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

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

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Description: The purpose of this AGA Institute Clinical Practice Update is to rapidly review the emerging evidence and provide timely expert recommendations regarding the management of patients with inflammatory bowel disease during the COVID-19 pandemic.

Methods: This expert commentary was commissioned and approved by the AGA Institute Clinical Practice Updates Committee (CPUC) 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 CPUC and external peer review through standard procedures of *Gastroenterology*.

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

Abbreviations:

2019-nCoV – 2019 novel coronavirus

SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2

COVID-19 – COronaVIrus Disease 2019

SARS-CoV – severe acute respiratory syndrome

MERS-CoV – Middle Eastern respiratory syndrome

ACE2 – Angiotensin-converting enzyme 2

GI – Gastrointestinal

IBD – Inflammatory bowel disease

CD – Crohn's disease

UC – Ulcerative colitis

BSG – British Society of Gastroenterology

IOIBD – International Organization for the Study of Inflammatory Bowel Disease

Anti-TNF – Anti-tumor necrosis factor

CAR-T – Chimeric antigen receptor T-cell

AAK1 – AP2-associated protein kinase-1

PAPR – Powered air-purifying respirators

CMV – Cytomegalovirus

RSV – Respiratory syncytial virus

PCR - Polymerase chain reaction

Introduction

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 a month, scientists identified a novel coronavirus and named it 2019-nCoV. This virus was designated as 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 COVID-19.[1] Shortly thereafter, the COVID-19 rapidly spread through Wuhan and by February 2020 there were over 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 are over 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 prior coronaviruses that are known or presumed to enter the human population from animals.[4] The respiratory manifestations are similar to two prior coronavirus outbreaks, the severe acute respiratory syndrome (SARS-CoV) from 2002/3 and the Middle Eastern respiratory syndrome (MERS-CoV). SARS-CoV-2 is thought to be transmitted via droplets and possibly by airborne inhalation of aerosolized particles.[5] Droplet transmission occurs typically in close contact (≤1 m) with a person who coughs or sneezes and when respiratory droplets come into contact with mucosal membranes of the mouth, nose, or of 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 <5μm in diameter) that can remain in the air for long periods of time and be transmitted to others over distances greater than 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 gastrointestinal (GI) tract from swallowing virus and due to the ACE2 expression in the intestines.[12] Additional recent reports have focused on both the GI-related manifestations of COVID-19 as well as 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 for 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 AGA Institute Clinical Practice Updates Committee (CPUC) 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 CPUC 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 both for the patients with inflammatory bowel disease (IBD) and their contacts, as well as for 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 IBD at Increased Risk for Infection with SARS-CoV-2 or Development of COVID-19?

It is understandable why patients with Crohn's disease (CD) and ulcerative colitis (UC) 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 routinely assessed in these patients. However, it has been established that while viral RNA has been identified in roughly 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 ICU)[16]; while another study showed that roughly 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 had concurrent fever and respiratory symptoms as well. Given the prevalence of non-specific 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 IBD 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 one to two months as the cases worldwide grow. Established cases should be reported at COVIDIBD.ORG.[18]

Do IBD 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 outcome data, we must rely

upon 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 (BSG)[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 three categories: 1) the patient with IBD who is NOT infected with SARS-CoV-2, 2) the patient with IBD who is infected with SARS-CoV-2 and asymptomatic (e.g. IBD is in remission and has not developed manifestations of COVID-19) and 3) the patient with IBD who has confirmed COVID-19, with or without active bowel inflammation or other digestive symptoms.

[level 2 subheading:] **The Patient with IBD 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 non-adherence. 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 healthcare 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 (e.g. infliximab, ustekinumab, 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 pre-screening 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 a prior 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.

[level 2 subheading] **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 prior to 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 temporarily held. The available monoclonal antibody therapies (anti-tumor necrosis factor (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.

[level 2 subheading] **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 BSG 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 whose IBD is 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 anti-viral 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 attention to 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 FDA approval) for the treatment of cytokine-release syndrome, a condition that has become more common in the era of chimeric antigen receptor T-cell (CAR-T) cancer therapies.[23] Tocilizumab had positive phase 2 data published in CD[24], and will be actively studied in COVID-19 patients[25,26], as will another anti-IL 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 (AAK1) 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/.

In regard to the 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 if 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 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 non-endoscopic 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 (CMV) if non-invasive 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 PAPR) 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 CMV 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 are 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 RSV 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 three days, at which point the decision to proceed with a calcineurin inhibitor or infliximab will be made. While urgent endoscopic procedures that may change or direct therapy remain indicated, during the pandemic, CMV testing may be done as a serum PCR 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 clearly will be some patients that 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 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 may 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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Table 1. Management Issues for Patients with IBD During the COVID-19 Pandemic

- **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?**

Abbreviations:
IBD = inflammatory bowel disease
SARS-CoV-2 = Severe Acute Respiratory Syndrome of CoronaVirus 2
COVID-19 = COronaVIrus Disease 2019

Figure 1. **Management of Patients with IBD during the COVID-19 Pandemic.**

Abbreviations: IBD = inflammatory bowel disease, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, COVID-19 = COronaVIrus Disease 2019, mAbs = monoclonal antibodies, 5-ASA = 5-aminosalicylic acid medications

Figure legend:

* 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 COIVD-19 pandemic.)*

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