and not meet stool number criteria for testing. No routine test is sufficiently sensitive to rule out CDI in these patients. Using a perirectal swab to collect a sample for NAAT may be reasonable in patients with ileus(49). However, sensitivity is unknown in these patients and a negative test should not rule out disease; a positive result may reflect colonization and should be interpreted in the clinical context. CDI should be strongly considered in patients with ileus and concomitant shock, abdominal pain, lactic acidosis, and/or leukocytosis (≥15,000 white blood cells [WBC]/μL) or leukopenia (<4,000 WBC/μL)(20). Empiric anti-CDI antibiotics should be initiated before confirmatory testing for patients with suspected fulminant CDI(47). Abdominal computed tomography is recommended to assess for complications (50) and may support the diagnosis, as 80–90% of patients with fulminant CDI have signs of colitis on imaging(51, 52). Colonoscopy is not routinely recommended for suspected CDI, but when used in case of diagnostic uncertainty or delivery of fecal microbiota transplant (FMT), pseudomembranous colitis is present in 50–85%(52–55).

TREATMENT

CDI treatment is determined by disease severity. This review will focus on treatment of fulminant disease, defined in the 2017 IDSA/SHEA guidelines as CDI with hypotension or shock, ileus, or megacolon(47). There is little primary data on treatment of fulminant disease, and many of the recommendations are extrapolated from studies of severe CDI. Further, although severe disease is defined in the 2017 IDSA/SHEA guidelines as CDI with WBC ≥15,000/μL or creatinine >1.5 mg/dL(47), this criteria was not routinely applied across studies, making comparisons difficult.

In addition to the measures discussed below, all patients should receive supportive care focusing on volume resuscitation, electrolyte replacement, and management of organ failure.

If possible, non-CDI antibiotics should be discontinued or de-escalated(20, 56). Importantly, early interdisciplinary management by intensivists, infectious diseases clinicians, gastroenterologists and surgeons is crucial for prioritizing therapies and prompt mobilization for FMT or surgery in case of clinical deterioration.

Antibiotics

The cornerstone of therapy for fulminant CDI is oral vancomycin, a glycopeptide antibiotic with minimal systemic absorption(57). A 2007 randomized controlled trial (RCT) established its superiority to oral metronidazole for severe CDI cure (97% vs. 76%, p=0.02) (58). Although the study population was largely not critically ill (only 6% required ICU admission), several subsequent meta-analyses have shown increased cure (59, 60) and decreased mortality (61) with vancomycin compared to oral metronidazole for patients with severe CDI. Vancomycin duration should be at least 10 days, but may be extended depending on the patient's clinical course. Although low dose vancomycin (125 mg by mouth every 6 hours) may be sufficient(62, 63), the 2017 IDSA/SHEA guidelines recommend high dose (500 mg by mouth every 6 hours) for fulminant disease based on theoretical concern for decreased drug delivery to the distal colon in cases of ileus(47). The European guidelines recommend low dose, which is most appropriate without ileus or toxic megacolon(64).

Combination therapy with intravenous (IV) metronidazole in addition to oral vancomycin is recommended for fulminant disease based on a 2015 retrospective cohort study that showed lower mortality with combination therapy than vancomycin monotherapy in ICU patients with severe disease(65). However, a subsequent 2019 retrospective cohort study in fulminant CDI did not show a mortality benefit for combination therapy(66). Despite this, IV metronidazole may reach higher intra-colonic levels than oral therapy in patients with ileus, and IV metronidazole is therefore still recommended for fulminant CDI.

In addition to oral vancomycin and IV metronidazole, vancomycin should be given per rectum in patients with ileus, based on experience from case series (54, 67) and small comparative studies(68, 69). The IDSA/SHEA guidelines recommend 500 mg vancomycin in 100 mL normal saline as a retention enema, however larger volumes and concentrations (e.g. 1 g/500 mL normal saline) may allow for more proximal reflux into the colon(47, 67). Despite theoretical risk of colon perforation with rectal vancomycin, none of these studies (including 105 patients total) reported this complication(54, 67–69).

There are several second-line adjunctive antibiotics that may benefit selected patients who are not candidates for FMT or surgery. Fidaxomicin, an oral antibiotic with proven benefit for reducing CDI recurrence(70, 71), was associated with a trend toward mortality benefit in a sub-group analysis of 130 patients with severe CDI in a 2018 RCT(72). Currently fidaxomicin's high cost limits routine use, however given its apparent clinical benefit use may increase in the next several years. Bezlotoxumab, a monoclonal antibody against toxin B, decreases CDI recurrence, especially in patients with severe and/or recurrent CDI, and should be considered in this population(73). Intravenous immune globulin works by a similar mechanism and small studies have found limited benefit(74), but large volume of administration may limit its use in ICU patients. IV tigecycline is an option of last resort(55,

75, 76), although the largest study did not show a benefit(77) and it has significant gastrointestinal side effects.

