Gastroenterology 2020;159:350–357

CLINICAL PRACTICE UPDATES

AGA Clinical Practice Update on Management of Inflammatory Bowel Disease During the COVID-19 Pandemic: Expert Commentary

David T. Rubin,[1] Joseph D. Feuerstein,[2] Andrew Y. Wang,[3] and Russell D. Cohen[1]

[1]*Inflammatory Bowel Disease Center, University of Chicago Medicine, Chicago, Illinois;* [2]*Division of Gastroenterology and Center for Inflammatory Bowel Diseases, Beth Israel Deaconess Medical Center, Boston, Massachusetts; and* [3]*Division of Gastroenterology and Hepatology, University of Virginia, Charlottesville, Virginia*

The purpose of this American Gastroenterological Association (AGA) Institute Clinical Practice Update was to rapidly review the emerging evidence and provide timely expert recommendations regarding the management of patients with inflammatory bowel disease during the coronavirus disease 2019 pandemic. This expert commentary was commissioned and approved by the AGA Institute Clinical Practice Updates Committee and the AGA Governing Board to provide timely perspective on a topic of high clinical importance to the AGA membership, and underwent internal peer review by the Clinical Practice Updates Committee and external peer review through standard procedures of *Gastroenterology*.

Keywords: IBD; Crohn's Disease; Ulcerative Colitis; Coronavirus; SARS-CoV-2; Immunosuppression.

In December 2019, numerous people in the city of Wuhan, in the Hubei Province of China, developed infection and respiratory symptoms from an unknown pathogen. Within 1 month, scientists identified a novel coronavirus and named it 2019 novel coronavirus. This virus was designated as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses, and the World Health Organization subsequently named the disease produced by SARS-CoV-2 as coronavirus disease 2019 (COVID-19).[1] Shortly thereafter, COVID-19 spread rapidly through Wuhan, and by February 2020 there were more than 14,000 confirmed cases and 305 deaths in China and 23 other countries. By the time quarantine and other methods of containment were started, the virus had already spread worldwide. On March 11, 2020, the World Health Organization declared COVID-19 a pandemic and, as of April 2, 2020, there were more than 1,000,000 confirmed cases of COVID-19 and more than 46,000 deaths.[2] COVID-19 has affected all age groups from children to older adults, more men than women, and has worse outcomes in patients with comorbid chronic illnesses, such as respiratory illnesses, diabetes, obesity, and hypertension.[3]

SARS-CoV-2 is an RNA virus and has similarities to earlier coronaviruses that are known or presumed to enter the human population from animals.[4] The respiratory manifestations are similar to 2 earlier coronavirus outbreaks, SARS-CoV from 2002/2003 and Middle Eastern respiratory syndrome CoV. SARS-CoV-2 is thought to be transmitted via droplets and possibly by airborne inhalation of aerosolized particles.[5] Droplet transmission typically occurs in close contact ($\leq$1 m) with a person who coughs or sneezes and when respiratory droplets come into contact with mucosal membranes of the mouth, nose, or the conjunctiva of the eyes. Additionally, transmission of COVID-19 can occur by contact with surfaces contaminated with respiratory droplets. Airborne transmission occurs through virions within droplet nuclei (generally particles <5 μm in diameter) that can remain in the air for long periods of time and be transmitted to others over distances >1 m. Airborne transmission is not likely to be a major mode of transmission in the community, but is definitely a concern in clinical situations where aerosols are generated, such as endotracheal intubation, nasopharyngeal suctioning, and endoscopic procedures.[6] In addition, because SARS-CoV-2 is detectable in stool, it has been postulated that fecal transmission may be possible, but this has not been confirmed.[7,8] A recent report confirmed detection of viral particles in stool, but suggested that it was at quantities that were not infectious.[9]

SARS-CoV-2 enters cells via the angiotensin-converting enzyme 2 (ACE2) receptor. The spike protein of the virus is primed by the transmembrane protease serine 2 precursor, which facilitates virus–cell membrane fusions.[10] ACE2 receptors are expressed on different cell types in the body and appear to be most expressed in intestine, but can be found in many other organs including lung, tongue, and pancreas.[11]

