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## COVID-19 and Inflammatory Bowel Disease: Lessons Learned, Practical Recommendations, and Unanswered Questions



On March 11, 2020, the World Health Organization declared the 2019 novel coronavirus (severe acute respiratory syndrome coronavirus-2 [SARS-CoV-2]) epidemic a global pandemic.<sup>1</sup> Physicians, scientists, and patients scrambled to gain an understanding of the implications of this dire situation, and societies and organizations tried to provide guidance of best practices and precautions. In the inflammatory bowel disease (IBD) community, the International Organization for the study of IBD convened their expert members and performed a RAND panel assessment to develop recommendations for patients and providers.<sup>2</sup> Others developed an international open registry to collect data about patients with IBD who developed Coronavirus Disease (COVID-19), the Surveillance Epidemiology of COVID-19 Under Research Exclusion (SECURE-IBD), to collect evidence on how coronavirus disease-2019 (COVID-19) impacted patients with IBD. To date, SECURE-IBD has amassed 3493 cases with outcomes<sup>3</sup> and published initial analyses.<sup>4-6</sup> In addition, there were multiple articles published with individual or multicenter experiences, city or regional experiences, and many case reports about IBD or immune-mediated disease outcomes.<sup>7-14</sup> Separately, there was significant activity by translational and basic scientists working to define and describe the pathophysiology of SARS-CoV-2 infections.

Early reports and expert opinions were necessary to guide the world in their approach to this unprecedented global problem, but the substantial amount of progress made warrants an updated review and discussion. In this commentary, we outline the emerging

evidence and lessons learned about COVID-19 and the IBD population, enumerate unanswered questions that remain to be addressed, and provide practical recommendations.

### Are Patients with IBD at Increased Risk of Contracting SARS-CoV-2?

Initial expert opinion from the International Organization for the study of IBD at the start of the pandemic suggested that patients with IBD were likely not at increased risk to contract SARS-CoV-2. Recent evidence has described the biologic plausibility that patients with IBD may have differential risk for contracting SARS-CoV-2 because the receptor for the virus, angiotensin-converting enzyme receptor 2 (ACE2), seems to be differentially expressed in inflamed IBD mucosa with up-regulation in the colon, but down-regulation in the small intestine.<sup>15-17</sup> SARS-CoV-2 receptor expression also seems to be impacted by IBD medications, with infliximab notably being associated with decreased ACE2.<sup>17</sup>

Recent reports from large cohorts have provided evidence that patients with IBD do not appear to be at increased risk of COVID-19. Patients with IBD in the US Veterans Affairs health care system had a similar incidence of confirmed SARS-CoV-2 compared with the general Veterans Affairs population (0.23% vs 0.20%;  $P = .29$ ).<sup>18</sup> Similar results were seen in 2 European population-based cohorts. The incidence of COVID-19 in patients with IBD in the Netherlands compared with the general population was comparable (287.6 vs 330.0 per 100,000 patients;  $P = .15$ ).<sup>19</sup> A population-based cohort study from Denmark found that patients with IBD may actually have a lower prevalence of SARS-CoV-2 than the general population (2.5% vs 3.7%;  $P < .01$ ).<sup>20</sup> Further, patients with IBD receiving immunosuppressive medications do not seem to be at an increased risk of contracting COVID-19.<sup>21,22</sup> The

humoral immune response against SARS-Cov2 leads to the production of antibodies of different classes, and serologic testing is another tool to assess SARS-Cov2 infection prevalence.<sup>23</sup> Studies from Italy and Germany showed a similar SARS-Cov2 seroprevalence in patients with IBD treated with biological therapy as in the general population.<sup>24</sup>

The sum of these data suggests that patients with IBD are not at higher risk of contracting SARS-CoV-2 than the general population. However, it is important to note that these findings may be influenced by social behaviors during the pandemic, in particular the potential for patients with IBD to be more likely to “shield” or social distance owing to a perceived higher risk.