Fecal microbiota transplant

FMT, which improves gut microbial alteration associated with CDI, prevents recurrence in over 90% of cases of refractory CDI(78). While not approved by the U.S. Food & Drug Administration, mounting evidence suggests FMT may also be beneficial for severe and fulminant CDI. The earliest case series of FMT for severe CDI from 2009 included 15 patients and demonstrated over 70% cure(79). Most patients had hypoalbuminemia, leukocytosis, and renal failure, but the authors did not report data on shock, ileus or megacolon(79). Other small case series have described resolution of shock secondary to CDI after FMT(N=5)(80) and CDI cure in patients too unstable for surgery (N=9)(81). Larger studies have shown acceptable outcomes and safety profiles for FMT in high-risk populations including elderly and immunocompromised patients(82–84). These studies included patients with severe or fulminant CDI but did not report outcomes specifically for these sub-groups.

Three retrospective cohort studies, published between 2019–2020, compared FMT to antibiotic therapy for severe and fulminant CDI (Table 3)(85–87). Of these studies, the study by Tixier et al. included the most critically ill patients: 63% required vasopressors and 65% required mechanical ventilation. FMT was associated with decreased mortality in all patients (odds ratio [OR] 0.23, 95% CI 0.06–0.97) and a trend towards mortality reduction in patients with fulminant CDI (N=33, OR 0.31, 95% CI 0.07–1.50)(85). Cheng et al. reported on a larger number of patients with fulminant CDI (N=199) and did show decreased mortality with FMT in this group (9.1% vs. 21.3%, p=0.02)(87).

Although these studies showed improved outcomes with FMT, which patients benefit, and at which stage of their disease course, is not clearly defined. Hocquart et al. showed that FMT ≤7 days after CDI diagnosis was associated with decreased mortality compared to antibiotics (OR 0.08, 95% CI 0.02–0.34)(86, 88), and Cheng et al. (described above) included patients who did not improve despite 5 days of maximal medical therapy(87). Based on these studies, it may be reasonable to perform FMT for critically ill patients who do not improve early in their course, however more studies, including RCTs, are needed to determine timing and patient criteria for FMT.

Surgery

Approximately 25% of patients with fulminant CDI (52) require surgery and post-operative mortality is between 30–50%(51, 52, 89–95). Early surgical consultation is crucial for appropriate patient selection.

Similar to FMT, which patients benefit from surgery has not been rigorously studied. A meta-analysis indicated that surgery improves mortality in patients who fail medical therapy (OR 0.70, 95% CI 0.49–0.99), however the analyzed studies did not define specific inclusion criteria(96). One single-center study demonstrated that surgery was associated with decreased mortality in patients with peak lactate between 2.2–4.9 mmol/L, but did not benefit patients with peak lactate ≥5 mmol/L(52). Similarly, several studies have

demonstrated that mortality increases with time to surgery, indicating a possible benefit of early surgery, although causality is unproven(90, 92, 93). These studies reflect an ideal surgical window—after patients do not respond to medical therapy but before they are too ill to survive surgery—that is difficult to specifically define. Further, no studies (either RCTs or observational studies) have compared surgery to FMT, which has shown benefit in similarly critically ill patients(85). Which patients would most benefit from FMT or surgery is unclear and deserves further study.

Once the decision is made to operate, there are two common surgical techniques. Total abdominal colectomy (TAC) with end ileostomy was the procedure of choice until approximately 2011(89). In 2011, a single center study showed decreased mortality with loop ileostomy (LI) with intraoperative colonic lavage and antegrade vancomycin flushes compared to historical patients treated with TAC (19% vs. 50%, p=0.006)(97). Few patients (<1%) with LI require subsequent TAC, and LI has the benefit of potential for technically easier subsequent re-anastamosis than the ileo-rectal re-anastamosis required after TAC(95). Due to these benefits, use of LI increased after 2011(95). However, the largest comparative study, published in 2019, did not show a mortality difference between LI and TAC (26.0% vs. 31.1%, p=0.28)(95). TAC should be performed in cases of abdominal compartment syndrome, colon perforation or necrosis(98). In other cases, as with the decision to operate, surgical technique should be decided by an experienced surgeon.

PREVENTION

Infection prevention measures reduce HA-CDI as part of an infection control “bundle”(99). Notably, patients with CDI should have single-occupancy rooms, and providers should wear gown and gloves and use patient-specific equipment (e.g. dedicated stethoscopes)(47, 100). Hand cleaning with soap and water is recommended as alcohol-based hand sanitizers do not reduce *C. difficile* spore burden(101).

