

Management of IBD Patients During the COVID-19 Pandemic



Gary R. Lichtenstein, MD
Professor of Medicine
Director, Center for Inflammatory Bowel Disease
Perelman School of Medicine of the University of Pennsylvania
Philadelphia, Pennsylvania

G&H Do patients with inflammatory bowel disease have a greater risk of becoming infected with coronavirus disease 2019?

GL The best current estimates are that individual patients with inflammatory bowel disease (IBD) who are not on immune suppressants or corticosteroids have the same risk of coronavirus disease 2019 (COVID-19) as the general population. Studies have shown that some individuals with immune suppression may also have a similar incidence as the general population, whereas others with immune suppression, in particular those on corticosteroids, are thought to have higher rates. It is important, however, to recognize that this has not been studied in randomized clinical trials; rather, a lot of these data are based on small cohort studies and retrospective chart reviews. Many of these studies have been from individual practices or registries, which may have referral bias.

G&H What appears to be the typical presentation of COVID-19 in patients who become infected?

GL COVID-19 can vary from mild, moderate, to severe, and has been characterized as having different clinical stages. Staging for COVID-19 has been proposed by Siddiqi and colleagues. Stage 1 is mild and early infection. Patients may have mild constitutional symptoms, a fever greater than 99.6 °F, dry cough, diarrhea, headache, lymphopenia, increased prothrombin time, increased D-dimers, and mild lactate dehydrogenase (LDH) elevation. Stage 2 is more moderate infection and is associated

with pulmonary involvement, with stage 2A being without hypoxia and stage 2B being with hypoxia. In stage 2, patients may have shortness of breath, abnormal radiographic findings, elevated transaminases, and below-normal serum procalcitonin levels. Stage 3 is the most severe stage, the hyperinflation stage, and includes patients who have acute respiratory distress syndrome, systemic inflammatory response syndrome (SIRS), shock, cardiac failure, and elevated inflammatory markers (eg, C-reactive protein [CRP], LDH, interleukin [IL]-6, D-dimers, and troponins).

G&H Do patients with COVID-19 typically present with gastrointestinal symptoms?

GL Some patients may, which can create a diagnostic challenge, as gastrointestinal symptoms, especially diarrhea, may also be a sign of an IBD flare. Several papers have been published on this issue from initial data on the outbreak. In *Gut*, Jin and colleagues looked at 651 patients and found that 11.45% had 1 gastrointestinal symptom: nausea, vomiting, or diarrhea. In *Gastroenterology*, Xiao and colleagues found that 53% of 73 patients had positive stool RNA for COVID-19. In *The Lancet Gastroenterology and Hepatology*, Wu and colleagues found that 55% of 74 patients had positive stool samples for a mean of 27.9 days. However, a study conducted by Wölfel and colleagues, which was published in *Nature*, looked at 9 patients and found that the live virus was not isolated from stool samples. Whether or not COVID-19 is live in stool is controversial and still being evaluated. A study by Han and colleagues, published in the *American Journal of*

Gastroenterology, examined 206 patients with COVID-19 and found that 19.4% had diarrhea as the first symptom of their illness. The diarrhea lasted 1 to 14 days, and the average duration was 5 days with a frequency of 4 bowel movements per day.

Thus, COVID-19 and a flare of IBD may initially present in the same fashion with diarrhea, but the diarrhea can be differentiated. A flare of IBD does not

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typically resolve after 5 days; it persists until there is a specific intervention introduced, such as the use of a corticosteroid. In addition, an IBD flare may be associated with more than 4 bowel movements per day. In an IBD patient presenting with diarrhea, it is also important to consider the other typical symptoms of COVID-19 (eg, cough, shortness of breath, fever, chills, repeated shaking chills, myalgias, headache, pharyngitis, and new loss of taste and/or smell). It is important to ask a patient if he or she is aware of exposure to anyone infected with COVID-19. In the evaluation of the patient, it is also important to discern whether a cough is present and whether the patient has an abnormal chest radiograph or abnormal chest computed tomography findings. There have been characteristic radiographic findings associated with the presence of COVID-19 that may lead a clinician to diagnose a patient with abnormal chest radiography as having COVID-19. Other associated findings may also be present, including leukopenia, lymphopenia, and elevated serum CRP. CRP can be elevated in both individuals with COVID-19 and those with IBD, making it difficult to differentiate between the conditions. It is important, however, to differentiate if the patient is having symptoms subsequent to acquiring COVID-19 or due to a flare of

his or her known IBD because the treatment of each of these disorders is profoundly different.

