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Gastroenterology for Geriatric Patients (S Katz and A Afzali, Section Editors)

Treatment of Severe and Fulminnant *Clostridioides difficile* Infection

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Abstract

Purpose of review This article will review current management strategies for severe and fulminant *Clostridioides difficile* infection (CDI).
Recent findings Clostridioides difficile is the most common nosocomial cause of infectious diarrhea. With the rise of hypervirulent strains of CDI, almost 8% of patients hospitalized with CDI are afflicted with severe CDI (SCDI) or fulminant CDI (FCDI). A significant proportion of these patients do not respond to recommended anti-CDI antibiotic therapy such as oral vancomycin and fidaxomicin. Current recommendations suggest that patients with refractory CDI should proceed to colectomy or diverting loop ileostomy with colonic lavage. However, both of these surgical interventions result in high rates of post-surgical mortality approaching 30%. Fecal microbiota transplantation (FMT) is a promising therapy that is recommended in recurrent CDI. Recent studies have found that FMT can safely produce cure rates between 70 and 90% in patients with SCDI and FCDI, while significantly decreasing rates of CDI-related mortality and colectomy. A patient population likely to benefit the most from FMT is elderly patients due to their increased risk for CDI, treatment failure, and high comorbidity burden that may preclude surgical intervention.
Summary FMT should be considered in patients with SCDI or FCDI particularly when traditional anti-CDI antibiotics are ineffective.

Introduction

Between 2000 and 2010, the incidence of *Clostridioides difficile* infections among hospitalized adults effectively doubled due to the emergence of the ribotype 027 strain of *C. difficile* [1]. This hypervirulent strain demonstrated increased toxin production, leading to increased disease severity, recurrence, and a 15% increase in CDI-related mortality [2, 3].

The most recent set of CDI management guidelines was published by the Infectious Disease Society of America (IDSA) in 2018 [4]. Compared to its prior iteration in 2010 [5] and the American College of Gastroenterology's 2013 guidelines [6], there are three notable changes. Fecal microbiota transplantation is now recommended therapy for recurrent CDI, metronidazole is no longer recommended as first-line therapy for CDI, and fidaxomicin was added as alternative therapy for non-severe and severe CDI. Disappointingly, treatment for fulminant CDI has been unchanged. Only high dose oral vancomycin (with the addition of IV metronidazole and vancomycin per rectum for cases of ileus or toxic megacolon) is recommended therapy for fulminant CDI, with colectomy serving as salvage therapy.

Identification of severe or fulminant CDI

Severe and fulminant CDI represents infection highly associated with poor outcomes including organ dysfunction, colectomy, and mortality. A variety of objective clinical findings and parameters have been associated with development of CDI, including severe elderly age, serum white blood cell count > 20,000 cells/mL, serum albumin concentration < 2.5 g/dL, colonic obstruction or ileus, colorectal inflammation on diagnostic imaging, and infection with the ribotype 027 strain of *Clostridioides difficile* [7–9]. More recently, increasing rates of community-acquired CDI have been described, defined as diagnosis of CDI within 72 h of hospitalization without documented overnight stay in a healthcare facility within the 12 weeks preceding admission [10]. Healthcare-associated CDI compared to community-acquired CDI results in higher rates of mortality (9.3% vs 1.3%) and subsequent recurrence (21% vs 13.5%) when CDI is acquired in a healthcare setting [11].

Comparison of the 2013 ACG guidelines and the 2018 IDSA guidelines reflects obvious differences in the clinical criteria used to stratify CDI severity, a reflection of the difficulty in the predicting disease course in CDI. As such, studies have attempted to identify alternative methods of predicting severe CDI using established laboratory tests. Comparing stool *Clostridioides difficile* toxin (CDT) concentrations between patients with mild-moderate CDI to those with severe CDI, CDT was significantly higher in those with severe CDI (651 ng/mL vs 164 ng/mL, $p = 0.001$) and a cut off of > 2500 ng/mL was associated with a 46.6% versus 10.3% mortality rate [12].

