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## Impact of the COVID-19 pandemic on inflammatory bowel disease patients: A review of the current evidence

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### Abstract

Since the initial coronavirus disease 2019 (COVID-19) outbreak in China in December 2019, the infection has now become the biggest medical issue of modern medicine. Two major contributors that amplified the impact of the disease and subsequently increased the burden on health care systems were high mortality among patients with multiple co-morbidities and overcapacity of intensive care units. Within the gastroenterology-related community, particular concern was raised with respect to patients with inflammatory bowel disease (IBD), as those patients are prone to opportunistic infections mainly owing to their immunosuppressive-based therapies. Hence, we sought to summarize current knowledge regarding COVID-19 infection in patients with IBD. Overall, it seems that IBD is not a comorbidity that poses an increased risk for COVID-19 acquisition, except in patients treated with 5-aminosalicylates. Furthermore, outcomes of the infected patients are largely dependent on therapeutic modality by which they are treated, as some worsen the clinical course of COVID-19 infection, whereas others seem to dampen the detrimental effects of COVID-19. Finally, we discussed the present and the future impact of COVID-19 pandemic and concomitantly increased health care burden on IBD-management.

**Key Words:** COVID-19; SARS-CoV-2; Inflammatory bowel disease; Crohn's disease; Ulcerative colitis

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**Core Tip:** Coronavirus disease 2019 (COVID-19) is the biggest medical issue of the 21<sup>st</sup> century so far. Within the gastroenterology-related community, COVID-19 is a concern in patients with inflammatory bowel disease (IBD), as those patients are prone to opportunistic infections owing to their immunosuppressive-based therapies. Hence, in this review, we summarized currently available data and concluded that patients with IBD are not at a higher risk for COVID-19 development, unless treated with 5-aminosalicylates, and that the outcomes of infected patients depend on their respective therapeutic modalities. Finally, we discussed the impact of the COVID-19 pandemic and the concomitantly increased health care burden on IBD-management.

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## INTRODUCTION

With the immense burden that coronavirus disease 2019 (COVID-19) posited on health care systems and the global economy in general, the disease is unequivocally the biggest medical concern of the 21<sup>st</sup> century so far[1]. Globally, by January 2021, there have been over 84 million confirmed cases of COVID-19, with more than 1.8 million deaths reported by the World Health Organization (WHO)[2]. The causative agent of the pandemic, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), belongs to the family of *Coronaviridae*, a group of viruses which have already been associated with epidemics in the early 2000s, *i.e.*, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS)[3,4]. Similar to its related viruses, SARS-CoV-2 primary pathologic manifestations occur in the respiratory system[5,6]. Initial clinical presentation is usually characterized by fever, cough, shortness of breath and specific loss of smell and taste, whereas in a smaller, yet significant amount of patients, the disease progresses to severe lung injury, resulting in the need for intensive care support and concomitant tertiary care equipment[7,8]. This raises two principal issues surrounding COVID-19 and explains why it has caused such a huge global impact. The issue first is high mortality in those patients and the other is the overcapacity of intensive care units (ICU), subsequently burdening health care systems. In the early phases of the pandemic, based on initial observations and knowledge about communicable diseases, particular concern was raised with respect to patients who were at high risk of acquiring severe illness. High risk patients mainly consist of the elderly, obese and patients with pre-existing comorbidities, especially those who are immunocompromised and immunosuppressed[9-11].

