THERAPEUTIC ADVANCES in
Gastroenterology

Review

The impact of the COVID-19 pandemic on *Clostridioides difficile* infection and utilization of fecal microbiota transplantation

Ther Adv Gastroenterol

2023, Vol. 16: 1–8

DOI: 10.1177/17562848231165581

© The Author(s), 2023.
Article reuse guidelines: sagepub.com/journals-permissions

Salam P. Bachour, Rahul Dalal and Jessica R. Allegretti

***Abstract*:** Previous research has demonstrated that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) gains cell entry through the angiotensin-converting enzyme 2 receptor, which is abundantly found throughout the gastrointestinal (GI) tract, resulting in a wide array of GI manifestations of coronavirus disease 2019 (COVID-19). By gaining entry into the intestinal epithelial and stromal cells, SARS-CoV-2 has been observed to cause intestinal inflammation and gut dysbiosis. Alterations in gut microbiota are known to be involved in the pathophysiology of *Clostridioides difficile* infection (CDI). During the initial stages of the COVID-19 pandemic, rates of CDI were similar to historical data despite the increased use of antibiotics. This may be due to increased emphasis on hygiene and protective equipment and reduced *C. difficile* testing as diarrhea was presumed to be COVID-19 related. Studies also demonstrated additional risk factors for CDI in COVID-19 patients, including length of hospitalization and new abdominal pain during admission. Although not associated with increased mortality, CDI was associated with increased length of hospital stay among patients admitted with COVID-19. Due to fecal viral shedding and concern of oral–fecal transmission of SARS-CoV-2, increased safety regulations were introduced to fecal microbiota transplantation (FMT) leading to reduced rates of this procedure during the COVID-19 pandemic. FMT for recurrent CDI during the COVID-19 pandemic remained highly effective without any reports of SARS-CoV-2 transmission. In addition, limited data show that FMT may be effective in treating COVID-19 and restoring healthy gut microbiota. The goal of this article is to review the impact that the COVID-19 pandemic has had on hospital-acquired CDI and the utilization of FMT.

Keywords: *Clostridoides difficile*, COVID-19, infectious diarrhea

Received: 11 November 2022; revised manuscript accepted: 6 March 2023.

Correspondence to:
Jessica R. Allegretti
Division of Gastroenterology, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115-6110, USA

Harvard Medical School, Boston, MA, USA
jallegretti@bwh.harvard.edu

Salam P. Bachour
Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA

Harvard Medical School, Boston, MA, USA

Rahul Dalal
Harvard Medical School, Boston, MA, USA

Division of Gastroenterology, Brigham and Women's Hospital, Boston, MA, USA

Introduction

Clostridioides difficile infection (CDI) remains a healthcare epidemic, impacting approximately half of a million individuals in the United States annually with a mortality rate of approximately 6%.[1] CDI most commonly occurs in those recently treated with antibiotics, those with suppressed immunity, the elderly, and those with recent exposure to the healthcare system – though community-acquired CDI is becoming more common.[1] Primary CDI is treated with oral vancomycin or fidaxomicin, although recent Infectious Disease Society of America guidelines positioned fidaxomicin over vancomycin as the preferred treatment.[2] However, 15–30% of patients experience recurrent CDI (rCDI), defined as a recurrence of symptoms within 8 weeks following treatment for CDI.[3–5] For patients who have failed appropriate treatment for three or more episodes of CDI, fecal microbiota transplantation (FMT) is indicated for the prevention of subsequent recurrences. FMT

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

consists of the infusion of healthy donor fecal microbiota into a recipient with the aim of restoring healthy microbial flora. FMT has been shown to be highly efficacious in rCDI.[6–9]

The worldwide coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had a significant impact on the healthcare system and healthcare delivery. In the early stages of the pandemic, there was a concern that SARS-CoV-2 infection would increase the risk of superimposed bacterial infections, which led to an increase in antibiotic utilization that could predispose individuals to CDI.[10] However, due to concern regarding fecal–oral transmission of SARS-CoV-2, pandemic regulations limited the availability of FMT, which is an important treatment option for recurrent or fulminant CDI.[11] This review aims to explore the pathophysiologic relationship and healthcare impact of the COVID-19 pandemic on CDI and FMT.