Other studies have utilized the median cycle threshold (MCT) in nucleic acid amplification testing (NAAT) of *C. difficile* toxin to predict CDI disease course. A lower MCT, which corresponds to a higher toxin burden leading to fewer PCR cycles needed for detection, was associated with greater rates of mortality, increased median length of stay, severe CDI, and failure of first-line anti-CDI therapies [13, 14]. In elderly patients with CDI, calprotectin levels greater than 2000 μg/g were found to be associated with a 25-fold higher rate of intensive care unit admission, colectomy, and mortality [15].

Treatment of severe and fulminant CDI

Medical management

Vancomycin has been a mainstay of anti-CDI therapy for severe and fulminant CDI. Multiple studies have demonstrated vancomycin's superiority over metronidazole in the treatment of severe CDI [16] even in the context of hypervirulent ribotype 027 *Clostridioides difficile* [17]. In a large cohort study comprised of 3130 severe CDI patients, patients receiving vancomycin had decreased 30-day mortality rates compared to those receiving metronidazole (19.8% vs 15.3%, $p = 0.01$) [18]. With increasing rates of metronidazole resistance in CDI, prompting the IDSA to drop metronidazole as first-line therapy in mild-moderate CDI, the discrepancy in CDI cure and subsequent outcomes will likely increasingly favor vancomycin over metronidazole. A more recent study of 122 patients with severe CDI demonstrated that patients who received metronidazole before switching to vancomycin ≥ 48 h had increased hospital length of stay (13 vs 7 days, $p < 0.001$), higher rates of acute kidney injury (AKI) (29.4% vs 8.7%, $p = 0.03$), and lower rates of cure (20% vs 45%, $p = 0.02$) compared to patients who received vancomycin at time of diagnosis [19].

Fidaxomicin has also been added to the list of recommended therapies for severe and fulminant CDI. In patients with CDI, a prospective, double-blind, randomized-controlled trial (RCT) found that fidaxomicin was non-inferior to vancomycin for CDI cure [20], and that the recurrence rates after 30 days was significantly lower in the fidaxomicin group (13.0% vs 26.6%, $p = 0.02$). In a subsequent double-blind RCT comparing fidaxomicin to vancomycin, subgroup analysis of patients with severe CDI demonstrated no significant differences in clinical cure (76.2% vs 70.5%) and rates of recurrence (8.3% vs 32.6%) [21].

As it pertains to fulminant CDI, the IDSA and ACG recommend a higher dose of oral vancomycin at 500 mg every 6 h. While such an approach intuitively makes sense, direct comparison of low dose (125 mg) and high dose (500 mg) oral vancomycin have not yielded significant differences in CDI-related mortality or complications [22, 23]. In cases of ileus and toxic megacolon, the addition of IV metronidazole results in decreased mortality compared to vancomycin monotherapy (15.9% vs 36.4%, $p = 0.03$) [24], while the addition of vancomycin enemas has not definitively been shown to improve outcomes [25]. Nevertheless, these expert recommendations should be followed due to the lack of alternative therapies available in these high-risk patients.

Tigecycline and intravenous immunoglobulin (IVIG) have also been investigated as potential treatments for severe CDI, however experience with these alternative treatments have been limited to case series [26–28].

Surgical management

Surgical management of CDI should be considered for cases of generalized peritonitis, toxic megacolon, and colonic perforation [29, 30]. Failure of medical management with anti-CDI antibiotics (refractory CDI), white blood cell count > 25,000 cells/mL, lactate > 5 mmol/L, septic shock, and multiorgan failure should prompt surgical evaluation [31] because mortality in refractory

fulminant CDI can approach 80% without surgery [32]. Surgical management decreases mortality in refractory fulminant CDI compared to continued medical management (OR 0.70) [33]. Unfortunately, there are no specific clinical parameters to specify when a patient's clinical course becomes refractory or when surgery is absolutely indicated.

