Coronavirus and Patients With Inflammatory Bowel Disease: Management Strategies for the Practicing Clinician

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INTRODUCTION
Coronavirus disease 2019 (COVID-19) is a respiratory and systemic zoonosis caused by a novel coronavirus of the Coronavirus family (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) and was initially reported in Wuhan, China, in December 2019. The disease was declared a pandemic on March 11, 2020, by the World Health Organization (1,2).

Although general guidance for patients has been provided by multiple organizations including the Centers for Disease Control and Prevention (CDC), patients with inflammatory bowel disease (IBD) are considered an at-risk population for COVID-19 because of the use of immune-modifying treatments and practical clinical guidance for their management during and after the pandemic is needed (3).

RISK OF COVID-19 IN THE IBD POPULATION
Patients with IBD are not believed to have an inherently increased risk of COVID-19, but there is obviously great interest in whether IBD therapies may increase the risk of infection with the coronavirus compared with others who are similarly exposed but not receiving immune-modifying therapies. It is currently unknown if patients with IBD with COVID-19 infection (on or off immunosuppressants) have a higher risk of mortality compared with patients in the general population, although a recent case series from New York City suggested that patients with immune-mediated diseases (including IBD) had similar hospitalization rates for COVID-19 as the general NYC population (4). In the absence of empiric evidence of an increased risk of infection, conservative guidance has been developed to provide protection either way (5). Ongoing collection of data in several multinational registries is occurring.

CLINICAL PRESENTATION OF PATIENTS WITH IBD WITH COVID-19
The clinical presentation of patients with COVID-19 has been described elsewhere and is most often characterized by fever and upper respiratory symptoms, including cough and dyspnea, which may progress into diffuse pneumonia and respiratory failure (6). Recently, the CDC added anosmia, shaking chills, diarrhea, nausea, and vomiting to the list of possible symptoms of COVID-19 (3). There are no specific symptoms that have so far emerged in the IBD population with COVID-19, but the presence of digestive symptoms is obviously a clinical challenge in patients who have IBD. The reported that the range of diarrhea (variably defined) in patients with COVID-19 is from 10% to as high as 50% in a hospitalized population in China (6–8). The duration of diarrhea with COVID-19 is from 1 to 14 days, with an average duration of 3.4 ± 3.1 days and a frequency of 4.3 ± 2.2 bowel movements per day (6–8).

Patients with COVID-19 may have leukocytosis, leukopenia, lymphopenia, abnormal liver enzymes, and notable elevated acute phase reactants. There have been no laboratory abnormalities found to be specific for patients with IBD who are infected with COVID-19.

APPRAOCH TO TESTING AND TREATMENT MODIFICATION
There are no prospective studies evaluating different management approaches to patients with IBD with COVID-19; however, an IBD expert research and development panel and another publication from the United Kingdom suggested treatment strategies for different patient scenarios (5,9).

During the pandemic, it is advocated that all patients with IBD avoid nonessential travel and stay at home to minimize potential exposures (3,5,9). Observational data of 1,099 patients in China did not identify immunomodulator use as a risk factor for severe COVID-19 (10). Most recently, the international registry of COVID-19 and IBD has published an analysis of the first 525 patients and, on multivariate analysis, identified that steroids were associated with the worst outcomes (intensive care unit admission, intubation, and death), whereas biologic therapies, the most frequent of which is anti-TNF, were not associated with an increase in these outcomes (11).

Testing has primarily been aimed at testing symptomatic individuals to identify them for isolation or to rule them out to provide alternative support and conserve medical resources. The polymerase chain reaction testing of nasopharyngeal swabs has a sensitivity of approximately 70%, so the possibility of false negatives must be considered when other clinical parameters exist or when known contact with other positive cases has occurred (12).
In the setting of a negative polymerase chain reaction test result but high suspicion for COVID-19 because of other symptoms or signs, repeat testing, careful monitoring, and presumptive positive management should be performed until the diagnosis is clear or the patient improves. If strong suspicion for COVID-19 with an initial negative swab, consider repeat swab; if still negative with high clinical suspicion, then self-isolation is appropriate for 14 days is advocated. If a patient has diarrhea and it is uncertain if this is due to a disease flare or COVID-19, we advocate to wait and see the course of the diarrhea for the next 5 days, given the diarrhea in COVID-19-positive patients is usually mild and self-limited typically lasting 5 days and follow biomarkers (e.g., C-reactive protein, calprotectin). Calprotectin is usually only mildly elevated in patients with COVID-19 with diarrhea, whereas in patients with IBD with active disease, significant elevation may occur. The reliability and effectiveness of serologic antibody testing and, ultimately, of vaccines will have additional special considerations for patients with IBD who are receiving immune therapies.