Gastrointestinal pathophysiology of COVID-19

Similar to SARS-CoV-1, the angiotensin-converting enzyme 2 (ACE2) serves as the functional viral receptor required for SARS-CoV-2 entry into host cells.[12–16] ACE2 host expression is commonly seen in the epithelial cells of the upper and lower respiratory tract, leading to the commonly observed respiratory symptoms associated with SARS-CoV-2. However, ACE2 is heavily expressed in the stratified epithelium of the upper esophagus in addition to the epithelial and stromal cells of all parts of the small intestine and colon.[14,17–20] This high expression of ACE2 in the absorptive enterocytes of the small intestine and colon is most likely the cause of the gastrointestinal (GI) manifestations of SARS-CoV-2.

GI symptoms have been reported among COVID-19 patients, and a meta-analysis of 60 studies comprising 4243 patients demonstrated that 17.6% of COVID-19 patients experienced GI symptoms, with higher rates in patients with severe COVID-19.[21–28] This meta-analysis found that anorexia was the most common GI manifestation (26.8%), followed by diarrhea (12.5%), nausea/vomiting (10.2%), and abdominal discomfort (9.2%).[21] In addition, patients presenting with GI symptoms typically present later than those with isolated respiratory symptoms; however, they have delayed viral clearance suggesting prolonged disease.[23,29] Notably, fecal shedding of viral RNA and nucleocapsid protein can be found up to weeks after nasopharyngeal PCR clearance.[15,16,21,23,24,29–32] Fecal shedding also occurs in patients who do not present with GI symptoms.[27,32,33]Interestingly, fecal calprotectin levels in COVID-19 patients have been shown to be elevated, regardless of presenting GI symptoms.[24,34,35] The combination of enterocyte viral replication and intestinal inflammation led to the release of microbial products and intestinal cytokines, promoting dysregulation of the intestinal barrier and dysbiosis of the gut microbiome.[23,24]

Clostridioides difficile and COVID-19

Clostridioides difficile, formerly known as *Clostridium difficile*, is a spore-forming, toxin-producing bacteria. When pathogenic, CDI is clinically characterized by diarrhea which is mediated by release of toxin by the vegetative form.

Initially, there was concern regarding the impact of the COVID-19 pandemic on CDI rates and severity. In the initial stages of the pandemic, while potential treatments were still being investigated, there was widespread use of antibiotics – increasing the risk of CDI, especially in hospitalized patients.[23,36–38] In addition, though overall emergency room utilization was decreased in the initial stages of the pandemic, studies demonstrated the rates of the emergency department visits that led to hospital admissions increased leading to crowded inpatient units which could contribute to CDI.[39,40] Conversely, the increased emphasis on personal protective equipment, enhanced cleaning protocols, and social distancing measures may serve as mitigating factors against nosocomial CDI.

Rates of CDI during the COVID-19 pandemic

Prior to the COVID-19 pandemic, the estimated global incidence of healthcare-associated CDI ranged from 2.8 to 15.8 cases per 10,000 patient-days.[41,42] Furthermore, incidence rates of CDI have been increasing over the last three decades.[42,43] In the COVID-19 era, the rate of healthcare-associated CDI has varied relative to historical data. In a multicenter, international systematic review of 11 studies that evaluated the rates of CDI during the pandemic, 4 studies

showed a decrease in CDI incidence compared to their respective institutional historical data, 6 showed no statistically significant change, and only 1 study showed an increase in CDI incidence.[36,44–49] Though onset of diarrhea was uncommonly reported, Allegretti *et al.* reported that in all patients with confirmed CDI and COVID-19, none presented with diarrhea at the time of admission.[45] Similarly, Granata *et al.* found that 32 of 38 confirmed CDI in COVID-19 patients were hospital acquired.[50] The rate of CDI may be impacted by the rate of CDI testing during the initial stages of the pandemic, with multiple studies showing an initial trend toward decreased testing in the early stages.[47,49,51]