While surgical management of CDI is potentially curative, it is by no means benign. A large database study found that 30-day mortality after surgical management for CDI was 32.7% [34] while a meta-analysis demonstrated mortality of 41.3% [29]. It is worthwhile to note that the latter study conducted by Bhangu and colleagues demonstrated that almost 89% of cases were managed with total abdominal colectomy (TAC). The IDSA guidelines have recently added diverting loop ileostomy (DLI) with colonic lavage with antegrade vancomycin flush as an alternative surgical approach, albeit with a weak recommendation based on low quality of evidence. Compared to TAC, DLI was found to improve rates of post-operative mortality (19% vs 50%, $p = 0.006$), with the added benefit of a preserved colon in 93% of patients [35]. However, a subsequent comparison did not indicate a clearly superior approach. Upon comparison of TAC to DLI, this study found 30-day mortality (23% vs 30%, $p = 1.0$) and 1-year mortality (46% vs 40%, $p = 1.0$) to be comparable [36].

In theory, patients that are more stable prior to surgery should have better post-operative outcomes, thus some experts have recommended early surgical intervention [37]. Unfortunately, it is unclear which patients would benefit from such an early and aggressive approach. Several models have been devised to identify patients who are likely to undergo a complicated course of CDI based on objective clinical parameters such as age, recent abdominal surgery, hypotension, reason for admission, level of care at time of CDI diagnosis, white blood cell count, and serum creatinine [38–40]. A complicated course was generally defined as ICU admission, colectomy, and/or death. Subsequent external validation demonstrated that the two prediction models by Na et al. and Hensgens et al. had a specificity of 87–90% and negative predictive value of 87–95% [41]. However, there was low sensitivity (26–46%) and positive predictive value (23–30%), thus these models would likely identify patients without complicated disease, but overestimate the number of patients with it. Use of these models to identify patients that should undergo early surgical intervention would likely result in a significant number of patients being unnecessarily exposed to surgical intervention, its risks, and its associated morbidities.

Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) is now recommended treatment for recurrent CDI [4, 6] due to high rates of cure [42] and superior rates of recurrence compared to oral vancomycin and fidaxomicin [43]. Even in immunosuppressed patients, FMT has been highly safe [44–47]. FMT quickly restores microbial diversity and a favorable balance of commensal bacteria resulting, which competitively inhibits *Clostridioides difficile* activity and restores gut barrier function [48–50]. Specific details about donor screening, FMT delivery, and post-FMT follow up are readily available [51•, 52]. The widespread reach of stool banks has simplified procurement of donor stool and decreases wait time to infusion, which may be critical in patients with fulminant CDI [53].

Rates of cure for SCDI after a single FMT have been promising, however cases of FCDI extrapolated from larger studies designed primarily to assess efficacy of FMT in recurrent CDI were initially disappointing. A multicenter, retrospective study demonstrated that among 45 patients with SCDI and 12 patients with FCDI, a single FMT produced cure rates of 91% and 66%, respectively [54]. Additional studies have demonstrated that FMT in patients with FCDI are not completely ineffective. In a case series of four patients with FCDI, FMT produced temporary improvements in hemodynamic stability and decreased vasopressor requirement for 3 to 5 days [55]. This clinical phenomenon led to development of various sequential FMT protocols.

Sequential FMT protocols by Fischer et al. [56••] and Cammarota et al. [57] have produced high rates of cure in cases of SCDI, FCDI, and refractory CDI. In the Fischer protocol, patients with SCDI or FCDI who fail PO vancomycin after a five-day course are offered FMT via colonoscopy. Absence of pseudomembranes visualized during colonoscopy generally predicts response to FMT, while the presence of pseudomembranes prompts re-initiation of oral vancomycin within 48 h of FMT due to high rates of failure. If CDI persists after another 5-day course oral vancomycin, FMT can be re-delivered in a sequential manner until pseudomembranes resolve. In a retrospective study of 57 patients undergoing this protocol, CDI cure was 100% in SCDI and 87% in FCDI [58]. The Cammarota protocol, which shortens the length of initial oral vancomycin therapy to 3 days and delivers FMT(s) every 3 days until resolution of pseudomembranes also found high rates of cure in SCDI and FCDI patients. In a randomized clinical trial consisting of patients with SCDI, a single FMT produced 75% cure while the sequential protocol achieved 100% cure [59].