The most common symptoms of COVID-19 are fever and respiratory symptoms, but it is now understood that a significant proportion of patients with COVID-19 will have alterations in bowel habits or other digestive symptoms. These symptoms may reflect inoculation of the

Abbreviations used in this paper: **ACE2, angiotensin-converting enzyme 2; AGA, American Gastroenterological Association; COVID-19, coronavirus disease 2019; GI, gastrointestinal; IBD, inflammatory bowel disease; IOIBD, International Organization for the Study of Inflammatory Bowel Disease; SARS-CoV, severe acute respiratory syndrome coronavirus.**

Most current article

0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2020.04.012

gastrointestinal (GI) tract from swallowing virus and be due to ACE2 expression in the intestines.[12] Additional recent reports have focused on both the GI-related manifestations of COVID-19 and the fact that virus is detectable in stool long after resolution of respiratory symptoms or even detection of virus in the oropharynx.[8]

While the COVID-19 pandemic is a global health emergency, patients with inflammatory bowel disease (IBD) have particular concerns for their risk of infection and management of their medical therapies. This Clinical Practice Update incorporates the emerging understanding of COVID-19 and summarizes available guidance for patients with IBD and the providers who take care of them. This expert commentary was commissioned and approved by the American Gastroenterological Association (AGA) Institute Clinical Practice Updates Committee and the AGA Governing Board to provide timely perspective on a topic of high clinical importance to the AGA membership, and underwent internal peer review by the Clinical Practice Updates Committee and external peer review through standard procedures of *Gastroenterology*.

Inflammatory Bowel Disease and COVID-19

There are a number of key questions that immediately come to mind for both patients with IBD and their contacts and the scientific community as a whole. These are highlighted in Table 1 and will be addressed in this update. Readers are advised that as the understanding of the novel coronavirus progresses, IBD-specific issues and recommendations may change as well.

Are Patients With Inflammatory Bowel Disease at Increased Risk for Infection With SARS-CoV-2 or Development of COVID-19?

It is understandable that patients with Crohn's disease and ulcerative colitis have specific concerns and potential for increased risk of infection with SARS-CoV-2. This is because control of the chronic inflammation often involves the use of immunosuppressive or immune-modifying therapies, some of which have well-described risks of other viral infections.[13,14] In addition, the need to be at medical facilities may increase the risk of exposure to SARS-CoV-2 due to receiving infusions at infusion centers or having endoscopic procedures.

Despite the potential for increased exposure to SARS-CoV-2, the limited available data and expert opinion suggest that patients with IBD do not appear to have a baseline increased risk of infection with SARS-CoV-2 or development of COVID-19.[15] It is unclear whether inflammation of the bowel per se is a risk for infection with SARS-CoV-2, but it is sensible that patients with IBD should maintain remission in order to reduce the risk of relapse and need for more intense medical therapy or hospitalization.

Does the Presence of Inflammation of the Bowel Impact the Clinical Course of Patients With COVID-19?

There is limited information, as documentation of bowel inflammation was not assessed routinely in these patients. However, it has been established that although viral RNA has been identified in roughly one-half of patients with COVID-19, persisting in many even after respiratory samples turned negative, there has not been a clear association with GI symptoms and the presence of viral RNA in the stool.[7,8] Diarrhea (patient-defined) was present in only 10.1% of hospitalized patients with COVID-19 in Wuhan, China (16.7% of those in the intensive care unit)[16]; and another study showed that roughly one-half of patients had digestive symptoms as part of their presentation to the hospital with COVID-19 and pneumonia, only one-third had diarrhea.[12] Of interest, patients with GI symptoms from the Zhejiang Province had a much lower incidence of GI symptoms (11.45%), reflecting the possibilities of different viral strains, reporting differences, or both.[17] In all of these reports, patients with digestive symptoms most frequently

Table 1. Management Issues for Patients With Inflammatory Bowel Disease During the COVID-19 Pandemic

Issues
What is the risk of infection with SARS-CoV-2 in patients with IBD?
What is the risk of COVID-19 in patients with IBD?
Does bowel inflammation increase risk of infection with SARS-CoV-2?
Do patients with IBD have different outcomes with COVID-19?
Do IBD therapies increase risk of infection or COVID-19?
Are any IBD therapies protective against COVID-19?
Should patients with IBD modify their therapies during the pandemic?
Should patients with IBD continue going to infusion centers?
For patients with IBD exposed to a COVID-19 positive patient, should their treatments be modified?
For patients with IBD infected with SARS-CoV-2 how should their IBD treatment be modified?
Should patients with IBD with COVID-19 change their treatments?
Does COVID-19 trigger relapses of IBD?
Does COVID-19 trigger new-onset IBD?