Risk factors for CDI in confirmed COVID-19 patients

Risk factors for CDI, regardless of COVID-19 status, have been well established, including recent antibiosis, recent hospitalization, and increased age ⩾65 years. Additional studies have shown a correlation between CDI and proton pump inhibitors, chronic kidney disease, active immunosuppression, and diabetes.[52,53]

During the COVID-19 pandemic, multiple studies observed increased antibiotic use, including antibiotic classes known to be high risk for CDI such as lincosamides, monobactams, and third-generation cephalosporins.[36,49,51,54] In the retrospective cohort study performed by Allegretti *et al.*, the median number of distinct antibiotics for all COVID-19 patients during their hospitalization was 4, and all COVID-19 patient who developed CDI were exposed to at least two antibiotics prior to their CDI diagnosis.[45] However, no statistically significant difference in antibiotic exposures was observed between CDI and non-CDI COVID-19 patients in this study. In contrast, one case–control study showed that antibiosis prior to CDI was an independent risk factor for CDI in COVID-19 patients.

Regarding other CDI risk factors, two studies reported higher rates of proton pump inhibitor use in COVID-19 patients with CDI than those without CDI.[45,55] Multiple studies showed either a trend or statistical significance with immunosuppression or recent steroid administration and CDI.[50,55] Lewandowski *et al.* identified length of hospitalization, intensive care unit stay, and new abdominal pain during hospitalization as independent predictors of hospital-acquired CDI.[48]

Morbidity and mortality of CDI in COVID-19 patients

The impact of CDI on COVID-19 severity is unknown. The mortality rate of COVID-19 patients with concurrent CDI ranged from 8% to 80%, with most studies showing no association between mortality and CDI.[45,50,55–57] In addition, the cause of death was rarely attributed to CDI. CDI was not associated with subsequent intensive care unit stay or mechanical ventilation. However, patients with concurrent CDI and COVID-19 infections had increased length of admission compared to non-CDI COVID-19 patients.[36,50,51,55]

FMT during the COVID-19 pandemic

FMT has been proven to be highly effective for the prevention of rCDI after a course of standard of care antibiotics and has shown promising results across multiple chronic conditions that have been linked with gut dysbiosis.[58–64] Furthermore, FMT is generally considered a safe and well-tolerated procedure, with a systematic review and meta-analysis showing no differences in adverse events in patients undergoing FMT compared to control groups.[65–67] Given the significant morbidity and mortality of CDI, FMT was recommended to be among non-delayable GI procedures during the COVID-19 pandemic.[68] However, given known fecal viral shedding of SARS-CoV-2, there was concern for transmission *via* FMT.

Availability and screening of FMT

Accessibility to FMT decreased during the COVID-19 pandemic. In the initial stages of the pandemic, the Food and Drug Administration recommended that stool samples obtained and prepared prior to 1 December 2019 be used until stool SARS-CoV-2 assays and protocols became established and readily available.[68] In addition, to decrease the risk of FMT transmission of SARS-CoV-2, expert consensus recommended that stool samples collected after this target date should be stored for 30 days before utilization. If the donor tested positive for COVID-19 in these 30 days, the stool sample was discarded and the

donor was unable to supply samples for 8 weeks following infection.[11] In addition, it is recommended that all donors be screened for history of symptoms, known exposure to COVID-19, travel history, and prior confirmed infection within 30 days of stool sample donation.[11,68] If patients pass this screen, it is recommended that they undergo laboratory testing. Along with the standard recommended stool and serologic screening for donors, it is recommended to test for COVID-19 infection through combined nasopharyngeal swab and IgM serological testing.[68] Furthermore, as stool assays have become more validated and available, these tests can be used to detect fecal COVID-19 when accessible.[69] Positive nasopharyngeal PCR, stool assay, or IgM serological testing should be considered an absolute exclusion from stool donation until 8 weeks after positive laboratory testing.