Importantly, FMT in patients with SCDI and FCDI can significantly decrease rates of mortality and colectomy. Between 2010 and 2014, Cammarota and colleagues described a quadrupling in the rate of CDI diagnoses in hospitalized patients; however, introduction of FMT in 2013 resulted in a significant decline in CDI-related colectomies [60]. In another retrospective study by Hocquart and colleagues, 3-month mortality among patients with SCDI was 42.2% in those receiving standard anti-CDI therapy and only 12.1% in those receiving an early FMT ($p < 0.0001$) [61••]. Among 430 patients with SCDI and FCDI, patients that received sequential FMT compared to anti-CDI antibiotics had lower 30-day CDI-related mortality (4.5% vs 10.2%, $p = 0.021$) and colectomy (2.7% vs 6.8%, $p = 0.042$) [62].

The effect of FMT on patients with refractory CDI who would have otherwise undergone surgical intervention may be even more substantial. In a retrospective cohort study containing 110 patients with refractory SCDI and FCDI, the introduction of a sequential FMT program was associated with decreased CDI-mortality (43.2% pre-FMT vs 12.1% post-FMT, $p < 0.001$) and colectomy (31.8% pre-FMT vs 7.6% post-FMT, $p = 0.001$) compared to traditional anti-CDI antibiotics [62]. A subset of 32 refractory CDI patients were considered too ill for colectomy by surgical consultation. Among these, the 17 patients who continued with anti-CDI antibiotics were compared to 15 who underwent sequential FMT, mortality improved dramatically (82.4% vs 20.0%, $p = 0.001$) [63].

There is growing evidence that FMT can be highly effective for SCDI and FCDI cure. Aside from improving rates of mortality in this patient population,

FMT has also been associated with decreased rates of colectomy. FMT adds to the armamentarium that clinicians have to combat complicated courses of CDI and may allow patients to avoid colectomy and all of the surgical risks and post-operative complications associated with such invasive procedures. Likewise, adding an additional medical therapy in the form of FMT further decreases clinical uncertainty surrounding recognizing patients as failing anti-CDI therapy. In cases where patients are poor surgical candidates due to comorbid conditions, FMT could replace surgical intervention as salvage therapy.

CDI in elderly patients

Elderly patients (age ≥ 65 years) are at higher risk of CDI than their younger counterparts [64, 65]. This has been attributed to increased exposure to CDI risk factors such as antibiotic use, hospitalization, stay in a long-term care facility, and multiple comorbid conditions [66]. However, researchers have also postulated that elderly patients have decreased immune function and altered gut motility that predisposes to *Clostridioides difficile* colonization and propagation [67, 68]. Elderly patients are also at higher risk for adverse outcomes compared to younger patients, accounting for the vast majority of CDI-related deaths and CDI-related mortality [69]. Elderly patients are also at higher risk of requiring colectomy as part of their CDI disease course [70].

Because CDI disproportionately affects elderly patients, studies of FMT for treatment of CDI have contained large numbers of elderly patients. A review article that included 115 FMTs delivered to elderly patients for recurrent CDI across 10 studies found a cure rate of 89.6% [71•]. A multicenter study described treatment response to FMT in 146 elderly patients with a diagnosis of recurrent CDI (61%), SCDI (30.8%), and FCDI (8.2%), with primary cure rates of 82%, 91%, and 66%, respectively [54]. Subsequent antibiotics given when a single FMT failed boosted cure rates to 95.9%. FMT was remarkably safe in this population, with only 6 serious adverse events (all hospitalizations due to CDI-related diarrhea) one that resulted in death. The majority of patients (69.2%) were also found to have improvements in functional status and quality of life after FMT, though these variables was not explicitly defined or quantified.

With regard to efficacy, a systemic review found that cure for recurrent CDI after a single FMT was decreased in patients ≥ 65 years compared to those < 65 years (87.0% vs 99.4%) [72]. Recurrence of CDI within 90 days was also noted to be higher in elderly patients (4.9% vs 0.1%). Overall, these studies highlight that FMT is effective and safe in elderly patients, however subsequent antibiotics or repeat FMT(s) may be necessary to induce lasting cure.

Conclusion

The treatment paradigm for severe and fulminant CDI has changed only marginally over the past two decades with the addition of fidaxomicin as alternative therapy. While colectomy or DLI are options for refractory cases, post-operative mortality continues to be high. The emergence of FMT as a viable option with high rates of cure in patients with SCDI and FCDI is promising step, which may allow a substantial portion of patients to avoid colectomy when traditional anti-CDI therapies fail. A patient population likely to benefit the most from

FMT is elderly patients due to their increased risk for CDI, treatment failure, and high comorbidity burden that may preclude surgical intervention.