had concurrent fever and respiratory symptoms. Given the prevalence of nonspecific digestive symptoms in the population, and especially in patients with IBD, the clinical implications of this are quite important. Patients who develop new digestive symptoms but who do not have fever or respiratory symptoms can be monitored for the progression of symptoms that might guide timing of testing for SARS-CoV-2 and, in patients with IBD, trigger additional treatment adjustments.

What Are the Outcomes if a Patient With Inflammatory Bowel Disease Develops COVID-19?

There are limited data from China and Europe on the outcomes of patients with IBD who develop CVOID-19. An international registry (SECURE-IBD[18]) has been established and is collecting information about patients with IBD and confirmed (test positive) COVID-19. It is too early to make definitive conclusions, but of 164 patients reported to the registry at the time of this writing, patients with severe IBD and COVID-19 (reported as Physician's Global Assessment) are more likely to be hospitalized related to their IBD or COVID-19 (or both). We anticipate more robust data in the upcoming 1–2 months as the cases worldwide grow. Established cases should be reported at covidibd.org.[18]

Do Inflammatory Bowel Disease Therapies Impact the Risk of Infection With SARS-CoV-2?

The most common question posed by patients with IBD and their providers is "what does one do with IBD therapies in patients during the current pandemic, especially in those suspected of or confirmed to have COVID-19?" In the absence of outcomes data, we must rely on the information to date, as well as expert guidance during these challenging times. To this end, we have incorporated the general guidance and consensus statements from the British Society of Gastroenterology[19] and from the International Organization for the Study of Inflammatory Bowel Disease (IOIBD).[15,20]

We divide the considerations for therapy management in IBD into the following categories: the patient with IBD who is not infected with SARS-CoV-2; the patient with IBD who is infected with SARS-CoV-2 and asymptomatic (eg, IBD is in remission and has not developed manifestations of COVID-19); and the patient with IBD who has confirmed COVID-19, with or without active bowel inflammation or other digestive symptoms.

