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

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**Word Count:** 2,162

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## Conflicts of Interest

RCU has served as a consultant and/or advisory board member for Bristol Myers Squibb, Eli Lilly, Janssen, Pfizer and Takeda. He has received research support from AbbVie, Boehringer Ingelheim and Pfizer. MDK has consulted for Abbvie, Janssen, Pfizer, and Takeda, is a shareholder in Johnson & Johnson, and has received research support from Pfizer, Takeda, Janssen, Abbvie, Lilly, Genentech, Boehringer Ingelheim, Bristol Myers Squibb, Celtrion, and

Arenapharm. DTR has received grant support from Abbvie, Genentech/Roche, Janssen Pharmaceuticals, Prometheus Laboratories, Shire, and Takeda; and has served as a consultant for Abbvie, Abgenomics, Allergan Inc., Biomica, Boehringer Ingelheim Ltd., Bristol-Myers Squibb, Celgene Corp/Syneos, Check-cap, Dizal Pharmaceuticals, GalenPharma/Atlantica, Genentech/Roche, Gilead Sciences, GlaxoSmithKline Services, Ichnos Sciences S.A., InDex Pharmaceuticals, Janssen Pharmaceuticals, Lilly, Narrow River Mgmt, Pfizer, Prometheus Laboratories, Reistone, Shire, Takeda, and Techlab Inc. Jean-Frederic Colombel has received research grants from AbbVie, Janssen Pharmaceuticals and Takeda; has received payment for lectures from AbbVie, Amgen, Allergan, Bristol-Myers Squibb Company, Ferring Pharmaceuticals, Shire, Takeda and Tillots; has received consulting fees from AbbVie, Amgen, Arena Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb Company, Celgene Corporation, Celltrion, Eli Lilly, Enterome, Ferring Pharmaceuticals, Genentech, Gilead, Iterative Scopes, Ipsen, Immunic, Imtbio, Inotrem, Janssen Pharmaceuticals, Landos, LimmaTech Biologics AG, Medimmune, Merck, Novartis, O Mass, Otsuka, Pfizer, Shire, Takeda, Tigenix, Viela bio; and hold stock options in Intestinal Biotech Development.

**Funding**

RCU is supported by a Career Development Award from the National Institutes of Health (K23KD111995-01A1).

**Keywords**

COVID-19; Crohn's disease; ulcerative colitis; inflammatory bowel disease

## Introduction

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.[1] 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 community (IBD), the International Organization for the study of IBD (IOIBD) convened their expert members and performed a RAND panel assessment to develop recommendations for patients and providers.[2] 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), in order to collect evidence on how COVID-19 impacted IBD patients. To date, SECURE-IBD has amassed 3,493 cases with outcomes[3] and published initial analyses.[4–6] In addition, there were multiple articles published with individual or multi-center experiences, city or regional experiences, and many case reports about IBD or immune-mediated disease outcomes.[7–14] 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 IOIBD at the start of the pandemic suggested that IBD patients were likely not at increased risk to contract SARS-CoV-2. Recent evidence has described the

biologic plausibility that IBD patients may have differential risk for contracting SARS-CoV-2 as the receptor for the virus, angiotensin converting enzyme receptor 2 (ACE2), appears to be differentially expressed in inflamed IBD mucosa with upregulation in the colon but downregulation in the small intestine.[15–17] SARS-CoV-2 receptor expression also appears to be impacted by IBD medications, with infliximab notably being associated with decreased ACE2.[17]

Recent reports from large cohorts have provided evidence that IBD patients do not appear to be at increased risk of COVID-19. IBD patients in the US Veterans Affairs (VA) healthcare system had a similar incidence of confirmed SARS-CoV-2 compared to the general VA population (0.23% versus 0.20%, p=0.29).[18] Similar results were seen in two European population-based cohorts. The incidence of COVID-19 in patients with IBD in the Netherlands compared to the general population was comparable (287.6 versus 330.0 per 100,000 patients, p=0.15).[19] A population based cohort study from Denmark found that patients with IBD may actually have lower prevalence of SARS-CoV-2 than the general population (2.5% versus 3.7%, p<0.01).[20] Further, patients with IBD receiving immunosuppressive medications do not appear to be at increased risk of contracting COVID-19.[21,22] Humoral immune response against SARS-Cov2 leads to the production of antibodies of different classes and serological testing is another tool to assess SARS-Cov2 infection prevalence.[23] Studies from Italy and Germany showed a similar SARS-Cov2 seroprevalence in IBD patients treated with biological therapy as in general population.[24]