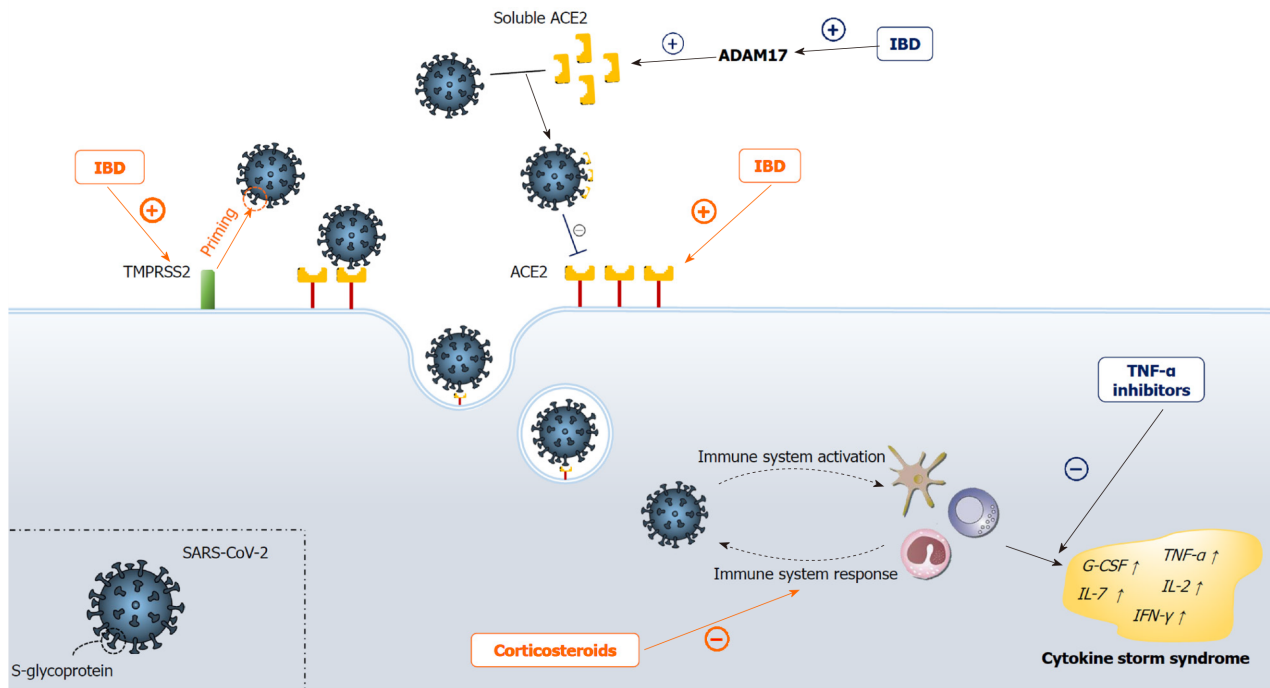
Therefore, within the gastroenterology-related community consisting of both medical staff and patients, inflammatory bowel disease (IBD) emerged as an important concern, mainly owing to the IBD therapeutic approach as opposed to the disease itself. Although IBD pathophysiology includes immune dysregulation, the available data does not support the notion that patients with IBD are at a higher risk of acquiring communicable diseases[12-14]. Nevertheless, the IBD therapeutic approach is mainly based on a palette of immunosuppressants, medications whose role in promoting opportunistic infections has been well-established[15-18]. Hence, major organizations instantly provided recommendations for the management of patients with IBD[19-21]. However, knowledge regarding SARS-CoV-2 evolves on a daily basis, resulting in updates to recommendations in order to reach an optimal approach for patients with IBD. In this review, we sought to address the main concerns regarding the relationship between of IBD and COVID-19. Specifically, we summarized the current data and tried to elucidate whether IBD is associated with a higher risk of COVID-19 infection, whether infected patients have worse outcomes than the general population and finally, we discussed how the COVID-19 pandemic and concomitantly increased health care burden influenced IBD-management.



## THE RISK OF COVID-19 INFECTION AMONG PATIENTS WITH IBD

Early in the pandemic, a major concern among gastroenterologists was about the occurrence of COVID-19 among patients with IBD for several reasons. SARS-CoV-2 binds to targeted cells *via* angiotensin-converting enzyme 2 (ACE2), a protein constitutively expressed by epithelial cells of the blood vessels, lung, kidney and especially the intestines, where ACE2 expression is among the highest in humans[22-24]. Moreover, as shown by proteomic tissue analysis, ACE2 gastrointestinal expression is increased in IBD patients, especially among the Crohn's disease (CD) subgroup, where expression is markedly higher than in ulcerative colitis (UC)[25]. ACE2 has been also implicated in the pathophysiology of IBD, having a dual-role: aggravation of colitis *via* the classical renin/angiotensin II/aldosterone pathway and amelioration of colitis *via* the ACE2/MAS-1 receptor pathway[26-29]. Except for ACE2, SARS-CoV-2 pathogenesis depends on the specific "spike" glycoprotein that mediates fusion of the coronavirus envelope with the host cell membrane[30]. This protein is activated through the trypsin-like protease, the transmembrane protease serine 2 (TMPRSS2), the activity of which has been shown to be up-regulated in IBD[31]. Furthermore, in up to 50% of COVID-19 patients, fecal samples were positive for SARS-CoV-2 virus, with more than one-fifth of the samples testing positive even after subjects tested negative from respiratory samples, implicating the fecal route of SARS-CoV-2 transmission[32,33]. This could be even more important, as patients with IBD are more frequently assessed with invasive gastrointestinal procedures such as esophagogastroduodenoscopy and ileocolonoscopy compared with the non-IBD population, subsequently exposing both the patient and the examiner to a higher risk of infection[34]. Finally, the use of IBD immunosuppressive therapies has been associated with an increased risk of infections[13,14]. All of these findings suggest that patients with IBD should be the "perfect" host for SARS-CoV-2 viral infection (Figure 1). However, results from a recent systematic review that comprised 13 cohort studies and 5 single case reports from all around the world suggest that patients with IBD do not seem to have a higher risk of COVID-19 infection with respect to the general population, not even in IBD patients treated with immunosuppressive drugs [35]. Another systematic review and meta-analysis by Singh *et al*[36] concluded similarly and additionally determined that there was no difference in COVID-19 occurrence between IBD subgroups, *i.e.*, between CD and UC. Regarding the IBD therapeutic strategies, Singh *et al*[36] demonstrated that no use of therapeutics was associated with an increased risk of COVID-19 acquisition aside from the use of 5-aminosalicylic acid (5-ASA). In fact, Taxonera *et al*[37] evaluated the age-standardized incidence of COVID-19 in IBD patients, and suggested that COVID-19 incidence might be overestimated in the IBD population. Unfortunately, larger studies did not conduct a comparable evaluation.