The Patient With Inflammatory Bowel Disease Who Is Not Infected With SARS-CoV-2

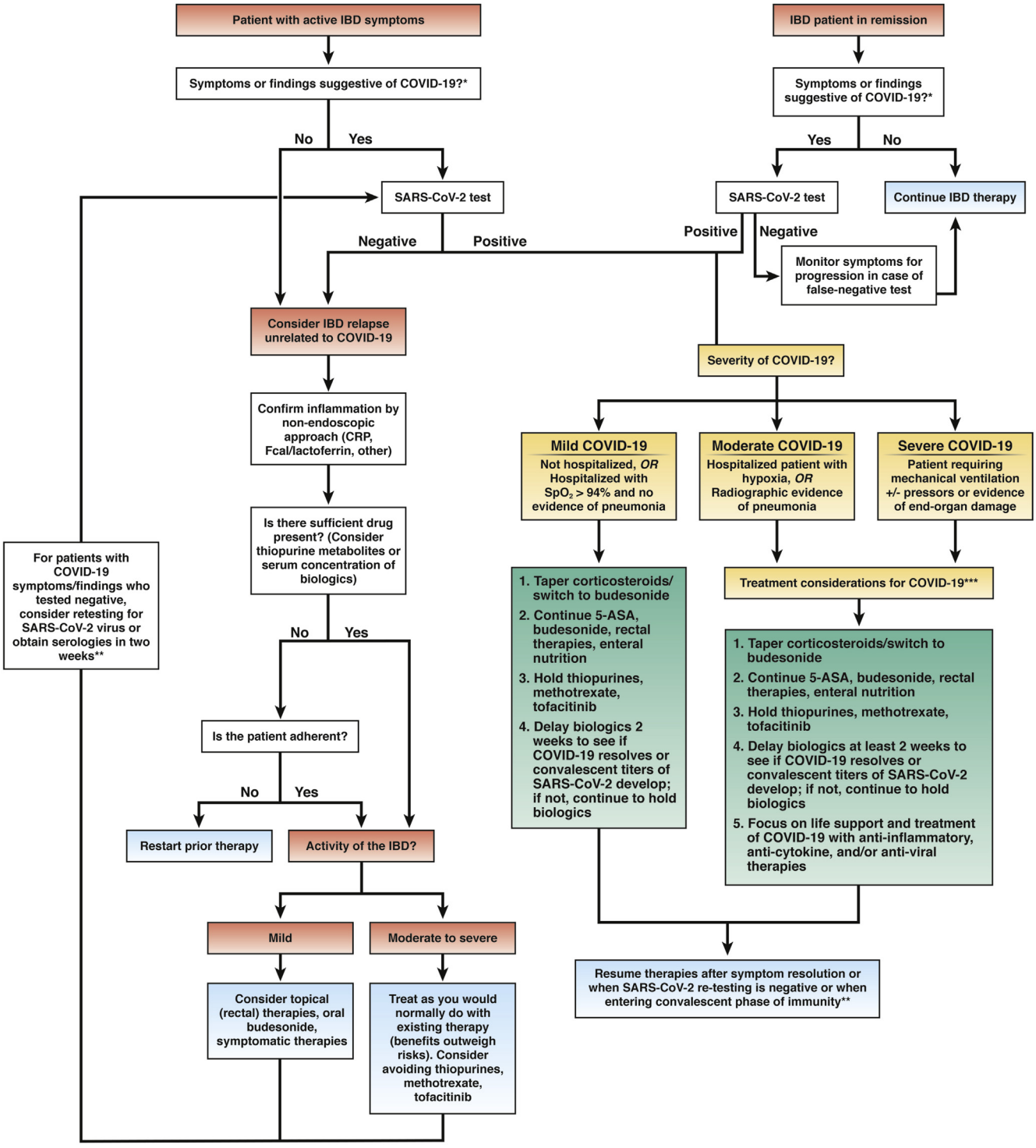
The available data and expert opinions suggest that patients with IBD are not at higher risk of infection with SARS-CoV-2. Therefore, the general recommendation is to stay on IBD therapies with a goal of sustaining remission, ideally defined as a composite of both symptomatic (clinical) remission and objectively confirmed inflammation control (endoscopic improvement and normalized laboratory values). Patients should be advised to maintain their current regimens and to avoid relapse due to nonadherence. Aside from the obvious negative consequences of a relapse, relapsing IBD will strain available medical resources, may require steroid therapy, or necessitate hospitalization, outcomes that are all much worse than the known risks of existing IBD therapies. Similar to the recommendations to the general population, patients with IBD should practice strict social distancing, work from home, have meticulous hand hygiene, and separate themselves from known infected individuals. The Wuhan IBD Center experience of their 318 patients demonstrates the benefit of this approach.[21] The health care team there instituted immediate alerts to their population to stay at home and practice strict social distancing. Despite being in the epicenter of COVID-19 in Wuhan, none of their patients subsequently developed COVID-19.[21]

Patients with IBD and their providers have expressed concerns about going to infusion centers for delivery of infusible IBD therapies (eg, infliximab, ustekinumab, and vedolizumab). The IOIBD consensus supports ongoing use of infusion centers, provided that the center had a COVID-19 screening protocol in place. Infusion centers should have a protocol that includes prescreening of patients for exposure or symptoms of COVID-19, fever checks at the door, adequate spacing between chairs (minimum of 6 feet), masks and gloves used by providers and provided to patients, and adequate deep cleaning after patient departure. Elective switching to injectable therapies is not recommended, and an earlier trial exploring this in patients receiving infliximab who were switched to adalimumab was associated with relapses.[22] In addition, switching to home infusions may seem appealing as a way to limit exposure, but this is not recommended. There are many uncontrolled variables, and there is a serious risk that a nurse-provider traveling from home to home may become infected and act as a vector to other patients.