As previously discussed, the most important measure to prevent CDI is limiting antibiotic use. For patients who do require systemic antibiotics, one open-label RCT showed that vancomycin prophylaxis reduces CDI among hospitalized patients at high risk of CDI(102). Several retrospective cohort studies have similarly shown that vancomycin prophylaxis is effective for preventing recurrent CDI in patients with a history of CDI who require systemic antibiotics(103, 104), although questions remain about bias and adverse effects of oral vancomycin. There is heterogeneous and low-quality data on probiotics for CDI prevention, although there is a signal for effectiveness among high risk patients(105). Despite this, probiotics are not guideline-recommended due to concern for invasive infection among immunocompromised and severely debilitated patients(47).

CONCLUSIONS

CDI is prevalent in hospitalized patients and can cause significant morbidity and mortality. Critical care clinicians should be aware of CDI risk associated with different antibiotics, indications for CDI testing, therapeutic options, and methods of CDI prevention. For patients with fulminant CDI, early involvement of a multi-disciplinary team is critical for selecting

patients for advanced therapies including FMT and surgery. Although literature on fulminant CDI is increasing, high-quality studies are required to address evidence gaps, including which patients benefit from FMT or surgery, and which patients should receive prophylaxis.

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Table 1.

Risk factors for *Clostridioides difficile* infection.

Risk factor (citation)	Strength of association (95% CI)	Patient population
Patient characteristic		
Age[a] (11)	SMD 0.06 (−0.05%–0.16%)	ICU
ESRD (17)	RR 2.6 (2.0–3.4)	Hospitalized
DM (18)	OR 1.2 (1.1–1.3)	Community
IBD (18)	OR 5.2 (2.5–10.8)	Community
Hematologic malignancy (18)	OR 1.9 (1.1–3.2)	Community
Solid malignancy (18)	OR 1.5 (1.01–2.3)	Community
Antibiotics		
3rd-generation cephalosporins (23)	OR 3.2 (1.8–5.7)	Hospitalized
Clindamycin (23)	OR 2.9 (2.0–4.0)	Hospitalized
4th-generation cephalosporins (23)	OR 2.1 (1.3–3.5)	Hospitalized
Carbapenems (23)	OR 1.8 (1.3–2.7)	Hospitalized
Fluoroquinolones (23)	OR 1.7 (1.2–2.4)	Hospitalized
Penicillin combinations (23)	OR 1.5 (1.1–2.2)	Hospitalized
Number of antibiotics		
2 (24)	HR 2.5 (1.6–4.0)[b]	Hospitalized
3–4 (24)	HR 3.3 (2.2–5.2)[b]	Hospitalized
5+ (24)	HR 9.6 (6.1–15.1)[b]	Hospitalized
Other medications		
Corticosteroids (18)	OR 1.7 (1.1–2.4)	Community
PPIs (35)	OR 0.8 (0.3–2.5)	ICU
Tube feeding (105)	OR 3.1 (1.1–8.7)	Hospitalized

[a]Compared ages of ICU patients with CDI to ICU patients without CDI.

[b]Referent=1.

Abbreviations: CDI=*Clostridioides difficile* infection; CI=confidence interval; DM=diabetes mellitus; ESRD=end-stage renal disease; HR=hazard ratio; IBD=inflammatory bowel disease; ICU=intensive care unit; OR=odds ratio; PPIs=proton-pump inhibitors; RR=risk ratio; SMD=standardized mean difference.

Table 2.

Treatment options for fulminant *Clostridioides difficile* infection.