The sum of these data suggests that IBD patients 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 due to 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 due to 95% confidence intervals crossing one.[4] As of December 6th, 2020, a total of 3,493 cases have been reported to SECURE-IBD and while the magnitude of the earlier findings remain unchanged, the increased mortality rate is now statistically significant. For example, the U.S. SMR is 1.4 (95% CI 1.1-1.7). Although the observed excess mortality among IBD patients may be due to reporting bias, potential drivers of COVID-19 mortality among IBD patients may include chronic intestinal inflammation, non-IBD comorbidities, and exposure to corticosteroids and other immunosuppressive medications. In contrast, a separate EHR-based study across 31 institutions compared 232 patients with IBD diagnosed with COVID-19 to propensity matched controls without IBD and found no differences in COVID-19 hospitalization or mortality.[25]

Among patients with IBD, as in the general population, key risk factors for more severe COVID-19 infection appear to be advancing age and the presence of comorbid conditions. In the initial report from SECURE-IBD, the primary outcome (ICU/ventilator/death) was observed in 37 (7%) of 525 patients overall. However, among patients over 60 years of age 10/101 (20%) experienced this outcome versus 0 of 29 pediatric cases (<20 years).[4] Older age (>65 years) was also demonstrated to be significantly associated with COVID-19 mortality in an Italian multi-center cohort (OR 19.6, 95% CI 2.95-130.6).[8] 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 >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).[19] In SECURE-IBD, having ≥2 comorbidities was associated with 3-fold risk of requiring ICU, ventilator, or death (aOR, 2.9, 95% CI,1.1–7.8).[4] 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.[4,8,19]

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 reduce mortality.[4,8,25] We believe these are two different distinct clinical scenarios. Use of steroids in patients with IBD at or prior to infection may allow a greater degree of viral replication early in the course of illness while 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.[4,5] 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.[4,5] 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 reduced odds of hospitalization (OR 0.40, 95% CI 0.19 to 0.81).[26] In an analysis of nearly 1500 cases reported to SECURE-IBD, Ungaro et al demonstrated reduced risk of severe COVID-19 in patients treated with anti-TNF monotherapy versus anti-TNF in combination with thiopurine or thiopurine monotherapy.[5] More data are needed to fully evaluate the safety of other classes of IBD medications, though to date no clear signals have been observed with methotrexate, ustekinumab, vedolizumab, or

tofacitinib.[5,10] 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.[27–29]

**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.[30] 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.[31–33] 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.[34] 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.[17] 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.[35] However there are conflicting data as a recent report on hospitalized COVID-19 patients observed that those with digestive symptoms on admission had lower mortality.[36] The question of whether there is fecal-oral transmission of SARS-CoV2 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 which 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.[37] However, it is still unclear if the humoral response to SARS-CoV-2 will be attenuated in IBD patients. Data from Germany showed a lower seroprevalence of anti-SARS-CoV-2 antibodies in immune-mediated disease patients on cytokine inhibitors compared with general population although this 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.[9,24] 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 COVID-19 patients who developed neuropathology.[38] These will be important questions 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 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. While 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 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 six months, several critical research gaps remain. Observations on impact medications such as aminosalicylates 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.

**Conclusion**

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. While 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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**Tables**

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

| New Knowledge | Clinical Implication / Recommendation |
|---|---|
| IBD patients including those on biological therapy do not appear to be at increased risk of contracting SARS-CoV-2 compared to the general public | Standard precautions (wear a mask, wash your hands, and social distance) are sufficient for most IBD patients |
| Age and co-morbidities 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 to 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 | Most other IBD therapies do not appear to be |

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| small molecules do not appear to be associated an increased risk of severe COVID-19. | associated with substantial COVID-19 safety signals, and hence should be continued during the pandemic.<br><br>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). |