Incidence of recurrent *Clostridioides difficile* infection (CDI) after a primary infection is escalating. After treatment with antibiotics is stopped, the risk of recurrent CDI is 20% to 30% after a single infection, 40% to 50% after a second infection, and over 60% among patients who have experienced three or more infections.

Primary and first recurrence CDIs are typically treated with oral vancomycin or fidaxomicin regimens. Although it has not yet been approved by the Food and Drug Administration (FDA), fecal microbiota transplantation (FMT) is widely used to manage recurrent CDI. FMT has demonstrated success rates of over 85% in preventing CDI recurrences compared with a 40% to 50% success rate with antibiotic regimens.

Because FMT therapies are derived from donor stool samples, transmission of infectious agents from asymptomatic stool donors to FMT recipients is a possible risk. Donor screening procedures to prevent this exist, but serious adverse events related to transmission of infectious agents (including extended-spectrum beta-lactamase-producing *Escherichia coli*, enteropathogenic *E. coli* and Shiga toxin-producing *E. coli*) have been documented.

The current COVID-19 pandemic presents additional concerns for providers to consider when making decisions about the use of FMT. Our understanding of this virus and its transmission pattern is still evolving. Right now, experts believe that the average incubation period for COVID-19 is five days, and that individuals who are asymptomatic can be responsible for community spread of this novel coronavirus. Although respiratory droplets are believed to be the primary mode of virus transmission, reports of feco-oral transmission and reports of prolonged shedding in the stool after recovery from respiratory illness are also emerging.

To update clinicians on the current state of knowledge about FMT and issues to consider during the COVID-19 pandemic, Mayo Clinic researchers published an article in the Red Section of *The American Journal of Gastroenterology* in 2020. Co-authors Sahil Khanna, M.B.B.S., M.S., and Darrell S. Pardi, M.D., are gastroenterologists at Mayo Clinic’s campus in Rochester, Minnesota, whose research focuses on the epidemiology, risk factors and treatment of CDI.

**Figure.** To prevent transmitting COVID-19 via FMT using donor stool, especially if this virus continues to spread populationwide, testing and COVID-19 status matching of both stool donors and FMT recipients must occur.
risk of persistently positive nucleic acid-based assay after resolved CDI,” explains Dr. Khanna. In general, patients with primary and recurrent CDI typically meet all of these four criteria:

- Presence of CDI risk factors such as antibiotic exposure
- Diarrhea with or without abdominal pain
- Positive nucleic acid-based or toxin-based assay
- Response to treatment with vancomycin or fidaxomicin, with symptoms recurring shortly after stopping the antibiotic

“It’s important to note that primary nonresponse to antibiotic treatment is extremely rare and suggests an alternate diagnosis,” explains Dr. Khanna.

In individuals who do not meet all four criteria, especially numbers two and four in the list above, Dr. Khanna notes that an alternate diagnosis should be considered.

“In general, patients who meet all four criteria in this list are good candidates for FMT,” says Dr. Khanna. “Some patients with refractory or fulminant CDI also may benefit from FMT.”

**Challenges of stool banking during the COVID-19 pandemic**

Dr. Khanna emphasizes that to prevent transmitting COVID-19 via FMT using donor stool, especially if this virus continues to spread population-wide, testing and COVID-19 status matching of both stool donors and FMT recipients must occur.

**Screening and testing stool donors for COVID-19**

“Several factors underscore the importance of screening stool donors for COVID-19,” explains Dr. Khanna. “We know that patients with COVID-19 can present with diarrhea, that individuals who are asymptomatic can shed in stool and enable feco-oral transmission, and that the virus is also detectable in stool, even when it’s undetectable in the respiratory tract.”

Unfortunately, multiple issues also make donor screening for COVID-19 challenging at this time. Current obstacles include a shortage of available tests for those who are symptomatic, the fact that respiratory swab-based tests are not validated for asymptomatic donors, a lack of validated stool assays for asymptomatic donors, and the fact that the fecal carriage and transmission may be possible in asymptomatic donors who don’t have a positive nasal swab test.