Safety and efficacy of FMT during the COVID-19 pandemic

Pre-pandemic systematic meta-analyses have demonstrated that FMT is superior to oral vancomycin in treating relapsing and refractory CDI.[70] One meta-analysis comprising of 37 studies (7 randomized controlled trials and 30 case series) demonstrated a 92% positive response to FMT for the treatment of refractory and relapsing FMT, though with a moderate to high degree of heterogeneity.[70] In addition to being efficacious, FMT has been demonstrated to be highly safe in the treatment of CDI. Studies have shown that the pooled rate of adverse events following FMT ranges from 31% to 39%; however, these adverse events are mild in character.[71,72] Most commonly, patients experience abdominal pain (~6%), diarrhea (~5%), nausea (4.6%), and abdominal bloating (3.9%). Importantly, rates of significant adverse events ranged from 0% to 7%, with the most common significant adverse event being CDI. No deaths attributed to FMT have been reported. One study showed that younger patients, patients with history of irritable bowel syndrome, and preexisting inflammatory bowel disease were risk factors for GI symptoms following FMT.[72]

Although no studies have directly compared the safety and efficacy of FMT during the pandemic to pre-pandemic data, available retrospective and prospective studies have demonstrated similar efficacy of FMT for CDI in patients with and without coinfection with COVID-19 during the pandemic compared to pre-pandemic literature. A retrospective cohort study by Khanna *et al.* demonstrated that in 57 patients undergoing FMT for rCDI during the COVID-19 pandemic, only three patients developed rCDI following FMT with one patient requiring repeat FMT. Only one patient developed respiratory symptoms following FMT, however tested negative for COVID-19.[73] No significant adverse events were reported in this study.

In a prospective study of 21 patients undergoing FMT for rCDI and refractory CDI during the COVID-19 pandemic, 18 patients completed 8-week follow-up. In these patients, there were no recurrences of CDI following FMT. In addition, two patients had concurrent COVID-19 pneumonia and CDI, both of which resolved following FMT.[74] Improved COVID-19 symptoms were also seen in a case series of two patients undergoing FMT for rCDI with concurrent COVID-19.[75] Furthermore, in one case series, FMT performed 1 month after resolved COVID-19 showed improved resolution of residual GI symptoms and restoration of normal gut microbiota.[76] Lastly, a retrospective study of 86 patients who had coinfection of CDI and COVID-19 demonstrated that in patients that received both antibiotics and FMT had decreased abdominal pain, decreased relapse rates of CDI, and decreased biomarkers of inflammation compared to those who only received antibiotics.[77] In the 46 patients who underwent FMT, no adverse events were reported. In these studies, the authors speculate that FMT may have contributed to modulation of the gut–lung axis which is implicated in the pathogenesis of COVID-19.[71,72]

Conclusion

CDI remains a leading healthcare epidemic in the United States. Given the potential for life-threatening, fulminant colitis, time-sensitive management of CDI and rCDI remains paramount. During the COVID-19 pandemic, CDI rates have remained stable or may be paradoxically decreased compared to historical data—despite the widespread increased antibiotic administration. This is most likely due to increased emphasis on mitigating hygienic factors such as increased handwashing and the use of protective personal equipment. Though decreased CDI testing and inappropriate

attribution of diarrhea to COVID-19 rather than CDI may have confounded these results.

During the COVID-19 pandemic, FMT remains a safe and effective therapeutic intervention in patients with rCDI. Increased safety regulations and stool viral assay testing have helped ease concern for fecal–oral transmission of COVID-19 *via* FMT. As the healthcare system returns to pre-COVID-19 capacities and behaviors, it is vital to continue hospital hygiene, antibiosis stewardship, and safe, time-sensitive treatment for CDI and rCDI.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Salam P. Bachour: Writing – original draft.

Rahul Dalal: Writing – review & editing.