Compliance with ethical standards

Conflict of interest
Yao-Wen Cheng declares that he has no conflict of interest. Monika Fischer declares that she has no conflict of interest.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
• Of importance
••Of major importance

1. Gould CV, McDonald LC, Lessa FC. Current status of *Clostridium difficile* infection epidemiology. Clin Infect Dis. 2012;**55**(suppl_2):S65–70.
2. Rao K, Micic D, Natarajan M, Winters S, Kiel MJ, Walk ST, et al. Clostridium difficile ribotype 027: relationship to age, detectability of toxins A or B in stool with rapid testing, severe infection, and mortality. Clin Infect Dis. 2015;61(2):233–41.
3. Vindigni SM, Surawicz CM. C. difficile infection: changing epidemiology and management paradigms. Clin Transl Gastroenterol. 2015;6(7):e99–9.
4. McDonald LC, et al. Clinical practice guidelines for Clostridium difficile infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018;66(7):e1–e48.
5. Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald L, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol. 2010;31(5):431–55.
6. Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, et al. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. Am J Gastroenterol. 2013;108(4):478–98 quiz 499.
7. Miller M, et al. Health care-associated Clostridium difficile infection in Canada: patient age and infecting strain type are highly predictive of severe outcome and mortality. Clin Infect Dis. 2010;50(2):194–201.
8. Lessa FC, et al. NAP1 strain type predicts outcomes from Clostridium difficile infection. Clin Infect Dis. 2014;58(10):1394–400.
9. Henrich TJ, et al. Clinical risk factors for severe Clostridium difficile-associated disease. Emerg Infect Dis. 2009;15(3):415–22.
10. Chitnis AS, Holzbauer SM, Belflower RM, Winston LG, Bamberg WM, Lyons C, et al. Epidemiology of community-associated Clostridium difficile infection, 2009 through 2011. JAMA Intern Med. 2013;173(14):1359–67.
11. Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK, Dunn JR, et al. Burden of Clostridium difficile infection in the United States. N Engl J Med. 2015;372(9):825–34.
12. Cohen NA, Miller T, Na'aminh W, Hod K, Adler A, Cohen D, et al. Clostridium difficile fecal toxin level is associated with disease severity and prognosis. United European Gastroenterol J. 2017;6(5):773–80.
13. Davies KA, Planche T, Wilcox MH. The predictive value of quantitative nucleic acid amplification detection of Clostridium difficile toxin gene for faecal sample toxin status and patient outcome. PLoS One. 2018;13(12):e0205941.
14. Garvey MI, et al. Can a toxin gene NAAT be used to predict toxin EIA and the severity of Clostridium difficile infection? Antimicrob Resist Infect Control. 2017;6(1):127.
15. Rao K, Santhosh K, Mogle JA, Higgins PD, Young VB. Elevated fecal calprotectin associates with adverse outcomes from Clostridium difficile infection in older adults. Infect Dis. 2016;48(9):663–9.