Below and in Table 1, we suggest management based both on the clinical activity of the IBD and on the stage of SARS-CoV-2 infection and progressive COVID-19 (13).

**APPROACH TO THE PATIENT WITH IBD DURING THE PANDEMIC**

Patients with IBD who are in remission and off prednisone should continue their medical therapy, including immune modulators, small molecules, and biological therapies. This should include continuing infusions, provided that the infusion center has appropriate screening and safety maneuvers in place.

For patients with active IBD, the usual evaluation of the degree of inflammation, exclusion of enteric pathogens, and assessment of drug adherence, exposure, and PK should occur. However, given the newer consideration that COVID-19 may present as nonspecific digestive symptoms, careful consideration whether this is indeed typical of the patient’s usual IBD symptoms or different may provide insight into whether this may be COVID-19 rather than all the other causes for IBD relapse. If this is indeed similar to a patient’s usual IBD symptoms or an obvious explanation is identified (such as Clostridioides difficile infection), then addressing the cause of the relapse is recommended. This may include continuation of current medical therapy with optimization to reobtain a state of remission. If new immune-based treatments are needed, then avoiding prednisone when possible is preferred, recognizing that many of the therapies currently available were studied for induction without the use of concomitant steroids. Patients using prednisone should avoid high-dose therapy (=20 mg daily) and attempt to lower therapy to the least effective dose or even to switch to oral budesonide formulations or topical formulations. If treating a patient with corticosteroids, initial use of oral budesonide formulations or topical formulations is preferred. Conversion of conventional corticosteroid to budesonide might also be considered with appropriate dosing management. Studies of high-dose steroids in other viral infections have demonstrated worse outcomes or delayed viral clearance (14).

**PATIENTS WITH KNOWN OR SUSPECTED COVID-19**

There are several considerations for the patient with IBD who is receiving steroids or immune therapies and who tests positive for confirmed COVID-19. The first is whether these therapies may worsen the disease course. Although it is intuitive to worry about this, there are no data suggesting this is the case. In fact, in the inflammatory phase of COVID-19, it is possible that anti-cytokine therapies may reduce the damage that occurs (15,16). The other practical reality is that many of these therapies have half-lives such that they will still be present during the viral infection, even if they are held, discontinued, or dosing is delayed. Therefore, recommendations to hold or stop therapies are made based on assumptions of a patient’s immune system to respond to the infection, which may in fact be of no consequence.

The general recommendations for the patient with IBD who has confirmed COVID-19 are physical isolation and to stop or delay dosing of immune-based therapies and to work expeditiously to reduce the dose of prednisone until the symptoms of COVID-19 are completely gone for at least 72 hours. Resumption of therapy after all symptoms resolve is reasonable, but as testing options improve, resumption of therapy may be directed when the patient tests negative for SARS-CoV-2 or enters the convalescent phase of immunity.

For patients with active IBD and known or suspected COVID-19, we must balance the severity of the IBD with the severity of the COVID-19. Nonimmune-based therapies such as aminosalicylates, oral budesonide, or rectal therapies may continue, but other immune treatments should be held until COVID-19 has resolved. If IBD is moderately to severely active, and the COVID-19 symptoms are mild, temporary measures to stabilize IBD should be considered, but consensus currently supports the use of IBD therapies similar to the prepanedemic era if necessary. When COVID-19 is progressive or more severe, focus should be on supportive care of the patient with COVID-19, and any treatments considered for IBD should be in consultation with other members of multidisciplinary services of pulmonary infectious disease and possibly the clinical trials teams, with consideration of treatments that may have efficacy in both the bowel and the systemic inflammatory reaction of COVID-19. Surgery for the IBD in the setting of COVID-19 should be considered with careful balancing of benefits and risks.