Jessica R. Allegretti: Conceptualization; Supervision; Writing – review & editing.

Acknowledgements
None.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
Not applicable.

ORCID iD
Jessica R. Allegretti https://orcid.org/0000-0003-3585-2425

References

1. Guh AY, Mu Y, Winston LG, *et al.* Trends in U.S. burden of *Clostridioides difficile* infection and outcomes. *N Engl J Med* 2020; 382: 1320–1330.
2. Johnson S, Lavergne V, Skinner AM, *et al.* Clinical practice guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of *Clostridioides difficile* infection in adults. *Clin Infect Dis* 2021; 73: e1029–e1044.
3. Connelly TM and Messaris E. Predictors of recurrence of Crohn's disease after ileocolectomy: a review. *World J Gastroenterol* 2014; 20: 14393–14406.
4. Allegretti JR, Kearney S, Li N, *et al.* Recurrent *Clostridium difficile* infection associates with distinct bile acid and microbiome profiles. *Aliment Pharmacol Ther* 2016; 43: 1142–1153.
5. Song JH and Kim YS. Recurrent *Clostridium difficile* infection: risk factors, treatment, and prevention. *Gut Liver* 2019; 13: 16–24.
6. Cammarota G, Ianiro G, Tilg H, *et al.* European consensus conference on faecal microbiota transplantation in clinical practice. *Gut* 2017; 66: 569–580.
7. Brandt LJ, Aroniadis OC, Mellow M, *et al.* Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent *Clostridium difficile* infection. *Am J Gastroenterol* 2012; 107: 1079–1087.
8. Borody TJ, Paramsothy S and Agrawal G. Fecal microbiota transplantation: indications, methods, evidence, and future directions. *Curr Gastroenterol Rep* 2013; 15: 337.
9. Gupta A, Cifu AS and Khanna S. Diagnosis and treatment of *Clostridium difficile* infection. *JAMA* 2018; 320: 1031–1032.
10. Rawson TM, Moore LSP, Zhu N, *et al.* Bacterial and fungal coinfection in individuals with coronavirus: a rapid review to support COVID-19 antimicrobial prescribing. *Clin Infect Dis* 2020; 71: 2459–2468.
11. Ianiro G, Mullish BH, Kelly CR, *et al.* Screening of faecal microbiota transplant donors during the COVID-19 outbreak: suggestions for urgent updates from an international expert panel. *Lancet Gastroenterol Hepatol* 2020; 5: 430–432.
12. Hoffmann M, Kleine-Weber H, Schroeder S, *et al.* SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020; 181: 271–280.e8.
13. Li F, Li W, Farzan M, *et al.* Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. *Science* 2005; 309: 1864–1868.

14. Bourgonje AR, Abdulle AE, Timens W, *et al*. Angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 and the pathophysiology of coronavirus disease 2019 (COVID-19). *J Pathol* 2020; 251: 228–248.

15. Wang W, Xu Y, Gao R, *et al*. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA* 2020; 323: 1843–1844.

16. Xiao F, Tang M, Zheng X, *et al*. Evidence for gastrointestinal infection of SARS-CoV-2. *Gastroenterology* 2020; 158: 1831–1833.e3.

17. Hamming I, Timens W, Bulthuis MLC, *et al*. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004; 203: 631–637.

18. Hashimoto T, Perlot T, Rehman A, *et al*. ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. *Nature* 2012; 487: 477–481.

19. Zhang H, Kang Z, Gong H, *et al*. Digestive system is a potential route of COVID-19: an analysis of single-cell coexpression pattern of key proteins in viral entry process. *Gut* 2020; 69: 1010–1018.

20. Du M, Cai G, Chen F, *et al*. Multiomics evaluation of gastrointestinal and other clinical characteristics of COVID-19. *Gastroenterology* 2020; 158: 2298–2301.e7.

21. Cheung KS, Hung IFN, Chan PPY, *et al*. Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from a Hong Kong cohort: systematic review and meta-analysis. *Gastroenterology* 2020; 159: 81–95.