To address these challenges, Dr. Khanna recommends screening stool donors for travel history, COVID-19 symptoms and contact with individuals infected with COVID-19. Donors who meet these screening criteria should be considered for COVID-19 testing (nasal swab or stool). Stool from these donors should be processed, stored and held for at least 14 days. After the 14-day hold, the donors in this group should be re-screened and retested for COVID-19. Stool taken from donors who fail the second round of screening should be discarded.

As COVID-19 diagnostic tests become more widely available and validated for screening asymptomatic individuals, Dr. Khanna says that stool donors should undergo routine screening using nasal swab and stool tests. “The use of multiple tests may also be appropriate to compensate for low testing sensitivity and to reduce the occurrence of false-negative,” explains Dr. Khanna. “Protocols for accepting stool from donors post-exposure could include the use of serological tests like an immunoglobulin G response to denote recovery from previous exposure.”

**Managing recurrent CDI during the COVID-19 pandemic**

Microbiome replacement therapies such as FMT can be considered for about 5% to 10% of patients with CDI. Patients diagnosed with recurrent CDI should first complete antibiotic therapy for acute diarrhea. According to Dr. Khanna, most patients with CDI will require about four to five days of vancomycin until diarrhea resolves, followed by a regimen tapering to the lowest effective dose: 125 mg four times daily for two weeks, twice daily for one week, once daily for a week and then every other day.

For patients with response to antibiotics, Dr. Khanna notes that FMT could be delayed until the pandemic is better controlled. However, surgery or rescue FMT may be appropriate for patients with fulminant CDI or those who do not respond to maximal guideline-based combination therapy. If FMT is required, Dr. Khanna lists these three options to consider:

- Use banked stool donated before December 2019.
- Use stool obtained from a donor within the recipient’s household.
- Screen the recipient for COVID-19 (noting symptoms, travel history and, if available, test results). If the recipient tests positive for COVID-19, any otherwise well-screened donor may be used.

If FMT is regarded as the only option for a recipient who tests negative for COVID-19, use of donor stool obtained before December 2019 or stool from a donor who tested negative for coronavirus is appropriate.

Dr. Khanna is hopeful that the guidance outlined in the article in *The American Journal of Gastroenterology* will help providers manage
recurrent CDI in the era of a pandemic such as COVID-19. He also acknowledges use of FMT to treat CDI requires additional surveillance of the recipient and the development of additional laboratory tests to detect this virus.

“Follow-up after fecal transplant is needed for patients undergoing FMT during the pandemic. A validated stool assay for detection of COVID-19 is also needed,” explains Dr. Khanna. “Dr. Pardi and I are working together to make progress on these steps.”

For more information

Next steps
Dr. Khanna emphasizes that future research related to microbiome replacement therapies must also focus on developing methods to remove viruses and bacterial pathogens in donor stool and creating synthetically grown, defined microbial consortia to avoid the risk of transmitting pathogens, including the novel coronavirus. Even after the current COVID-19 pandemic ends, producers of microbiome replacement therapies will need to eliminate the possibility of transmitting pathogens to FMT recipients.

Understanding Post-Infection Irritable Bowel Syndrome: A Large Population-Based Study

Gastrointestinal (GI) infections are extremely common in the U.S., with 1 in 6 Americans reporting an episode of foodborne illness annually. Campylobacter is the most common cause of bacterial gastroenteritis in the U.S. Typically, campylobacter infection resolves after initial treatment. But some patients develop a poorly understood condition characterized by chronic GI symptoms of irritable bowel syndrome, known as post-infection irritable bowel syndrome (PI-IBS).

Mayo Clinic researchers seeking to learn more about PI-IBS recently conducted a study to examine the prevalence, risk factors, and symptom type and severity associated with PI-IBS in a large, population-based cohort of patients with laboratory-confirmed campylobacter. The results of this study were published in Clinical Gastroenterology and Hepatology in 2020.