The Patient With IBD Who Is Infected With SARS-CoV-2 but Without Manifestations of COVID-19

Testing for SARS-CoV-2 is becoming more widespread, and point-of-care tests using sensitive nucleic acid detection or serologic antibodies are in development. In addition, there are discussions about testing patients before endoscopic procedures or surgery, even if they have no specific symptoms to suggest COVID-19. Therefore, the situation in which a patient is known to have been infected with the virus but does not have the disease is possible and will increase. IOIBD specifically explored this scenario in development of their guidance statements.[20]

In this scenario, patients should be actively moved to lower doses of prednisone (<20 mg/d) or transition to budesonide when feasible. Thiopurines, methotrexate, and tofacitinib should be held temporarily. The available



*Symptoms and findings of COVID-19: fever (83%–99%); cough (59%–82%); fatigue (44%–70%); anorexia (40%–84%); shortness of breath (31%–40%); sputum production (28%–33%); myalgias (11%–35%); headache, confusion, rhinorrhea, sore throat, hemoptysis, vomiting, and diarrhea (<10%); lymphopenia (83%); CT chest: bilateral, peripheral ground glass opacities. **Reference:** CDC—Interim Clinical Guidance for Management of Patients With Confirmed Coronavirus Disease (COVID-19). https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html. Accessed April 2, 2020.

**Clearance of SARS-Cov-2 may enable resumption of IBD therapy; role of serologic antibody testing unclear at the current time. *(Viral clearance testing may or may not be possible or appropriate, given local testing capabilities and health system-approved epidemiological testing strategies during the COVID-19 pandemic.)*

***Treatment of COVID-19 under investigation, consider therapies that have safety and efficacy in IBD.

monoclonal antibody therapies (anti-TNF therapies, ustekinumab, or vedolizumab) should have their dosing delayed for 2 weeks while monitoring for development of COVID-19. The general considerations here do not readily acknowledge the half-lives of these therapies, as all of these medications may continue having systemic or tissue effects despite discontinuation. Restarting therapy after 2 weeks if the patient has not developed manifestations of COVID-19 is reasonable. It is likely that soon we will be able to perform serial testing for SARS-CoV-2 or look for disappearance of IgM and development of IgG antibodies in order to know which phase of infection the patient has entered. This will provide more precision and comfort regarding the timing of restarting any therapy that has been held. Given that SARS-CoV-2 can persist in stool longer than what is detected from nasopharyngeal swabs, it is not known whether this should be a preferred test. However, from a practical point of view, serial stool testing is not likely to be adopted. Therefore, the clinical significance of stool testing for SARS-CoV-2 in this setting remains to be seen.

The Patient With IBD Who Has Confirmed COVID-19 With or Without Bowel Inflammation

The third scenario is the most challenging, as there are implications for management of the IBD as well as management of COVID-19. Both the British Society of Gastroenterology and IOIBD statements address the approach to management of the IBD medications in this scenario, but the details about assessing the state of the IBD are complex. We have developed a general algorithm for this approach in Figure 1.

For the patient with COVID-19, adjustment of the medical therapy for IBD is appropriate, based on the understanding of the immune activity of the therapy and whether that therapy may worsen outcomes with COVID-19. First to consider is the patient with IBD in remission. Adjustment of IBD therapies is focused on reducing immune suppression during active viral replication in an attempt to reduce the likelihood of complications. It should be known that anti-cytokine–based treatments are being studied for COVID-19 therapy, and it is possible that we will learn that, for example, continuing anti-TNF therapies might reduce progression to acute respiratory distress syndrome and multi-organ system failure. However, in the absence of those data, guidance is currently based on deciding whether to hold or to continue specific IBD therapies. Of additional interest are the antiviral therapies and other anti-cytokine therapies that are being studied for COVID-19. Choosing therapies that may have secondary benefit in IBD (or at least do not induce bowel inflammation) would be appropriate to consider.

There has been some interesting research into potential medical therapies to treat patients with COVID-19; in particular there has been focus on a therapy that is used primarily for rheumatoid arthritis, the interleukin-6 blocker tocilizumab. Used in rheumatoid arthritis and giant-cell arteritis, this agent also has proven efficacy (and US Food and Drug Administration approval) for the treatment of cytokine-release syndrome, a condition that has become more common in the era of chimeric antigen receptor T-cell cancer therapies.[23] Tocilizumab had positive phase 2 data published in Crohn's disease,[24] and will be actively studied in COVID-19 patients,[25,26] as will another anti-interleukin agent, sarilumab.[27] Separately, the Janus kinas inhibitor baracitinib (but not tofacitinib), may interfere with the virus entering cells by inhibiting AP2-associated protein kinase-1–mediated endocytosis.[28] In addition, hydroxychloroquine, which has received international attention as a possible therapeutic agent in these patients, was one of the older medications used for IBD, albeit in uncontrolled fashion.[29,30] Readers are encouraged to get the latest updates on these and other anti-inflammatory therapies at https://clinicaltrials.gov/.