### Are Patients with IBD Who Develop COVID-19 at Increased Risk of Adverse Outcomes?

Emerging evidence suggests that, when patients with IBD develop COVID-19, the course of illness may be somewhat more severe. The initial report from SECURE-IBD calculated age and sex-standardized mortality ratios (SMRs), comparing patients with IBD reported to the database to general population data reported from China, Italy, and the United States. Observed SMRs varied from 1.45 to 1.76, suggesting a 50% higher COVID-related mortality in patients with IBD; however, these findings were not statistically significant owing to 95% confidence intervals (CI) crossing 1.<sup>4</sup> As of December 6, 2020, a total of 3493 cases have been reported to SECURE-IBD and although the magnitude of the earlier findings remain unchanged, the increased mortality rate is now statistically significant. For example, the US SMR is 1.4 (95% CI, 1.1-1.7). Although the observed excess mortality among patients with IBD may be due to reporting bias, potential drivers of COVID-19 mortality among patients with IBD may include chronic intestinal inflammation, non-IBD comorbidities,

and exposure to corticosteroids and other immunosuppressive medications. In contrast, a separate electronic health record–based study across 31 institutions compared 232 patients with IBD diagnosed with COVID-19 with propensity-matched controls without IBD and found no differences in COVID-19 hospitalization or mortality.<sup>25</sup>

Among patients with IBD, as in the general population, key risk factors for more severe COVID-19 infection seem to be advancing age and the presence of comorbid conditions. In the initial report from SECURE-IBD, the primary outcome (intensive care unit admission/ventilator support/death) was observed in 37 of 525 patients (7%) overall. However, among patients >60 years of age 20 of 101 (20%) experienced this outcome versus 0 of 29 pediatric cases (<20 years).<sup>4</sup> Older age (>65 years) was also demonstrated to be significantly associated with COVID-19 mortality in an Italian multicenter cohort (OR, 19.6; 95% CI, 2.95–130.6).<sup>8</sup> Additionally, the number of non-IBD comorbidities is also a risk factor for more severe COVID-19. In the same Italian study, having a Charlson Comorbidity Index of >1 was associated with increased mortality (OR, 16.7; 95% CI, 1.8–153.9). Similarly, a Dutch nationwide cohort study identified >1 comorbidity as an independent risk factor for hospitalization (OR, 4.20; 95% CI, 1.58–11.17).<sup>19</sup> In SECURE-IBD, having ≥2 comorbidities was associated with a 3-fold risk of requiring intensive care unit admission, ventilator support, or death (aOR, 2.9; 95% CI, 1.1–7.8).<sup>4</sup> Aside from age and non-IBD comorbidities, associations between other demographic and clinical characteristics (sex, IBD type, IBD disease activity) and the severity of COVID-19 have been inconsistent or relatively small in magnitude.<sup>4,8,19</sup>

In terms of the risk of IBD medications, current or recent use of systemic corticosteroids to treat IBD at the time of COVID-19 infection has been consistently associated with more severe outcomes, despite emerging data suggesting that dexamethasone use in severe COVID-19 may decrease mortality.<sup>4,8,25</sup> We believe these are 2 different distinct clinical scenarios. The use of steroids in patients with IBD at

or before infection may allow a greater degree of viral replication early in the course of illness, whereas treatment of later stage infections with prednisone may blunt the cytokine storm characteristic of more severe cases with respiratory failure. In addition, data have suggested that mesalamines may be associated with an increased risk of severe COVID-19.<sup>4,5</sup> However, the effect size of this association has attenuated with time and, given the unexpected nature of this finding and potential for unmeasured confounding, requires further investigation.<sup>4,5</sup> Reassuringly, anti-tumor necrosis factor (TNF) therapy has not been associated with more severe COVID-19. An analysis of 600 cases of individuals with rheumatic diseases demonstrated that anti-TNF therapy was associated with a decreased odds of hospitalization (OR, 0.40; 95% CI, 0.19–0.81).<sup>26</sup> In an analysis of nearly 1500 cases reported to SECURE-IBD, Ungaro et al<sup>5</sup> demonstrated a decreased risk of severe COVID-19 in patients treated with anti-TNF monotherapy versus anti-TNF in combination with thiopurine or thiopurine monotherapy. More data are needed to fully evaluate the safety of other classes of IBD medications, although to date no clear signals have been observed with methotrexate, ustekinumab, vedolizumab, or tofacitinib.<sup>5,10</sup> As a side note, there are active trials of anti-TNF as well as JAK inhibitors therapies (tofacitinib and baricitinib) as treatments for COVID-19.<sup>27–29</sup>