16. Davis MB, et al. A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile–associated diarrhea, stratified by disease severity. Clin Infect Dis. 2007;45(3):302–7.
17. Johnson S, et al. Vancomycin, metronidazole, or tolevamer for Clostridium difficile infection: results from two multinational, randomized, Controlled Trials. Clin Infect Dis. 2014;59(3):345–54.
18. Stevens VW, Nelson RE, Schwab-Daugherty EM, Khader K, Jones MM, Brown KA, et al. Comparative effectiveness of vancomycin and metronidazole for the prevention of recurrence and death in patients with Clostridium difficile infection. JAMA Intern Med. 2017;177(4):546–53.
19. Shah, S., B. Ereshefsky, L. Pontiggia, and M. Cawley. 2019. "Impact of Delayed Oral Vancomycin for Severe Clostridium difficile Infection." Hosp Pharm 54 (5):294-299. https://doi.org/10.1177/0018578718787439
20. Louie TJ, Miller MA, Mullane KM, Weiss K, Lentnek A, Golan Y, et al. Fidaxomicin versus vancomycin for Clostridium difficile infection. N Engl J Med. 2011;364(5):422–31.
21. Cornely OA, Nathwani D, Ivanescu C, Odufowora-Sita O, Retsa P, Odeyemi IA. Clinical efficacy of fidaxomicin compared with vancomycin and metronidazole in Clostridium difficile infections: a meta-analysis and indirect treatment comparison. J Antimicrob Chemother. 2014;69(11):2892–900.
22. Fekety R, Silva J, Kauffman C, Buggy B, Deery HG. Treatment of antibiotic-associated Clostridium difficile colitis with oral vancomycin: comparison of two dosage regimens. Am J Med. 1989;86(1):15–9.
23. Lam SW, et al. Effect of vancomycin dose on treatment outcomes in severe Clostridium difficile infection. Int J Antimicrob Agents. 2013;42(6):553–8.
24. Rokas KE, Johnson JW, Beardsley JR, Ohl CA, Luther VP, Williamson JC. The addition of intravenous metronidazole to oral vancomycin is associated with improved mortality in critically ill patients with Clostridium difficile infection. Clin Infect Dis. 2015;61(6):934–41.
25. Malamood M, et al. Vancomycin enemas as adjunctive therapy for Clostridium difficile infection. J Clin Med Res. 2015;7(6):422–7.
26. Larson KC, Belliveau PP, Spooner LM. Tigecycline for the treatment of severe Clostridium difficile infection. Ann Pharmacother. 2011;45(7–8):1005–10.
27. Britt NS, et al. Tigecycline for the treatment of severe and severe complicated Clostridium difficile infection. Infect Dis Ther. 2014;3(2):321–31.
28. Coffman K, Chen XJ, Okamura C, Louie E. IVIG–A cure to severe refractory NAP-1 Clostridium difficile colitis? A case of successful treatment of severe infection, which failed standard therapy including fecal microbiota transplants and fidaxomicin. IDCases. 2017;8:27–8.
29. Bhangu A, Nepogodiev D, Gupta A, Torrance A, Singh P, West Midlands Research Collaborative. Systematic review and meta-analysis of outcomes following emergency surgery for Clostridium difficile colitis. Br J Surg. 2012;99(11):1501–13.
30. Steele SR, McCormick J, Melton GB, Paquette I, Rivadeneira DE, Stewart D, et al. Practice parameters for the management of Clostridium difficile infection. Dis Colon Rectum. 2015;58(1):10–24.
31. Lamontagne F, Labbé AC, Haeck O, Lesur O, Lalancette M, Patino C, et al. Impact of emergency colectomy on survival of patients with fulminant Clostridium difficile colitis during an epidemic caused by a hypervirulent strain. Ann Surg. 2007;245(2):267–72.
32. Bhangu S, Bhangu A, Nightingale P, Michael A. Mortality and risk stratification in patients with Clostridium difficile-associated diarrhoea. Color Dis. 2010;12(3):241–6.
33. Stewart DB, Hollenbeak CS, Wilson MZ. Is colectomy for fulminant Clostridium difficile colitis life saving? A systematic review. Color Dis. 2013;15(7):798–804.
34. Kulaylat AS, Kassam Z, Hollenbeak CS, Stewart DB Sr. A surgical Clostridium-associated risk of death score predicts mortality after colectomy for Clostridium difficile. Dis Colon Rectum. 2017;60(12):1285–90.
35. Neal MD, et al. Diverting loop ileostomy and colonic lavage: an alternative to total abdominal colectomy for the treatment of severe, complicated Clostridium difficile associated disease. Ann Surg. 2011;254(3):423–7 discussion 427-9.
36. Fashandi AZ, Martin AN, Wang PT, Hedrick TL, Friel CM, Smith PW, et al. An institutional comparison of total abdominal colectomy and diverting loop ileostomy and colonic lavage in the treatment of severe, complicated *Clostridium difficile* infections. Am J Surg. 2017;213(3):507–11.
37. Hall JF, Berger D. Outcome of colectomy for Clostridium difficile colitis: a plea for early surgical management. Am J Surg. 2008;196(3):384–8.
38. Hensgens MP, Dekkers OM, Goorhuis A, LeCessie S, Kuijper EJ. Predicting a complicated course of Clostridium difficile infection at the bedside. Clin Microbiol Infect. 2014;20(5):O301–8.
39. van der Wilden GM, et al. Fulminant Clostridium difficile colitis: prospective development of a risk scoring system. J Trauma Acute Care Surg. 2014;76(2):424–30.
40. Na X, Martin AJ, Sethi S, Kyne L, Garey KW, Flores SW, et al. A multi-center prospective derivation and validation of a clinical prediction tool for severe Clostridium difficile infection. PLoS One. 2015;10(4):e0123405.
41. Beauregard-Paultre C, et al. External validation of clinical scores to predict complications of *Clostridium difficile* infection. Open Forum Infect Dis. 2017;4(suppl_1):S402–2.
42. Kassam Z, Lee CH, Yuan Y, Hunt RH. Fecal microbiota transplantation for Clostridium difficile infection: systematic review and meta-analysis. Am J Gastroenterol. 2013;108(4):500–8.