With regard to IBD therapies, aminosalicylates, topical rectal therapy, dietary management, and antibiotics are considered safe and may be continued. Oral budesonide is likely safe as well and can continue if it is needed for ongoing control of the IBD. Systemic corticosteroids should be avoided and discontinued quickly, if possible, with appropriate caution if there is a concern for adrenal insufficiency from chronic corticosteroid use. Thiopurines, methotrexate, and tofacitinib should be discontinued during the acute illness. Anti-TNF therapies and ustekinumab should also be held during the viral illness. The IOIBD group was uncertain whether holding vedolizumab was necessary in this situation, but in a patient whose IBD is stable, holding it during the time of viral illness is appropriate.

If the patient has COVID-19 and digestive symptoms, ongoing supportive care of the primary COVID-19 is reasonable, but investigating the cause of the digestive

Figure 1. Management of patients with IBD during the COVID-19 pandemic. 5-ASA, 5-aminosalicylic acid medication; CRP, C-reactive protein; mAb, monoclonal antibodies. *Symptoms and findings of COVID-19: fever (83%–99%); cough (59%–82%); fatigue (44%–70%); anorexia (40%–84%); shortness of breath (31%–40%); sputum production (28%–33%); myalgias (11%–35%); headache, confusion, rhinorrhea, sore throat, hemoptysis, vomiting, and diarrhea (<10%); lymphopenia (83%); computed tomography chest: bilateral, peripheral, ground-glass opacities.[38] **Clearance of SARS-Cov-2 may enable resumption of IBD therapy; role of serologic antibody testing unclear at the current time. (Viral clearance testing may or may not be possible or appropriate, given local testing capabilities and health system-approved epidemiological testing strategies during the COIVD-19 pandemic.) ***Treatment of COVID-19 under investigation, consider therapies that have safety and efficacy in IBD.

symptoms in an IBD patient is critically important. First, exclude known enteric infections, such as *Clostridioides difficile* or other GI pathogens. Second, confirm active inflammation with nonendoscopic approaches, including C-reactive protein, fecal calprotectin, or cross-sectional imaging, although these tests should be interpreted with caution, as they may be abnormal due to COVID-19. If the results suggest relapsing IBD, treatment of the IBD should be based on the activity of the inflammation and severity of the IBD.

Per multi-society recommendations on endoscopic procedures during the COVID-19 pandemic, only urgent and emergent endoscopic procedures should be performed. In the case of the patient with IBD and patients in general, this applies in situations "where [the] endoscopic procedure will urgently change management." Clinical scenarios that might prompt endoscopy during this pandemic include the need to obtain biopsies to diagnose new severe IBD, to exclude cytomegalovirus if noninvasive tests are equivocal, or in patients with severe disease or suspected cancer where mucosal inspection might direct surgical intervention.[31] Furthermore, the AGA Institute presently recommends the use of N95 (or N99 or powered air-purifying respirators) masks, instead of surgical masks, and double-gloving as part of appropriate personal protective equipment for health care workers performing both upper and lower GI endoscopies, regardless of COVID-19 status.[1]

For mildly active disease, clinicians should utilize the safer therapies mentioned above. For moderately to severely active disease, holding therapies may not be safe or practicable. In this setting, the risks and benefits of escalating IBD therapy must be carefully weighed against the severity of the COVID-19. For an outpatient with mild COVID-19 symptoms, IOIBD supports using any of the usual treatments that would be considered pre-COVID-19.