## Are Gastrointestinal Symptoms of COVID-19 Common in Patients with IBD?

Early in the pandemic, it was appreciated that digestive symptoms occurred in some patients with COVID-19, and this has obvious implications for patients with IBD. In the original report of COVID-19 from Wuhan, China, 48% of the hospitalized patients had digestive symptoms, which were most often diarrhea and abdominal pain, although most of these patients also had concurrent respiratory symptoms and fever.<sup>30</sup> Subsequent studies have

confirmed these symptoms as well as nausea and vomiting, with the duration of diarrhea (defined differently) varying from 1 to 14 days.<sup>31–33</sup> The Centers for Disease Control and Prevention subsequently added digestive symptoms of anosmia, diarrhea, nausea, and vomiting to the list of presenting symptoms associated with COVID-19.<sup>34</sup> The presence of these symptoms suggested the possibility of viral entry through the intestinal mucosa, further supported by prior research identifying expression of ACE2, the site of viral binding and endocytosis, throughout the intestinal tract.<sup>17</sup> Also of interest is whether the presence of digestive symptoms predicts the severity of COVID-19. A pooled analysis of multiple studies demonstrated that abdominal pain was associated with increased odds of severe COVID-19 (OR, 3.93; 95% CI, 1.64–9.38), but there were only marginally increased odds with nausea or vomiting (OR, 1.65; 95% CI, 1.06–2.57), and no association with diarrhea.<sup>35</sup> However, there are conflicting data; a recent report on patients hospitalized with COVID-19 observed that those with digestive symptoms on admission had lower mortality.<sup>36</sup> The question of whether there is fecal–oral transmission of SARS-CoV-2 also has not been resolved.

## Do Patients with IBD Mount an Altered Antibody Response to SARS-CoV-2?

Detailed studies of the antibody response to SARS-CoV-2 in patients with IBD will be crucial not only to understanding the immune response to virus with implications for vaccine research, but also because of the possibility of emergence of cross-reactive antibodies that could contribute to long-term complications of COVID-19. The vast majority of patients with mild-to-moderate COVID-19 experience robust IgG antibody responses against the viral spike protein and have titers that are stable for approximately 5 months, which significantly correlate with SARS-CoV-2 neutralization.<sup>37</sup> However, it remains unclear if the humoral response to SARS-CoV-2

**Table 1.** Summary of New Knowledge and Clinical Implications/Recommendations

New Knowledge	Clinical Implication/Recommendation
Patients with IBD, including those on biological therapy, do not seem to be at increased risk of contracting SARS-CoV-2 compared with the general public	Standard precautions (wear a mask, wash your hands, and social distance) are sufficient for most patients with IBD
Age and comorbidities in addition to IBD confer increased risk of severe COVID-19	As with other non-IBD populations, older age (>65) and the presence of non-IBD comorbidities should be used to risk stratify patients with IBD and inform clinical/treatment decisions as well as lifestyle decisions such as work, school, and the degree of physical distancing (“shielding”).
Systemic corticosteroids significantly increase the risk of severe COVID-19	Corticosteroid use to treat IBD should be minimized to the extent reasonably possible throughout the pandemic.
Combination therapy and thiopurine monotherapy are associated with severe COVID-19 compared with anti-TNF monotherapy, especially in older patients.	In selected high-risk patients (older, multiple comorbidities), withdraw of combination therapy in favor of anti-TNF monotherapy should be considered, particularly in patients who have achieved a durable deep remission.
Biologics (in particular anti-TNF agents) and small molecules do not appear to be associated an increased risk of severe COVID-19.	Most other IBD therapies do not appear to be associated with substantial COVID-19 safety signals, and hence should be continued during the pandemic. Prior recommendations to temporarily hold biologics and other IBD therapies in the setting of acute COVID-19 infection should be reconsidered, given paucity of data suggesting a harmful effect of such treatments.
Mesalamines may be associated with an increased risk of severe COVID-19	We in general would not avoid use of mesalamines but, until further data are available to confirm or refute this observation, recommend avoiding in situations where their efficacy is limited (Crohn’s disease and after escalating to a biologic in ulcerative colitis).