22. Jin X, Lian J-S, Hu J-H, *et al*. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut* 2020; 69: 1002–1009.

23. Pan L, Mu M, Yang P, *et al*. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study. *Am J Gastroenterol* 2020; 115: 766–773.

24. Zhang J, Garrett S and Sun J. Gastrointestinal symptoms, pathophysiology, and treatment in COVID-19. *Genes Dis* 2020; 8: 385–400.

25. Zhang J-J, Dong X, Cao Y-Y, *et al*. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy* 2020; 75: 1730–1741.

26. Jiehao C, Jin X, Daojiong L, *et al*. A case series of children with 2019 novel coronavirus infection: clinical and epidemiological features. *Clin Infect Dis* 2020; 71: 1547–1551.

27. Patel KP, Patel PA, Vunnam RR, *et al*. Gastrointestinal, hepatobiliary, and pancreatic manifestations of COVID-19. *J Clin Virol* 2020; 128: 104386.

28. Villapol S. Gastrointestinal symptoms associated with COVID-19: impact on the gut microbiome. *Transl Res* 2020; 226: 57–69.

29. Han C, Duan C, Zhang S, *et al*. Digestive symptoms in COVID-19 patients with mild disease severity: clinical presentation, stool viral RNA testing, and outcomes. *Am J Gastroenterol* 2020; 115: 916–923.

30. Zhang J, Wang S and Xue Y. Fecal specimen diagnosis 2019 novel coronavirus-infected pneumonia. *J Med Virol* 2020; 92: 680–682.

31. Pan Y, Zhang D, Yang P, *et al*. Viral load of SARS-CoV-2 in clinical samples. *Lancet Infect Dis* 2020; 20: 411–412.

32. Xu Y, Li X, Zhu B, *et al*. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. *Nat Med* 2020; 26: 502–505.

33. Parasa S, Desai M, Thoguluva Chandrasekar V, *et al*. Prevalence of gastrointestinal symptoms and fecal viral shedding in patients with coronavirus disease 2019: a systematic review and meta-analysis. *JAMA Netw Open* 2020; 3: e2011335.

34. Effenberger M, Grabherr F, Mayr L, *et al*. Faecal calprotectin indicates intestinal inflammation in COVID-19. *Gut* 2020; 69: 1543–1544.

35. Ojetti V, Saviano A, Covino M, *et al*. COVID-19 and intestinal inflammation: role of fecal calprotectin. *Dig Liver Dis* 2020; 52: 1231–1233.

36. Granata G, Petrosillo N, Al Moghazi S, *et al*. The burden of *Clostridioides difficile* infection in COVID-19 patients: a systematic review and meta-analysis. *Anaerobe* 2022; 74: 102484.

37. Huttner BD, Catho G, Pano-Pardo JR, *et al*. COVID-19: don't neglect antimicrobial stewardship principles! *Clin Microbiol Infect* 2020; 26: 808–810.

38. Chen N, Zhou M, Dong X, *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; 395: 507–513.

39. Ghaderi H, Stowell JR, Akhter M, *et al*. Impact of COVID-19 pandemic on emergency department

visits: a regional case study of informatics challenges and opportunities. *AMIA Annu Symp Proc* 2022; 2021: 496–505.

40. Jeffery MM, D'Onofrio G, Paek H, *et al*. Trends in emergency department visits and hospital admissions in health care systems in 5 states in the first months of the COVID-19 pandemic in the US. *JAMA Intern Med* 2020; 180: 1328–1333.

41. Balsells E, Shi T, Leese C, *et al*. Global burden of *Clostridium difficile* infections: a systematic review and meta-analysis. *J Glob Health* 2019; 9: 010407.

42. Finn E, Andersson FL and Madin-Warburton M. Burden of *Clostridioides difficile* infection (CDI)–a systematic review of the epidemiology of primary and recurrent CDI. *BMC Infect Dis* 2021; 21: 456.

