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Acute severe ulcerative colitis: confronting an intensified stressor during the COVID-19 pandemic

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COVID-19 has been a threat multiplier that affects all aspects of life. The medical and psychosocioeconomic effects of the COVID-19 pandemic and pre-existing medical conditions such as acute severe ulcerative colitis are multidirectional, and include the impacts of COVID-19 and acute severe ulcerative colitis on each other, and their influences on the welfare of patients, their families, health-care providers, and the health-care system. The risk of adverse outcomes of COVID-19 has been reported to be higher in patients with ulcerative colitis than in patients with Crohn's disease.¹ The management of acute severe ulcerative colitis, which can be a medical and surgical emergency in some cases, was challenging even before the pandemic. My colleagues in the UK should be proud of their health-care system, and should be congratulated for quickly adapting their practice patterns. In *The Lancet Gastroenterology & Hepatology*, Shaji Sebastian and colleagues² showed that adverse effects of the COVID-19 pandemic on the care and outcomes of patients with acute severe ulcerative colitis can be successfully contained.

IBD health-care providers have been forced by the initial waves of the COVID-19 pandemic to devise timely and effective ways to deliver care without compromising the safety of patients or themselves. Societal guidelines are based on case series, surveys, or expert opinions,^{3,5} resulting in discrepancies in real-world clinical practice. For example, the guidelines recommended the continuation of IBD medications in those without COVID-19 symptoms,^{3,5} but in a web registry-based study, a third of patients discontinued IBD medications, particularly anti-tumour necrosis factor agents and immunomodulators.⁶ Sebastian and colleagues² provide multicentre, case-control data for consecutive patients with acute severe ulcerative colitis during the COVID-19 pandemic. Compared with the pre-pandemic period, the health-care system and providers in the UK were able to deliver rescue therapy in a shorter time, despite the fact that patients more often required rescue medical (including the use of intravenous steroids, biologicals, ciclosporin, or tofacitinib) or surgical therapy. Therefore, clinical outcomes, comprising the response to rescue

therapy, the requirement for colectomy or diverting ileostomy, the length of hospital stay, intensive care unit admission, postoperative complications, and outcomes at 3-month follow-up were similar between the pandemic and pre-pandemic periods. Less than 2% of patients in this study developed COVID-19.² These outcomes probably resulted from the efficiency of the health-care system and quick adaptation of practice through shifting to ambulatory pathways, timely administration of rescue therapy, and multidisciplinary approaches. However, more frequent use of medical or surgical rescue therapy during the pandemic suggests that the patients might have been more sick or taken longer to seek care, possibly stemming from logistical and accessibility barriers to medical, endoscopic, surgical, or ancillary services^{7,8} or safety concerns.⁹ This gap must be bridged during the next phase of the pandemic.

The COVID-19 pandemic is far from over. It continues to be a threat to patients with acute severe ulcerative colitis and the general population, posing an ever-growing risk to our global health-care system. Although we remain hopeful for the eventual alteration of the disease course through vaccination, our understanding of COVID-19 is still evolving. Learning from reactive experiences and lessons of Sebastian and colleagues² is a valuable step for us to proactively develop an effective strategy and care path for the management of patients with acute severe ulcerative colitis in the next phase and aftermath of the pandemic.

I declare no competing interests.

Bo Shen

bs3270@cumc.columbia.edu

Columbia University Irving Medical Center/New York-Presbyterian Hospital, New York, NY 10032, USA

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A defined microbiome therapeutic prevents recurrent *Clostridioides difficile*



A common complication of *Clostridioides difficile* infection, recurrence is associated with high health care use, morbidity, mortality, and decreased quality of life.¹ Perturbation of the host gastrointestinal microbiome is associated with the pathogenesis of both initial and recurrent *C difficile* infection.² A diverse microbiome is inherently resistant against colonisation by pathogens, such as *C difficile*. Risk factors, such as antibiotics, lead to an acute disruption of the microbial diversity (termed as dysbiosis) and reduced colonisation resistance. Exposure to the *C difficile* spore or vegetative form in this state leads to colonisation and active infection.² Unlike most other gastrointestinal infections, *C difficile* infection is not self-limiting and is managed with antibiotics.³ *C difficile* infection and the antibiotics used to treat it in turn further disrupt colonisation resistance, worsen dysbiosis, and predispose to recurrences. Antibiotics used to treat *C difficile* infection are not sporicidal and spores are implicated in the pathogenesis of recurrence in the absence of environmental re-exposure. The risk of recurrence after three or more episodes of *C difficile* infection is greater than 50%.³ This risk, along with the high mortality of *C difficile* infection and the fact that *C difficile* is the most common bacterial infection in hospitals, necessitates development of strategies to reduce recurrences.

Narrow spectrum antibiotics (fidaxomicin or ridinilazole), innovative antibiotic regimens (extended vancomycin or fidaxomicin courses), and bezlotoxumab are efforts towards preventing recurrent *C difficile* infection.^{3,4} Targeting microbiome disruption prevents recurrent *C difficile* infection by restoring microbiome diversity and enriching with Firmicutes and Bacteroidetes.⁵ A common method to restore the microbiome is faecal

microbiota transplantation (FMT), which prevents further infection in more than 85% of patients with multiply recurrent *C difficile* infection. Despite high success and durability, FMT is challenging due to lack of regulation, heterogeneity, adverse events, and unforeseeable disruptions.^{6,7} Guidance on methodology from regulatory bodies is not enforced. A scarcity of reporting on the different components of FMT (donor, recipient, and procedural) suggests a widely heterogeneous clinical practice. Multidrug-resistant and Shiga toxin-producing *Escherichia coli* transmission raises safety concerns.⁸ The COVID-19 pandemic has disrupted FMT with concerns of transmissibility and absence of a validated stool assay for this virus.⁷ Standardised capsule and enema-based donor derived products have shown positive results in phase 1–3 clinical trials, circumventing some of these issues, but continue to be reliant on donor stool and challenged by unforeseen circumstances.⁹ The next obvious phase of microbiota restoration is to eliminate reliance on donor stool, standardise dose composition to further enhance safety, and reduce heterogeneity.

In *The Lancet Gastroenterology & Hepatology*, Dina Kao and colleagues¹⁰ report on a lyophilised capsule-based microbiota restoration product named Microbial Ecosystem Therapeutics 2 (MET-2), which has a unique composition of 40 bacterial species derived and identified from human stool culture. Subsequent manufacturing is independent of donor stool availability. MET-2 capsules contain up to 10⁹ colony forming units with a 9-month room temperature stability. In this open-label trial, 19 patients with two or more episodes of *C difficile* infection received antibiotics followed by MET-2. MET-2 prevented recurrent *C difficile* infection for 30 days in 15 (79%) of 19 patients with

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