G&H Has the COVID-19 pandemic changed the treatment recommendations for IBD patients?

GL The current belief is that the risk of infection with COVID-19 is the same whether a patient has IBD or not. Independent of treatment, patients with Crohn's disease or ulcerative colitis (including those with an ostomy or total proctocolectomy with an ileal pouch–anal anastomosis) are not perceived to have a greater risk of infection than the general population. However, it is uncertain whether active inflammation from IBD increases the risk of becoming infected with COVID-19.

Several studies have demonstrated that corticosteroid use has been shown to be associated with a higher likelihood of developing complicated COVID-19. If a patient with IBD develops COVID-19, corticosteroids should be stopped if possible. If an IBD patient is on immune suppressants such as azathioprine, 6-mercaptopurine, methotrexate, anti-tumor necrosis factor (TNF) therapy (such as infliximab, adalimumab, golimumab [Simponi, Janssen], and certolizumab pegol [Cimzia, UCB]), ustekinumab (Stelara, Janssen), or vedolizumab (Entyvio, Takeda), the patient should continue using these therapies unless he or she becomes infected with COVID-19. If the patient becomes infected, he or she should stop these therapies and then restart them once he or she recovers from COVID-19. However, the aforementioned treatments have very long half-lives, so it takes them a long time to leave the patient's system. For example, infliximab has a half-life of 7.7 to 9.5 days, adalimumab 14 days, vedolizumab approximately 25 days, and ustekinumab 20 to 39 days. The time until excretion out of the body can be determined by multiplying 5 times the half-life, which means that it may be 4 months until some of these drugs are out of the patient's system.

Recent data presented from the SECURE-IBD registry have helped the management of patients with IBD. Use of corticosteroids has been associated with a fairly low overall mortality in patients under 20 years of age; however, in older patients, the use of corticosteroids appears to be a significant risk factor for developing worse outcomes with COVID-19. This is of interest because there are 4 randomized, controlled trials that were recently published in *JAMA* that have demonstrated improved mortality in patients with severe COVID-19 who took corticosteroids. Thus, the administration of corticosteroids early on in COVID-19 appears dangerous, whereas treatment of patients with stage 3 COVID-19 with corticosteroids has been shown to decrease patient mortality. The use of anti-TNF therapy and anti-IL-12/23

inhibition (ustekinumab), as well as anti-integrin therapy (vedolizumab), appears to be safe. More data are needed to fully evaluate the other classes of medications.

G&H What is the SECURE-IBD registry?

GL This prospective registry was created to rapidly define the impact of COVID-19 on patients with IBD and evaluate how factors such as age, comorbidities, and IBD treatments affect outcomes. The goal is to openly share findings on the outcomes of COVID-19 with the IBD community. The statistics are publicly updated on the registry's website, COVIDIBD.org. IBD health care providers across the world can fill out a web-based survey, and deidentified data are collected on patient location, demographics, IBD characteristics, comorbidities, and COVID-19 outcomes.

Data from the SECURE-IBD registry have emphasized that corticosteroid use is associated with the development of more severe COVID-19 and that the use

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of ustekinumab, vedolizumab, and anti-TNF therapy appears not to increase the risk of severe COVID-19 complications in IBD patients. In general, it is suggested that clinicians should not use corticosteroids for any longer than they are needed in a patient having a disease-related flare and, in general, practitioners should try to use non-systemic corticosteroids such as budesonide.

G&H In terms of managing IBD during the COVID-19 pandemic, when can telemedicine be used and when is in-person evaluation needed?