Multiple authors struggled to explain the discrepancy between the expected and evidence-based COVID-19 incidence among populations with IBD[36,38]. Firstly, a major determinant to reduced COVID-19 incidence could be the tighter containment of patients with IBD, since people suffering from chronic diseases, especially patients treated with immunosuppressants, were warned by experts to follow strict social distancing measures, known as shielding, from the beginning of the pandemic. Furthermore, ACE2, the above-noted protein that is up-regulated in IBD, has two distinct functional forms. The full-length form of ACE2 possesses an extracellular domain that binds to the SARS-CoV-2 virus and transmembrane domain, which anchors the first domain to the plasma membrane and aids viral entry into the cell[39]. Conversely, the soluble form of ACE2 lacks a transmembrane domain and it is therefore a sort of a decoy receptor for SARS-CoV-2 virus in the blood[40,41]. Notably, the latter form is up-regulated in IBD patients, as a consequence of ACE2 membrane cleavage into the soluble form, in a process regulated by the tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) convertase ADAM17 (a disintegrin and metalloproteinase 17), the protease is up-regulated in patients with active IBD[42,43]. Furthermore, although SARS-CoV-2 is detectable in fecal samples and active viral replication in the enterocytes of the small intestine has been reported[33,44], to this day there is no firm evidence to imply that increased SARS-CoV-2 replication in intestines is proportional to intestinal ACE2 expression. This is substantiated by the fact that SARS coronavirus, a SARS-CoV-2 close relative, spreads through the upper respiratory tract (URT) very effectively despite only modest ACE2 expression in the URT[24]. Overall, it seems that SARS-CoV-2 also needs the presence of a co-receptor for host cell infection, similarly to HIV infection[45]. However, the hypothesized co-receptor that synergistically with ACE2 leads to SARS-CoV-2 infection has yet to be determined in future studies. The reasons for the increased risk of COVID-19 acquisition with 5-ASA are still unclear



**Figure 1 Pathogenetic pathway of intestinal severe acute respiratory syndrome coronavirus 2 infection with proposed inflammatory bowel disease effects.** The blue lines represent inflammatory bowel disease (IBD)/IBD approach-mediated reduction in either coronavirus disease 2019 (COVID-19) acquisition or poor outcomes of it, whereas the red lines represent IBD/IBD approach-mediated increase in risk for COVID-19 acquisition or poor outcomes. IBD: Inflammatory bowel disease; ADAM17: A disintegrin and metalloproteinase 17; TNF- $\alpha$ : Tumor necrosis factor- $\alpha$ ; ACE2: Angiotensin-converting enzyme 2; TMPRSS2: Transmembrane protease serine 2; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; IL: Interleukin; G-CSF: Granulocyte-colony stimulating factor; IFN- $\gamma$ : Interferon- $\gamma$ .

but, as discussed by Singh *et al*[36], the observed increase could be related to the fact that 5-ASA use may be a proxy for underlying UC in these circumstances. Namely, patients with UC have higher ACE2 levels (although, as we discussed, this is not a reliable indicator) and a population with UC tends to be older than a CD population [46], hence they are more prone to get tested, as Singh *et al*[36] argue. Despite the sensitivity of the fecal reverse transcription polymerase chain reaction (RT-PCR) test for the diagnosis of COVID-19, its diagnostic power still needs to be elucidated. D'Amico *et al*[47] hypothesized that fecal RT-PCR testing may be useful in IBD patients to distinguish disease re-exacerbation from SARS-CoV-2 superinfection, allowing better patient management and targeted therapy.