Study methods
The Mayo Clinic research team studied detailed, acute surveillance data obtained from the Minnesota Department of Health that included a large, population-based cohort of patients with laboratory-confirmed campylobacter. From this cohort, they identified 3,586 patients ages 18 to 80 who experienced new onset of GI symptoms. From 2011 through 2019, the researchers sent Rome III criteria and IBS symptom severity surveys to these individuals six to nine months after campylobacter infection. Using this data, the researchers estimated the prevalence of PI-IBS, and they identified and assessed several potential risk factors using multivariable logistic regression.

Results
According to Madhusudan (Madhu) Grover, M.B.B.S., this study shows that 1 in 5 of those patients diagnosed with campylobacter infection developed PI-IBS. Dr. Grover is a gastroenterologist at Mayo Clinic’s campus in Rochester, Minnesota, and the corresponding author for the article in Clinical Gastroenterology and Hepatology.

Among the 1,667 survey respondents, 249 (14.9%) had IBS prior to having campylobacter infection, and the remaining 1,418 did not have preexisting IBS. Within that group of 1,418, 301 (21%) subsequently met the Rome criteria for IBS after infection.

“Our data show that 1 in 5 of those diagnosed with campylobacter infection, the most common cause of bacterial gastroenteritis, may develop chronic GI symptoms of irritable bowel syndrome,” says Dr. Grover. “Most of these patients either have alternating diarrhea and constipation or diarrhea alone.”

Symptoms among those 301 survey respondents were distributed as follows:
- 159 (54%) had mixed IBS (IBS-M).
- 113 (38%) had IBS-diarrhea (IBS-D).
- 17 (6%) had constipation-predominant IBS (IBS-C).
- Five (2%) had unsubtyped IBS (IBS-U).

Dr. Grover and colleagues also noted that 65% of these respondents reported moderate to severe symptoms using the IBS-symptom severity scale score (IBS-SSS).
- The mean IBS-SSS was 218, indicating moderate symptom severity.
• 28% reported mild symptoms (IBS-SSS of 75-175).
• 47% reported moderate symptoms (IBS-SSS of 175-300).
• 18% reported severe symptoms (IBS-SSS > 300).

The researchers also documented shifts in IBS subtype post-infection in respondents with preexisting IBS.

• 78% diagnosed with IBS-M and 77% with IBS-D before infection retained their subtypes post-infection.
• 50% diagnosed with IBS-C before infection retained that subtype after infection.
• 40% diagnosed with IBS-C transitioned to IBS-M after infection.

Overall, among survey respondents with preexisting IBS, 38% had increased frequency of abdominal pain after campylobacter infection. “Patients who had IBS prior to infection may experience worsening of pain and changes in constipation toward diarrhea or mixed bowel habits,” says Dr. Grover. “Additionally, some patients may experience just bowel irregularities without pain following such infections.”

**Potential risk factors**
The researchers identified several risk factors that were associated with PI-IBS. Respondents who met the criteria for PI-IBS were more likely to be younger (mean age 43) and female (62%). And they were more likely to experience any of the following during the course of their gastroenteritis episode: significantly longer duration of diarrhea, frequent abdominal cramps, bloody stool or hospitalization. Study data also indicated that fever was inversely associated with PI-IBS.

Dr. Grover and colleagues also identified a number of environmental factors that may play a role in susceptibility for PI-IBS. These include food, especially restaurant dining less than one week before symptom onset; travel, with domestic travelers at higher risk than international travelers; and exposure to animals, especially domestic cats and non-poultry birds. Antibiotic use and exposure patterns were similar between the PI-IBS and control groups.

**Conclusions and next steps**
Dr. Grover believes that the study findings help paint a clearer picture of a poorly understood condition. This population-based study demonstrated a high risk of PI-IBS development among sporadic campylobacter cases.

“Clinicians need to be aware of this entity so that patients can be properly counseled and treated and avoid unnecessary testing,” explains Dr. Grover. “It is important to remember that females, younger individuals, and those who had bloody stools, abdominal cramps and hospitalization during acute enteritis are at a greater risk of developing PI-IBS.”