GL If a patient has perianal pain and is thought to potentially have an abscess, it is inappropriate to use telemedicine, as well as when a patient has significant abdominal pain and the clinician needs to see whether there is a

palpable mass or a voluntary guarding or rebound. An in-person visit is also needed when a patient seems sick enough to need urgent laboratory tests and possibly needs to be admitted to the hospital. In addition, if a patient looks sick during a telemedicine visit, he or she should be evaluated in person. Also, not all patients may have sphygmomanometers or thermometers readily available. Thus, in-person visits are still critical given the need for careful physical examination.

On the other hand, telemedicine is very helpful to monitor IBD patients who do not have significant abdominal pain or perianal pain or who do not need to have their vital signs urgently checked. In addition, not all patients want to come to the office; there is still voluntary avoidance of health care facilities (whether an office- or hospital-based practice) in an effort to prevent possible exposure to COVID-19.

G&H How has the use of colonoscopy been affected?

GL At first, all elective, nonurgent surgeries and endoscopies were delayed in an effort to be as protective as possible. However, this practice has unfortunately led to delays in appropriate patient care. This can be a significant issue in patients who need to undergo surveillance colonoscopies and may have had dysplasia. Such patients need careful and routine follow-up, and to avoid deleterious outcomes, care should not be postponed too long. Endoscopic procedures have now resumed, and all patients are urged to undergo routine examinations as clinically appropriate. Patients are being tested for COVID-19 prior to the procedure, and health care workers are using appropriate personal protective equipment to protect themselves as well as patients, given that there is not 100% sensitivity to COVID-19 nasal polymerase chain reaction testing. In addition to all patients undergoing nasal swab testing, they are being screened for symptoms of COVID-19. These are national recommendations and guidelines established in an effort to lessen the potential of unknown exposure to and spread of COVID-19.

G&H What has been the biggest challenge of managing IBD patients during the COVID-19 pandemic?

GL The main challenge has been the fear and avoidance behavior that many patients have exhibited. Many patients have been avoiding physicians and health care deliverers because of fear of acquiring COVID-19, and some have stopped treatment completely, believing that the treatment itself was dangerous. Sometimes patients have had irrational fears, but many times their fears

have been rational because COVID-19 can be lethal and these patients have a chronic disorder and may be immunosuppressed. Education of patients as to appropriate management of their disease is important to help them understand the course that should be taken.

G&H What are the largest questions that remain in this area?

GL There are still questions about appropriate treatment and a lot of uncertainty regarding vaccination. There are many different vaccines in development, including RNA vaccines and DNA vaccines. Patients are still uncertain as to whether they should avoid travel to certain places where they may be exposed to infected individuals, including whether they should go to work and whether they should stop going to the laboratory for testing if they are on immune modulators.

There has also been some exciting discussion on whether some of the therapies that are currently being used to treat IBD, such as anti-TNF therapy, can be used as primary treatment for early COVID-19, given their relatively safe outcomes thus far. I am aware of an adaptive phase 3 clinical trial (ACTIV-1 Immune Modulators [IM]; ClinicalTrials.gov identifier: NCT04593940) that has recently been started with the National Institutes of Health looking at infliximab and 2 other immune modulators in adult patients who are hospitalized with COVID-19. Researchers are looking to find out whether modulation of immune response decreases ventilator requirement and reduces the length of hospitalization, as well as whether these 3 treatments can restore the immune system's balance. Cytokines can lead to SIRS, acute respiratory distress syndrome, organ failure, and other serious complications, and are thus a major driver of morbidity and mortality; therefore, attenuation, if not elimination, of this stage with medical therapy might be an appropriate course of therapeutic intervention.

Disclosures

Dr Lichtenstein has consulted for AbbVie, American Regent, Celgene, CellCeutix, Eli Lilly, Endo Pharmaceuticals, Ferring, Gilead, Janssen Orthobiotech, Merck, Morphic

Therapeutics, Pfizer Pharmaceuticals, Prometheus Laboratories, Romark, Salix Pharmaceuticals/Valeant, Shire Pharmaceuticals, Takeda, and UCB; conducted research for Celgene, Janssen Orthobiotech, and UCB; served on the DSMB for Eli Lilly; received honorarium (CME program) from American Regent, Merck, and Romark; and received funding to the University of Pennsylvania (IBD fellow education) from Janssen Orthobiotech, Pfizer Pharmaceuticals, and Takeda.

Suggested Reading

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