For hospitalized patients with severe COVID-19 and risks of poor outcomes, IBD therapy likely will take a back seat, but choice of therapies for COVID-19 should take into account the co-existing IBD, if feasible. It is of interest that clearance of cytomegalovirus is enhanced when IBD therapy is added to ganciclovir[32] and that thiopurines and cyclosporine may have anti-coronavirus properties.[33,34]

If a patient is hospitalized for IBD and also has milder or incidentally identified COVID-19, focus on addressing the severe acute issues from the IBD is important, and standard algorithms applied to the care of hospitalized patients with IBD should be followed.[35] Given the evidence of poor outcomes in SARS and respiratory syncytial virus patients treated with high-dose corticosteroids, as well as some intriguing data on the possible roles of cyclosporine[34] or tacrolimus[36,37] as therapies that interfere with SARS-CoV viral replication, we suggest limiting IV steroids to 3 days, at which point the decision to proceed with a calcineurin inhibitor or infliximab will be made. Although urgent endoscopic procedures that can change or direct therapy remain indicated, during the pandemic, cytomegalovirus testing may be done as a serum polymerase chain reaction to avoid need for colonoscopic procedures, and ganciclovir started if quantitatively suggestive of active inflammation. Surgical consultation is advised, as per standard clinical practice, although the desire to minimize surgical interventions during the pandemic puts more emphasis on finding an effective medical "stop-gap" for these patients. However, there will clearly be some patients who, despite medical interventions, will still require surgery.

Take-Home Points

1. COVID-19 is the disease caused by the SARS-CoV-2 virus, but patients with IBD do not appear to be at a higher risk for infection with SARS-CoV-2 or development of COVID-19.
2. Patients with IBD who do not have infection with SARS-CoV-2 should not discontinue their IBD therapies and should continue infusion schedules at appropriate infusion centers.
3. Patients with IBD who have known SARS-CoV-2 but have not developed COVID-19 should hold thiopurines, methotrexate, and tofacitinib. Dosing of biological therapies should be delayed for 2 weeks of monitoring for symptoms of COVID-19.
4. Patients with IBD who develop COVID-19 should hold thiopurines, methotrexate, tofacitinib, and biological therapies during the viral illness. These can be restarted after complete symptom resolution or, if available, when follow-up viral testing is negative or serologic tests demonstrate the convalescent stage of illness.
5. The severity of the COVID-19 and the severity of the IBD should result in careful risk–benefit assessments regarding treatments for COVID-19 and escalating treatments for IBD.
6. Please submit cases of IBD and confirmed COVID-19 to the SECURE-IBD registry at covidibd.org.

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Correspondence
Address correspondence to: David T. Rubin, MD, Inflammatory Bowel Disease Center, University of Chicago Medicine, 5841 S. Maryland Avenue, MC 4076, Chicago, Illinois 60637. e-mail: drubin@uchicago.edu.

Acknowledgments
Author contributions: Conceptualization and writing: DTR, RDC. Critical editing: DTR, JDF, AYW, RDC. Approval of final manuscript: DTR, JDF, AYW, RDC.

Conflicts of interest
These authors disclose the following: David T. Rubin has received grant support from Takeda; has served as a consultant for Abbvie, Abgenomics, Allergan Inc, Boehringer Ingelheim Ltd, Bristol-Myers Squibb, Celgene Corp/Syneos, Dizal Pharmaceuticals, GalenPharma/Atlantica, Genentech/Roche, Gilead Sciences, Ichnos Sciences S.A., GlaxoSmithKline Services, Janssen Pharmaceuticals, Eli Lilly, Pfizer, Prometheus Laboratories, Reistone, Shire, Takeda, and Techlab Inc. Russell D. Cohen serves on the speakers' bureau for Abbvie and Takeda. He is a consultant for Abbvie, BMS/Celgene, Eli Lilly, Gilead Sciences, Janssen, Pfizer, Takeda, and UCB Pharma. He is principal investigator or has received grants from Abbvie, BMS/Celgene, Boehringer Ingelheim, Crohn's & Colitis Foundation, Genentech, Gilead Sciences, Hollister, Medimmune, Mesoblast Ltd, Osiris Therapeutics, Pfizer, Receptos, RedHill Biopharma, Sanofi-Aventis, Schwarz Pharma, Seres Therapeutics, Takeda Pharma, and UCB Pharma. His spouse is on the Board of Directors at Aerpio Therapeutics, Novus Therapeutics (Board of Directors), and NantKwest. The remaining authors disclose no conflicts.