## CLINICAL COURSE OF COVID-19 INFECTION IN PATIENTS WITH IBD

Since the detrimental effects of immunosuppressive agents on the host-cell defense against pathogens have been well-established, particular concern was raised with respect to the clinical course of COVID-19 in patients on various immunosuppressive therapies and ubiquitous therapeutic strategies for patients with IBD[15-17,48]. Furthermore, active IBD itself might worsen COVID-19 outcomes, as those patients are markedly frailer and more prone to adverse outcomes by virtually any infection[49, 50]. Finally, non-IBD patients with COVID-19 have high fecal calprotectin even after diarrhea resolves and COVID-19 patients with ongoing diarrhea have even higher levels in comparison with COVID-19 patients without diarrhea[51,52], suggesting that the presence of SARS-CoV-2 in the gastrointestinal tract is associated with greater intestinal inflammation. This indicates that COVID-19 could exacerbate inflammation and, subsequently, symptoms in IBD patients. However, it is very challenging to assign a symptom to the underlying disease, its exacerbation, or the concomitant infection, making these characteristics difficult to interpret. Of note, in the aforementioned studies[51,52], patients with diarrhea exhibited higher serum interleukin 6 concentrations, raising the possibility of more severe systemic inflammation in this group of patients[53].



Fortunately, an abundance of clinical studies demonstrated that most of the hypothesized adverse outcomes were not observed in IBD patients that acquired COVID-19. Nonetheless, in some cases this comorbidity seems to even dampen the deleterious effects of COVID-19. Considering the differences in the initial clinical presentation, although in concordance with the non-IBD population, fever and cough were the most common clinical findings. Further, COVID-19 positive IBD patients presented with diarrhea significantly more often than the general population[54-57]. This disparity could be associated with the influence of the underlying disease on the number of evacuations, justifying the greater percentage of diarrhea in IBD patients than in the general population. In contrast, the observed difference could also be due to the aforementioned exacerbation of IBD as a result of COVID-19 infection. The risk of severe COVID-19 outcomes, *i.e.*, the need for hospitalization, admission to the ICU, mechanical ventilation or death, were not higher among IBD patients in comparison to the general population, as demonstrated in multiple systematic reviews and meta-analyses[35,36,47]. These results are also in accordance with the latest data from the Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD), an international web-based database where physicians are encouraged to report all cases of COVID-19 in patients with IBD[58]. A total of 4038 IBD patients with confirmed COVID-19 were reported in the SECURE-IBD database as of January 6, 2021 with 19% of patients in need of hospitalization, 3% admitted to the ICU, and 3% in need of mechanical ventilation, where the case fatality rate was 2%. Of note, in a study by Lukin *et al*[59], the authors included a control group consisting of non-IBD patients with COVID-19. Rather interestingly, death and ICU admission were numerically lower in the IBD group than in the control group. Although these results should be taken with caution, it is possible that certain IBD medications led to the blunting of the cytokine release syndrome and subsequently to more favorable outcomes.