Dr. Grover and colleagues are hopeful that the model presented can help identify patients who are at high risk of PI-IBS development. He acknowledges that additional research is needed to clarify mechanisms of PI-IBS development and why only a subset of patients develops PI-IBS. “Our laboratory is looking into these mechanisms using animal models, and we are conducting studies assessing changes in gut sensory, motor and barrier function in these patients,” says Dr. Grover. “Dedicated longitudinal studies are needed to identify microbial and other novel host risk factors, as well as clinical trials to prevent and treat this chronic complication of infectious gastroenteritis,” concludes Dr. Grover.

**For more information**
The Use of Transoral Outlet Reduction Endoscopy To Manage Weight Regain After Gastric Bypass: A Comparison of 2 Endoscopic Techniques

Although Roux-en-Y gastric bypass (RYGB) is considered the most effective weight-loss intervention, it’s estimated that over 40% of patients experience weight regain after this procedure. One of the most common factors contributing to weight regain is the enlargement of gastrojejunal stoma size, which reduces satiety and allows patients to increase the volume of food consumed in one meal.

Dilated gastrojejunal stoma can be treated with revisional bariatric surgery. However, this intervention is technically difficult, has a higher risk of associated adverse events than primary bariatric surgery and may limit the patient’s options for future obesity interventions.

Transoral outlet reduction endoscopy (TORe) is a revisional therapy that can help manage weight regain after RYGB. During this procedure, an endoscopic suturing system is used to plicate and reduce the size of the gastrojejunal anastomosis. The goal is to delay gastric pouch emptying and enhance the sensation of satiety.

Performed on an outpatient basis, TORe has a superior safety profile when compared with revisional bariatric surgery. Mayo Clinic researchers recently conducted a systematic review and meta-analysis to examine the efficacy and safety of the two most commonly used techniques for performing TORe: full-thickness suturing plus argon plasma mucosal coagulation (ft-TORe) and argon plasma mucosal coagulation (APMC-TORe) alone. Results of the meta-analysis were published in *Gastrointestinal Endoscopy* in 2020.

**Methods**

To conduct the analysis, Mayo Clinic researchers performed a literature search for studies evaluating TORe that were published during or before 2020. Their search focused on multiple outcomes of interest, including percentage of total body weight loss (%TBWL), measured at three, six and 12 months after TORe; pre- and post-gastrojejunal anastomosis (GJA) diameter; GJA change; and adverse events. The researchers analyzed pooled effect estimates using a random-effects model and conducted meta-regression to identify associations between GJA diameter and weight loss. They also performed a comparative analysis of TORe versus TORe with gastroplasty.

Of the 16 studies included in the researchers’ analysis, nine involved ft-TORe (n = 737) and seven involved APMC-TORe (n = 888). In these studies, APMC-TORe was performed as a series of sessions (with the mean number of sessions ranging from 1.2 to 3), whereas ft-TORe was mostly performed as a single session.

**Results**

**Percentage TBWL in the ft-TORe treatment group:**
- 8%, with 95% confidence interval (CI), 6.3% to 9.7%, at three months
- 9.5%, with 95% CI, 8.1% to 11.0%, at six months
- 5.8%, with 95% CI, 4.3% to 7.1%, at 12 months

**Percentage TBWL in the APMC-TORe treatment group:**
- 9.0%, with 95% CI, 4.1% to 13.9%, at three months
- 10.2%, with 95% CI, 8.4% to 12.1%, at six months
- 9.5%, with 95% CI, 5.7% to 13.2%, at 12 months

**GJA diameter and weight loss in the ft-TORe treatment group**

The researchers identified no significant association between pre-TORe GJA diameter, post-TORe GJA diameter, or GJA diameter change and %TBWL at six months (P = .45, .08 and .06, respectively).
respectively). They did note a trend for greater weight loss with greater decrease in post-TORe GJA diameter and GJA diameter change.