43. DePestel DD and Aronoff DM. Epidemiology of *Clostridium difficile* infection. *J Pharm Pract* 2013; 26: 464–475.

44. Ochoa-Hein E, Rajme-López S, Rodríguez-Aldama JC, *et al*. Substantial reduction of healthcare facility-onset *Clostridioides difficile* infection (HO-CDI) rates after conversion of a hospital for exclusive treatment of COVID-19 patients. *Am J Infect Control* 2021; 49: 966–968.

45. Allegretti JR, Nije C, McClure E, *et al*. Prevalence and impact of *Clostridioides difficile* infection among hospitalized patients with coranavirus disease 2019. *JGH Open* 2021; 5: 622–625.

46. Bentivegna E, Alessio G, Spuntarelli V, *et al*. Impact of COVID-19 prevention measures on risk of health care-associated *Clostridium difficile* infection. *Am J Infect Control* 2021; 49: 640–642.

47. Ponce-Alonso M, Sáez de la Fuente J, Rincón-Carlavilla A, *et al*. Impact of the coronavirus disease 2019 (COVID-19) pandemic on nosocomial *Clostridioides difficile* infection. *Infect Control Hosp Epidemiol* 2021; 42: 406–410.

48. Lewandowski K, Rosołowski M, Kaniewska M, *et al*. *Clostridioides difficile* infection in coronavirus disease 2019 (COVID-19): an underestimated problem? *Pol Arch Intern Med* 2021; 131: 121–127.

49. Hawes AM, Desai A and Patel PK. Did *Clostridioides difficile* testing and infection rates change during the COVID-19 pandemic? *Anaerobe* 2021; 70: 102384.

50. Granata G, Bartoloni A, Codeluppi M, *et al*. The burden of *Clostridioides difficile* infection during the COVID-19 pandemic: a retrospective case-control study in Italian hospitals (CloVid). *J Clin Med* 2020; 9: E3855.

51. Luo Y, Grinspan LT, Fu Y, *et al*. Hospital-onset *Clostridioides difficile* infections during the COVID-19 pandemic. *Infect Control Hosp Epidemiol* 2021; 42: 1165–1166.

52. Eze P, Balsells E, Kyaw MH, *et al*. Risk factors for *Clostridium difficile* infections–an overview of the evidence base and challenges in data synthesis. *J Glob Health* 2017; 7: 010417.

53. Davies K, Lawrence J, Berry C, *et al*. Risk factors for primary *Clostridium difficile* infection; results from the observational study of risk factors for *Clostridium difficile* infection in hospitalized patients with infective diarrhea (ORCHID). *Front Public Health* 2020; 8: 293.

54. Teng C, Reveles KR, Obodozie-Ofoegbu OO, *et al*. *Clostridium difficile* infection risk with important antibiotic classes: an analysis of the FDA adverse event reporting system. *Int J Med Sci* 2019; 16: 630–635.

55. Manea E, Jipa R, Milea A, *et al*. Healthcare-associated *Clostridioides difficile* infection during the COVID-19 pandemic in a tertiary care hospital in Romania. *Rom J Intern Med* 2021; 59: 409–415.

56. Sehgal K, Fadel HJ, Tande AJ, *et al*. Outcomes in patients with SARS-CoV-2 and *Clostridioides difficile* coinfection. *Infect Drug Resist* 2021; 14: 1645–1648.

57. Sandhu A, Tillotson G, Polistico J, *et al*. *Clostridioides difficile* in COVID-19 patients, Detroit, Michigan, USA, March–April 2020. *Emerg Infect Dis* 2020; 26: 2272–2274.

58. Allegretti JR and Hamilton MJ. Restoring the gut microbiome for the treatment of inflammatory bowel diseases. *World J Gastroenterol* 2014; 20: 3468–3474.

59. Proença IM, Allegretti JR, Bernardo WM, *et al*. Fecal microbiota transplantation improves metabolic syndrome parameters: systematic review with meta-analysis based on randomized clinical trials. *Nutr Res* 2020; 83: 1–14.