COVID-19, coronavirus disease-2019; IBD, inflammatory bowel disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF, tumor necrosis factor.

will be attenuated in patients with IBD. Data from Germany showed a lower seroprevalence of anti-SARS-CoV-2 antibodies in immune-mediated disease patients on cytokine inhibitors compared with the general population, although this finding was not confirmed in a recent study in which biological therapy, including vedolizumab, did not prevent the mounting of an efficient humoral response to SARS-CoV2.<sup>9,24</sup> Longitudinal seroprevalence studies are necessary. Another aspect to consider is whether the virus may impact the host immune response by inducing autoantibodies, triggering cross-reactive antibodies, or altering IgA-microbe interactions in the gut. Studies have highlighted the possibility that COVID-19 could induce pathogenic autoantibody formation both in adult and pediatric patients with severe COVID-19 and in patients with COVID-19 who developed

neuropathology.<sup>38</sup> These questions will be important to consider as we address the impact of SARS-CoV-2 on IBD.

## Practical Recommendations

The accumulating evidence suggests that patients with IBD may be at increased risk of adverse outcomes, particularly patients who are older, have comorbidities, or are undergoing treatment with systemic corticosteroids. We advise that patients should continue on prescribed medications with the exception of corticosteroids, which should be tapered off or to the lowest possible dose. In addition, de-escalation of combination therapy with thiopurine and anti-TNF should be considered in high-risk patients in stable remission. Although the association between severe COVID-19 and mesalamines requires

further data, we would recommend limiting their use in situations of low clinical value (Crohn’s disease and after escalating to biologic therapy in ulcerative colitis). Given that the lack of adverse impact of biologics on COVID-19 outcomes, patients with asymptomatic or mild COVID-19 may be able to either continue or avoid prolonged holding of needed medications. A summary of clinical implications and recommendations is provided in [Table 1](#).

## What Are the Unanswered Questions about COVID-19 and Patients with IBD?

Despite prolific research regarding COVID-19 and IBD over the past 6 months, several critical research gaps remain. Observations on impact medications such as aminosaliculates from



the SECURE-IBD registry should be validated in large population-based cohorts. It will also be critical to understand the degree of immunity and long-term seroprotection to SARS-CoV-2, and how immunity is affected by the inflammatory disease process and by the treatments for IBD. Studies on the impact of COVID-19 on the natural history of IBD and possible emergence of de novo IBD and other immune-mediated diseases clearly are needed. In addition, it will be essential to evaluate vaccine effectiveness and safety among patients with IBD and how these are impacted by the type and degree of immune suppression, given that patients with IBD and other immune-mediated conditions have been excluded from clinical vaccine trials.

## Conclusions

The IBD community has made significant strides in developing an evidence base with which to inform patients and providers during the COVID-19 pandemic. Based on the current literature and this update, we conclude that, for the most part, patients with IBD are not at increased risk for SARS-CoV-2 infection compared with the general population and, with the exception of steroids, medications that treat IBD are not associated with clear harm in the setting of COVID-19. Although many questions remain, the international IBD community is well-positioned to advance our understanding of COVID-19 while continuing to provide excellent care to our patients.

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### Conflicts of interest

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