**GJA diameter and weight loss in the APMC-TORe treatment group**

The analysis suggests that larger pre-TORe GJA diameter and smaller post-TORe GJA diameter are associated with a higher %TBWL at six months (P < 0.001 and 0.04, respectively). Additionally, greater change in GJA diameter is associated with greater %TBWL at six months (P < 0.001).

**Adverse events**

The researchers noted that there were no mortalities associated with either procedure. Only one severe adverse event occurred after APMC-TORe, and none occurred after ft-TORe. Stricture formation was the most common adverse event, occurring in 3.3% of patients after ft-TORe and in 4.8% of patients after APMC-TORe, meta-regression of P = 0.38. All strictures were successfully treated using endoscopic dilation or conservative treatment.

**Conclusions**

Overall, this meta-analysis demonstrated that TORe has excellent safety with good outcomes. “Both ft-TORe and APMC-TORe can offer significant, sustained weight-loss outcomes, with a high safety profile,” explains Barham K. Abu Dayyeh, M.D., M.P.H., senior author of the article in *Gastrointestinal Endoscopy* and a gastroenterologist who specializes in bariatric and metabolic endoscopy at Mayo Clinic in Rochester, Minnesota. “The other key point to emphasize is that smaller GJA diameter and greater GJA reduction are correlated with greater weight loss after TORe.”

Given that both techniques are considered standard of care, Dr. Abu Dayyeh advises that when attempting to individualize the treatment approach for each patient, one should consider the following critical factors: the endoscopist’s level of experience, the learning curve required for these techniques, institutional preference, available resources, any procedural costs, and anesthesia- or sedation-related costs.

“Given that APMC-TORe requires repeat endoscopic procedures, the cost is a relevant discussion point in some countries,” explains Dr. Abu Dayyeh. “At Mayo Clinic, a single endoscopy is more costly than the endoscopic suturing device itself, and thus APMC-TORe with repeated sessions could pose a significant cost burden when compared with ft-TORe. On the other hand, APMC is less technically demanding and more universally available. At Mayo Clinic, we offer both techniques to our patients. In addition to the above-mentioned factors, we also consider the gastrojejunal anastomosis size and the gastric pouch volume.”

Dr. Abu Dayyeh notes that ft-TORe is more suitable for those patients with a larger gastrojejunal anastomosis or a larger gastric pouch that allows the endoscopist to effectively reduce the gastrojejunal anastomosis and perform a gastroplasty for pouch reduction within a single session.

**Next steps**

When asked what the future holds for this field, Dr. Abu Dayyeh explains that the next phase of research should focus on refining the TORe technique and offering personalized treatment approaches. “Our group is comparing the effect of two different approaches on weight loss — TORe alone versus TORe plus gastroplasty in patients with enlarged gastric pouch sizes. To advance our ability to individualize treatment, future studies should also investigate the performance of each technique in different GJA diameters.”

**For more information**


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**Q and A: How Obesity Affects IBD Management and Patient Outcomes**

In this Q and A, Amanda M. Johnson, M.D., discusses the prevalence of obesity in patients with inflammatory bowel disease (IBD), obesity’s potential role in the pathogenesis of IBD and current thinking about management of patients with IBD who are obese. Dr. Johnson is a gastroenterologist specializing in IBD at Mayo Clinic’s campus in Rochester, Minnesota, who co-authored a review article on this topic in *Gastroenterology and Hepatology* in 2020.
What is the prevalence of obesity in patients diagnosed with inflammatory bowel disease, and why is this an important topic to explore?

I think it is important to recognize that obesity is very prevalent within the IBD population. When we think about patients with inflammatory bowel disease, there is a tendency to envision a population of patients who are underweight and malnourished. However, this is simply not the case. We performed a study of all patients who received a diagnosis of IBD within Olmsted County from 1970 through 2010. Within that population, we found that the prevalence of obesity increased twofold to threefold when we compare those diagnosed from 1970 to 1980 with those diagnosed from 2000 to 2010. The reality is that the current prevalence of obesity among patients with IBD now parallels that of the general population. An estimated 15% to 40% of patients diagnosed with IBD are obese, with a body mass index (BMI) of 30 or higher. And when we add individuals who are overweight, those with a BMI of 25 to 30, that category includes nearly 60% of patients with IBD.