60. Allegretti JR, Mullish BH, Kelly C, *et al*. The evolution of the use of faecal microbiota transplantation and emerging therapeutic indications. *Lancet* 2019; 394: 420–431.

61. Johnsen PH, Hilpüsch F, Cavanagh JP, *et al*. Faecal microbiota transplantation versus placebo for moderate-to-severe irritable bowel syndrome: a double-blind, randomised, placebo-controlled, parallel-group, single-centre trial. *Lancet Gastroenterol Hepatol* 2018; 3: 17–24.

62. Bajaj JS, Kassam Z, Fagan A, *et al*. Fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: a randomized clinical trial. *Hepatology* 2017; 66: 1727–1738.

63. Costello SP, Hughes PA, Waters O, *et al*. Effect of fecal microbiota transplantation on 8-week remission in patients with ulcerative colitis: a randomized clinical trial. *JAMA* 2019; 321: 156–164.

64. Baruch EN, Youngster I, Ben-Betzalel G, *et al*. Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. *Science* 2021; 371: 602–609.

65. Green JE, Davis JA, Berk M, *et al*. Efficacy and safety of fecal microbiota transplantation for the treatment of diseases other than *Clostridium difficile* infection: a systematic review and meta-analysis. *Gut Microbes* 2020; 12: 1854640.

66. Agrawal M, Aroniadis OC, Brandt LJ, *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: 403–407.

67. Cammarota G, Ianiro G, Kelly CR, *et al*. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. *Gut* 2019; 68: 2111–2121.

68. Ianiro G, Mullish BH, Kelly CR, *et al*. Reorganisation of faecal microbiota transplant services during the COVID-19 pandemic. *Gut* 2020; 69: 1555–1563.

69. Di Pilato V, Morecchiato F, Rizzato C, *et al*. Validation of two commercial multiplex real-time PCR assays for detection of SARS-CoV-2 in stool donors for fecal microbiota transplantation. *Microorganisms* 2022; 10: 284.

70. Quraishi MN, Widlak M, Bhala N, *et al*. Systematic review with meta-analysis: the efficacy of faecal microbiota transplantation for the treatment of recurrent and refractory *Clostridium difficile* infection. *Aliment Pharmacol Ther* 2017; 46: 479–493.

71. Michailidis L, Currier AC, Le M, *et al*. Adverse events of fecal microbiota transplantation: a meta-analysis of high-quality studies. *Ann Gastroenterol* 2021; 34: 802–814.

72. Allegretti JR, Kassam Z, Fischer M, *et al*. Risk factors for gastrointestinal symptoms following successful eradication of *Clostridium difficile* by fecal microbiota transplantation (FMT). *J Clin Gastroenterol* 2019; 53: e405–e408.

73. Khanna S, Tande A, Rubin DT, *et al*. Fecal microbiota transplantation for recurrent *Clostridium difficile* infection during the COVID-19 pandemic: experience and recommendations. *Mayo Clin Proc* 2021; 96: 1418–1425.

74. Ianiro G, Bibbò S, Masucci L, *et al*. Maintaining standard volumes, efficacy and safety, of fecal microbiota transplantation for *Clostridium difficile* infection during the COVID-19 pandemic: a prospective cohort study. *Dig Liver Dis* 2020; 52: 1390–1395.

75. Biliński J, Winter K, Jasiński M, *et al*. Rapid resolution of COVID-19 after faecal microbiota transplantation. *Gut* 2022; 71: 230–232.

76. Liu F, Ye S, Zhu X, *et al*. Gastrointestinal disturbance and effect of fecal microbiota transplantation in discharged COVID-19 patients. *J Med Case Reports* 2021; 15: 60.

77. Boicean A, Neamtu B, Birsan S, *et al*. Fecal microbiota transplantation in patients co-infected with SARS-CoV2 and *Clostridioides difficile*. *Biomedicines* 2023; 11: 7.

Visit SAGE journals online
journals.sagepub.com/
home/tag

SAGE journals