43. Gough E, Shaikh H, Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent Clostridium difficile infection. Clin Infect Dis. 2011;53(10):994–1002.
44. Fischer M, Kao D, Kelly C, Kuchipudi A, Jafri SM, Blumenkehl M, et al. Fecal microbiota transplantation is safe and efficacious for recurrent or refractory Clostridium difficile infection in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2016;22(10):2402–9.
45. Kelly CR, Ihunnah C, Fischer M, Khoruts A, Surawicz C, Afzali A, et al. Fecal microbiota transplant for treatment of Clostridium difficile infection in immunocompromised patients. Am J Gastroenterol. 2014;109(7):1065–71.
46. Cheng Y-W, et al. Mo1954 – Fecal microbiota transplantation is safe and effective for the treatment of *Clostridium difficile* infection in patients with liver cirrhosis. Gastroenterology. 2019;**156**(6):S-898–9.
47. Cheng, Y. W., E. Phelps, V. Ganapini, N. Khan, F. Ouyang, H. Xu, S. Khanna, R. Tariq, R. J. Friedman-Moraco, M. H. Woodworth, T. Dhere, C. S. Kraft, D. Kao, J. Smith, L. Le, N. El-Nachef, N. Kaur, S. Kowsika, A. Ehrlich, M. Smith, N. Safdar, E. A. Misch, J. R. Allegretti, A. Flynn, Z. Kassam, A. Sharfuddin, R. Vuppalanchi, and M. Fischer. 2019. "Fecal microbiota transplantation for the treatment of recurrent and severe Clostridium difficile infection in solid organ transplant recipients: A multicenter experience." Am J Transplant 19 (2):501-511. https://doi.org/10.1111/ajt.15058.
48. Chang JY, Antonopoulos DA, Kalra A, Tonelli A, Khalife WT, Schmidt TM, et al. Decreased diversity of the fecal microbiome in recurrent Clostridium difficile-associated diarrhea. J Infect Dis. 2008;197(3):435–8.
49. Wilson KH, Perini F. Role of competition for nutrients in suppression of Clostridium difficile by the colonic microflora. Infect Immun. 1988;56(10):2610–4.
50. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell. 2014;157(1):121–41.
51.• Allegretti JR, et al. The 5D framework: a clinical primer for fecal microbiota transplantation to treat *Clostridium difficile* infection. Gastrointest Endosc. 2018;87(1):18–29.

Clinically-focused discussion of patient/donor selection for FMT and infrastructure necessary for delivery.

52. Krajicek E, et al. Nuts and bolts of fecal microbiota transplantation. Clin Gastroenterol Hepatol. 2019;17(2):345–52.
53. Panchal P, Budree S, Scheeler A, Medina G, Seng M, Wong WF, et al. Scaling safe access to fecal microbiota transplantation: past, present, and future. Curr Gastroenterol Rep. 2018;20(4):14.
54. Agrawal M, Aroniadis OC, Brandt LJ, Kelly C, Freeman S, Surawicz C, et al. The long-term efficacy and safety of fecal microbiota transplant for recurrent, severe, and complicated Clostridium difficile infection in 146 elderly individuals. J Clin Gastroenterol. 2016;50(5):403–7.
55. Weingarden AR, et al. Resolution of severe Clostridium difficile infection following sequential fecal microbiota transplantation. J Clin Gastroenterol. 2013;47(8):735–7.
56.•• Fischer M, et al. Faecal microbiota transplantation plus selected use of vancomycin for severe-complicated *Clostridium difficile* infection: description of a protocol with high success rate. Aliment Pharmacol Ther. 2015;42(4):470–6.