Therapy	Dose	Indication[a]	Evidence	Note
Best practices • Early multi-disciplinary management (intensivists, infectious diseases clinicians, gastroenterologists, surgeons) • Supportive care: Volume resuscitation, electrolyte repletion, management of co-existing organ failure • Discontinue non-CDI antibiotics as appropriate				
Antibiotics				
• Vancomycin	500 mg PO Q6H	Fulminant CDI	2007 RCT (N=68 patients with severe CDI) (57); several meta-analyses (58–60) demonstrating better outcomes than oral metronidazole	Cornerstone of therapy; low dose (125 mg PO Q6H) reasonable without ileus or megacolon (63)
• Metronidazole	500 mg IV Q8H	Fulminant CDI	2015 retrospective cohort showed lower mortality when added to oral vancomycin (64)	2019 retrospective cohort did not show mortality benefit (65) but may have benefit for ileus; guideline-recommended (47)
• Vancomycin	500 mg PR Q6H	Fulminant CDI with ileus	Small comparative studies (67, 68)	Should be added to oral vancomycin and IV metronidazole; weak recommendation (low quality of evidence) (47)
• Fidaxomicin[b]	200 mg PO BID or extended-pulsed regimen[c]	Not specifically guideline recommended	Trend toward improved cure in RCT subgroup with severe disease (71)	Expensive; proven to reduce CDI recurrence (70); not currently guideline recommended
• Bezlotoxumab[b]	10 mg/kg IV	Not specifically guideline recommended	Decreased recurrence in RCT subgroup with severe disease (72)	Antibody against *C. difficile* toxin B; not currently guideline recommended
• IVIG[b]	150–400 mg/kg IV	Not responding to vancomycin or metronidazole	Small case series (106–108) and meta-analysis (73)	Associated with significant volume administration
• Tigecycline[b]	100 mg IV x1, then 50 mg BID	Not responding to vancomycin or metronidazole	Small retrospective cohort (54)	Largest retrospective cohort (2017) did not show benefit (76)
Fecal microbiota transplant				
• FMT	Protocol-specific	Not specifically guideline recommended	Retrospective cohort study showed decreased mortality compared to antibiotics (86)	Questions remain regarding patient selection, timing, specific FMT protocols
Surgery				
• TAC	n/a	Consider in patients with rising WBC or lactate	Decreased need for re-operation compared to other procedures (88)	Questions remain regarding patient selection and timing; has not been compared to FMT
• LI	n/a	Consider in patients with rising WBC or lactate	Largest cohort study showed no mortality survival compared to TAC (94)	May be colon-preserving; not an option for abdominal compartment syndrome, colon perforation/necrosis (97)

[a] Indication based on 2017 Infectious Diseases Society of America/Society for Healthcare Epidemiology of America *C. difficile* guidelines(47)

[b] These therapies are listed in suggested order of benefit based on authors' opinion, but no specific RCTs have evaluated this. For patients not responding to oral vancomycin, intravenous metronidazole, and rectal vancomycin, decision on which of these medications to administer should be patient-specific and decided by an infectious diseases physician.

[c] 200 mg twice daily, days 1–5; every other day, days 7–25 (71)

Abbreviations: BID=twice daily; CDI=*Clostridioides difficile* infection; FMT=fecal microbiota transplant; IV=intravenous; IVIG=intravenous immune globulin; LI=loop ileostomy with intraoperative colonic lavage and antegrade vancomycin flushes; PO=by mouth; PR=per rectum; Q6H=every 6 hours; Q8H=every 8 hours; RCT=randomized controlled trial; TAC=total abdominal colectomy; WBC=white blood cell.

Table 3.

Summary of comparative studies evaluating fecal microbiota transplant (FMT) for severe or fulminant *Clostridioides difficile* infection.

Author, year (citation)	Country	Study design (N)	Inclusion criteria	Outcome	FMT specifics	Notes
Hocquart, 2019 (76)	France	Single center retrospective cohort (N=64)	One of WBC ≥15,000/μL, albumin <3 g/dL, Cr >1.47 mg/dL or >1.5x baseline; peritonitis, occlusive syndrome, megacolon, or shock	FMT independently associated with mortality reduction (OR 0.08 [95% CI, 0.02–0.34])	Fresh and frozen stool via NGT	Did not specify how many patients met each severe criteria
Tixier, 2019 (84)	USA	Single center matched retrospective cohort (N=48)	Severe or fulminant by 2017 IDSA/ SHEA criteria[a] (47)	FMT associated with mortality reduction (OR 0.23 [95% CI 0.06-0.97]); no difference in colectomy	Frozen stool via colonoscopy or flexible sigmoidoscopy	Very sick cohort (63% pressors, 65% intubated); groups well matched at baseline
Cheng, 2020 (86)	USA	Single center retrospective cohort pre-post FMT program (N=430; 199 fulminant, 110 refractory SFCDI)	Severe or fulminant by 2017 IDSA/ SHEA criteria[a] (47); refractory SFCDI[b] separate	FMT program associated with decreased CDI-related mortality and colectomy in all groups	Majority frozen-thawed stool via colonoscopy	Among fulminant CDI group (mean CCI 5.7), mortality decreased post-FMT (9.1% vs. 21.3%, p=0.02)

[a]2017 Infectious Diseases Society of America/Society for Healthcare Epidemiology of America *C. difficile* guidelines

[b]Refractory severe or fulminant CDI defined as severe or fulminant CDI with worsening or no significant improvement in parameters including diarrhea, leukocytosis, hypotension, need for vasopressors after 5 days of maximal CDI therapy.

Abbreviations: CCI=Charlson comorbidity index; CI=confidence interval; Cr=creatinine; FMT=fecal microbiota transplant; N=number of patients included (in fulminant group if multiple groups in study); NGT=nasogastric tube; OR=odds ratio; SFCDI=severe or fulminant refractory *Clostridioides difficile* infection; USA=United States of America; WBC=white blood cell