**CONCLUSIONS**

Although there are limited data on the risks and outcomes of COVID-19 in patients with IBD, general strategies to keep this population of patients safe include strict physical distancing. The symptoms and clinical presentation of COVID-19 in patients with IBD is likely similar to patients without IBD, but the presence of digestive symptoms associated with COVID-19 onset can be confusing and requires special attention to distinguish these symptoms from those of active IBD. In patients with IBD who have known or suspected COVID-19, immune-based therapies should be discontinued until the illness is cleared and, in the near future, may also be used after testing confirms clearance of virus or convalescent phase of immunity. In more severe COVID-19 cases, and when treatment of the COVID-19 with candidate therapies is considered, choice of therapies that may be safe or even have benefit in IBD is preferred. Ongoing data collection and observational studies will guide future management considerations related to widespread testing or utilization of vaccines in this special population.
| Table 1. Treatment options for IBD in the Setting of COVID-19 |
|-------------------------------------------------------------|
| **No SARS-CoV-2** | **SARS-CoV-2 positive, but NO COVID-19** | **Stage I: mild COVID-19—Early infection** | **Stage II: moderate COVID-19—Pulmonary involvement without or with hypoxia** | **Stage III: severe COVID-19—Systemic hyperinflammation** |
| IBD remission | Taper or discontinue prednisone. Continue all other IBD meds. | If IBD stable, wait for 2 weeks for COVID-19 to present or until convalescent titers of SARS-CoV-2 develop. Taper or discontinue prednisone. Discontinue thiopurines, MTX, and tofacitinib for 2 weeks. | Taper or discontinue prednisone. Discontinue thiopurines, MTX, and tofacitinib. Discontinue biological therapies. | Taper or discontinue prednisone. Discontinue immune-based IBD therapies. Focus on life support and if available, treatment of COVID-19 with antiviral or other anti-inflammatory/anticytokine therapies. |
| IBD mildly active | Treat with any IBD therapies necessary. Limit use of oral or IV steroids to shortest possible, choose alternatives when possible. | If IBD stable, wait for 2 weeks for COVID-19 to present or until convalescent titers of SARS-CoV-2 develop. If treatment is needed, budesonide, 5-ASA, and rectal therapies are okay. Consider holding immune therapies and biologics for 2 weeks. | If IBD stable, wait for 2 weeks for COVID-19 to resolve or until convalescent titers of SARS-CoV-2 develop. If treatment is needed, budesonide, 5-ASA, and rectal therapies are okay. Taper or discontinue prednisone. Discontinue thiopurines, MTX, and tofacitinib for 2 weeks. Delay dosing of biologics for 2 weeks. | Taper or discontinue prednisone. Discontinue thiopurines, MTX, tofacitinib. Discontinue biological therapies. |
| IBD moderately—severely active | Treat with any IBD therapies necessary. Limit the use of oral or IV steroids to the shortest possible and choose alternatives when possible. | Limited use of corticosteroids* ≤40 mg/d if necessary. Avoid thiopurines, MTX, and tofacitinib. Escalate to biological therapies as needed. If hospitalized, consider IV cyclosporine for UC, given limited evidence of benefit against coronavirus. | Limited use of steroids* ≤40 mg/d if necessary. Avoid thiopurines, MTX, and tofacitinib. Escalate to biological therapies as needed. | Limited use of steroids if necessary. Stop thiopurines, MTX, and tofacitinib. Escalate to biological therapies as needed based on benefits and risk. If available, treatment of COVID-19 with antiviral or other anti-inflammatory/anticytokine therapies. |
| | | | | Limited use of IV steroids for IBD only if necessary. Topical (rectal) therapy if needed. Discontinue immune therapies or biologics that are not working for the IBD. Careful consideration of other therapies for IBD only as absolutely needed. Consider cyclosporine for UC, given limited evidence of benefit against coronavirus. |

*aCorticosteroids—prednisone equivalent dose. COVID-19 = coronavirus disease 2019; IBD = inflammatory bowel disease; UC = ulcerative colitis. Stages of COVID-19 (13) |
| Stage I (mild)—Early infection: | For most individuals, this involves the presence of mild and often nonspecific symptoms such as malaise, dry cough, and fever. Gastrointestinal symptoms including anorexia, anosmia, ageusia, dyspepsia, and diarrhea can occur. |
| Stage II (moderate)—Pulmonary involvement without or with hypoxia: | Patients develop viral pneumonia with cough, fever, and may have hypoxemia (defined as PaO2/FiO2 of <300 mm Hg). |
| Stage III (severe)—Systemic hyperinflammation: | Imaging with CT of the chest or chest X-ray: ground-glass opacities or bilateral infiltrates. Hematologic: Elevated aminotransferase levels and increased lymphopenia. |
| Systemic involvement: Patient requiring mechanical ventilation +/- pressors or evidence of end organ damage. |
CONFLICTS OF INTEREST

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