Describes a sequential FMT protocol with high rates of success in patients with SCDI and FCDI.

57. Cammarota G, et al. Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent Clostridium difficile infection. Aliment Pharmacol Ther. 2015;41(9):835–43.
58. Fischer, M., B. Sipe, Y. W. Cheng, E. Phelps, N. Rogers, S. Sagi, M. Bohm, H. Xu, and Z. Kassam. 2017. "Fecal microbiota transplant in severe and severe-complicated Clostridium difficile: A promising treatment approach." Gut Microbes 8 (3):289-302. https://doi.org/10.1080/19490976.2016.1273998.
59. Ianiro G, Masucci L, Quaranta G, Simonelli C, Lopetuso LR, Sanguinetti M, et al. Randomised clinical trial: faecal microbiota transplantation by colonoscopy plus vancomycin for the treatment of severe refractory Clostridium difficile infection—single versus multiple infusions. Aliment Pharmacol Ther. 2018;48(2):152–9.
60. Cammarota G, Ianiro G, Magalini S, Gasbarrini A, Gui D. Decrease in surgery for Clostridium difficile infection after starting a program to transplant fecal microbiota. Ann Intern Med. 2015;163(6):487–8.
61.•• Hocquart M, et al. Early fecal microbiota transplantation improves survival in severe *Clostridium difficile* infections. Clin Infect Dis. 2018;66(5):645–50.

Great discussion about use of FMT in SCDI despite lack of randomized control trials.

62. Cheng Y-W, et al. Inpatient fecal microbiota transplant program decreases mortality and colectomy in severe and/or complicated Clostridium difficile infection: 101. Am J Gastroenterol. 2017;112:S48–50.
63. Cheng Y-W, et al. Fecal microbiota transplant decreases mortality in patients with refractory severe and severe complicated *Clostridium difficile* infection Not Eligible for Colectomy: 2017 Fellows-in-Training Award (Colon Category): 100. Am J Gastroenterol. 2017;**112**:S48–50.
64. Napolitano, L. M., and C. E. Edmiston, Jr. 2017. "Clostridium difficile disease: Diagnosis, pathogenesis, and treatment update." Surgery 162 (2):325-348. https://doi.org/10.1016/j.surg.2017.01.018.
65. Pépin J, Valiquette L, Cossette B. Mortality attributable to nosocomial Clostridium difficile–associated disease during an epidemic caused by a hypervirulent strain in Quebec. Can Med Assoc J. 2005;173(9):1037–42.
66. DePestel DD, Aronoff DM. Epidemiology of Clostridium difficile infection. J Pharm Pract. 2013;26(5):464–75.

67. Franceschi C, et al. Inflamm-aging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci. 2000;908:244–54.
68. Lovat LB. Age related changes in gut physiology and nutritional status. Gut. 1996;38(3):306–9.
69. Minino AM, et al. Deaths: final data for 2008. Natl Vital Stat Rep. 2011;59(10):1–126.
70. Kasper AM, Nyazee HA, Yokoe DS, Mayer J, Mangino JE, Khan YM, et al. A multicenter study of Clostridium difficile infection-related colectomy, 2000-2006. Infect Control Hosp Epidemiol. 2012;33(5):470–6.
71.• Burke KE, Lamont JT. Fecal transplantation for recurrent Clostridium difficile infection in older adults: a review. J Am Geriatr Soc. 2013;61(8):1394–8.
A systematic review of cure rates after FMT in elderly patients.
72. Li YT, Cai HF, Wang ZH, Xu J, Fang JY. Systematic review with meta-analysis: long-term outcomes of faecal microbiota transplantation for Clostridium difficile infection. Aliment Pharmacol Ther. 2016;43(4):445–57.

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