What is known about the impact of obesity on the natural history and outcomes of IBD?

While the ever-increasing prevalence of obesity within the IBD population is well documented in several studies, what remains unclear is the impact this may have on the clinical course of the IBD itself. Data pertaining to the impact of obesity on future IBD-specific outcomes is not only sparse, but conflicting. Some suggest that obesity may increase the risk of complications such as hospitalization, intestinal resections or corticosteroid use; however, there are also studies documenting that the risk of such complications is lower or even the same in patients who are obese when compared with individuals who are normal weight. With these mixed findings, it remains difficult to know what, if any, impact obesity may have on the clinical course of disease.

Does obesity impact IBD treatment or cause differences in clinical response?

There is data to suggest that obesity may indeed impact the pharmacokinetics of our available biologic therapies, namely absorption, volume of distribution and drug clearance. The two most common means by which IBD therapies are administered are subcutaneously or intravenously. Additionally, some of these drugs are weight based, while others are fixed doses. Understanding that obesity may alter the pharmacokinetics of these drugs raises questions about whether the administration of weight-based intravenous therapies such as infliximab may perform better in patients with IBD who are obese. While there are some data to support this hypothesis, there are also contrasting data to suggest that the type of drug delivery does not impact attainment of adequate drug levels and that there must be something intrinsic to obesity that is playing a role in the reduced response to therapy.

This hypothesis largely stems from the idea that obesity itself is considered a chronic low-grade inflammatory state. Adipose tissue is not biologically inert, but rather is responsible for producing a myriad of cytokines, including TNF-alpha, one of the main inflammatory cytokines implicated in the pathogenesis of active IBD. Therefore, it’s possible that the higher volumes of adipose tissue present in patients who are obese create a larger burden of inflammatory cytokines to target, as compared with those found in patients who are not obese. In the end, while there is some data to suggest that obesity alters the pharmacokinetics of our currently available medications, it remains a bit unclear to what degree it may impact response to therapy.

Do patients who are obese have differences in hospitalization or surgery outcomes?

Researchers have identified obesity as a risk factor for perioperative morbidity, with surgical site infections leading the list of associated complications. Patients who are obese also appear to be at increased risk of impaired wound healing, thromboembolic complications, lengthier hospital stays and increased need for short-term rehabilitation.

We know that obesity also makes surgery for IBD more challenging, particularly those requiring pelvic exposure, so these patients are at increased risk of short-term perioperative complications. These challenges include longer operative times and the need to convert laparoscopic procedures to open procedures. Stoma creation and pouch construc-
Digestive Diseases Update

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Gastroenterology & Hepatology Board Review — Online
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This online course is designed for candidates preparing for certification and maintenance of certification (MOC) examinations in gastroenterology and hepatology. The Gastroenterology and Hepatology Board Review includes relevant topics such as pathology, endoscopy, radiology and nutrition.

One of the main hypotheses about the role of obesity in patients with IBD focuses on the differences between metabolic and biochemical properties associated with visceral adipose tissue (VAT) versus subcutaneous adipose tissue (SAT). This distinction may be important, and there are a few studies suggesting that VAT, rather than BMI, might carry prognostic value in predicting measures such as postoperative outcomes and disease recurrence in patients with Crohn’s disease. We also need studies addressing potential confounding factors such as smoking status, corticosteroid use or disease activity, which may impact weight status at a singular point in time. To truly advance our understanding, future studies should incorporate prospective disease evaluation, improved control of confounding factors and assessment of obesity utilizing measures that reflect VAT. Ideally, this research will make use of cross-sectional imaging studies such as computerized tomography, magnetic resonance imaging or dual-energy X-ray absorptiometry, all of which have been used in VAT assessment.

For more information