The therapeutic choice emerged as a major determinant for COVID-19 prognosis in patients with IBD. Accumulating data implies that the use of systemic corticosteroids is associated with the highest risk of severe COVID-19 outcomes[35,36,47,58]. It is well known that corticosteroids affect the immune system *via* multiple mechanisms, including the inhibition of adhesion molecules, decreasing the expression of inflammatory cytokines and inducing apoptosis of activated lymphocytes. Moreover, in studies that tested the use of corticosteroids on MERS and SARS patients, authors have demonstrated a delayed viral clearance in patients receiving high-dose corticosteroids [60]. However, the effects of corticosteroid use on COVID-19 adverse outcomes in IBD is not as clear as it may seem. In a report from the large RECOVERY trial, in which the effects of dexamethasone on hospitalized COVID-19 patients were assessed, authors concluded that the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at the time of randomization but not among those receiving no respiratory support[61]. Furthermore, in a recently published meta-analysis by van Paassen *et al*[62], which included the largest number of studies and COVID-19 patients, the authors demonstrated the beneficial effects of corticosteroids use on short-term mortality and a reduction in the need for mechanical ventilation. Notably, the authors also found a signal of delayed viral clearance, but data in the studies were too uncertain to reach any firm conclusions. Three other meta-analyses that were conducted on this topic have rather conflicting reports. The WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group[63] concluded similarly to van Paassen *et al*[62], reporting that the administration of systemic corticosteroids was associated with lower 28-day all-cause mortality in comparison to placebo or usual care. Tlayjeh *et al*[64] found no difference in mortality or the necessity for mechanical ventilation, yet similarly to van Paassen *et al*[62], they observed a prolonged viral clearance time. Sarkar *et al*[65] demonstrated that in patients with COVID-19, corticosteroids may be associated with a twofold increase in mortality, yet their analysis was based on low-quality evidence with high variability. Considering the beneficial effects of corticosteroid use in COVID-19 patients, doubt was raised with respect to poor outcomes of their use in COVID-19 patients with concomitant IBD. It is possible that the corticosteroid use in these circumstances is merely an indicator from the subset of patients with active IBD who are predisposed to adverse outcomes. In fact, in a retrospective cohort study, Singh *et al*[66] reported that IBD patients who received corticosteroids up to 3 months before the diagnosis of COVID-19 had a higher risk of severe COVID-19 in comparison to patients who did not receive corticosteroids. Although the authors conducted an unadjusted analysis, because corticosteroid use in IBD is associated to worsening of the disease, these results could imply that in this setting corticosteroids were not the cause, but an indicator of higher risk for a severe COVID-19 clinical course[67].

Apart from corticosteroid use, as shown by multiple studies, the use of 5-ASA has been also associated with more severe COVID-19 outcomes[35,36,47,58,68]. This finding persisted even after controlling for confounding factors such as age, comorbidities, IBD disease characteristics and corticosteroid use. Since mechanisms by which 5-ASA exerts its anti-inflammatory effect are rather diverse and include peroxisome proliferator-activated receptor- $\gamma$  up-regulation, cyclooxygenase 2/prostaglandin E2 down-regulation, reactive oxygen species scavenging and many more[69], we could only hypothesize which of these pathways is responsible for more severe COVID-19 outcomes. Primarily, large, well-designed studies should be conducted to confirm that an increased risk really exists in the first place.

Immunomodulators, a group of medications used in IBD treatment that includes azathioprine, 6-mercaptopurine, and methotrexate have been known to inhibit the immune response to viral infections by multiple mechanisms[70,71]. However, the data regarding the role of immunomodulators in COVID-19 is quite reassuring, as conducted studies do not seem to demonstrate any difference in severe outcomes in comparison to the general population[35,36,47,58,68]. Since the effects of immunomodulators and corticosteroids on the suppression of the immune system are in part overlapping[72,73], we hypothesize that this provides further evidence toward the notion that the use of corticosteroids itself does not result in a more severe form of COVID-19. In fact, different results between the use of corticosteroids and immunomodulators from the above-noted studies could be due to the different clinical profiles of patients between the two groups, with corticosteroid use implying poor IBD control.

The most ambiguous results that emerged from observational studies is in relation to the use of biological agents, an immunosuppressive medication group used in the management of IBD which includes infliximab, adalimumab, golimumab, certolizumab pegol, ustekinumab and vedolizumab[74]. Biological agents, particularly TNF- $\alpha$  inhibitors, have been known to mitigate the host immune system response against infectious organisms, especially intracellular pathogens, such as mycobacterial, fungal and viral infections[75,76]. However, aside from the systematic review by Macaluso and Orlando[35] which showed no difference as opposed to the general population, available data suggests that patients treated with biological agents are significantly less prone to develop severe forms of COVID-19, distinctly in terms of mortality[36,58,68]. Accumulating evidence implies that COVID-19 severity is associated with a cytokine storm syndrome, an immune-mediated process characterized by hyperactivation of T cells and massive production of TNF- $\alpha$ , interleukin 2, interleukin 7, granulocyte-colony stimulating factor, interferon- $\gamma$  (IFN- $\gamma$ ), IFN- $\gamma$ -inducible protein 10, monocyte chemoattractant protein 1, and macrophage inflammatory protein 1- $\alpha$  [77]. Based on these findings, it is legitimate to hypothesize that the use of biological drugs which selectively inhibit specific cytokines or small molecules that simultaneously block multiple cellular pathways may play a role in the treatment of these patients. Interestingly, in two case reports, the remission of COVID-19 symptoms in IBD patients was achieved after treatment with biological agents[78,79]. This evidence is certainly insufficient to recommend the use of these drugs in COVID-19 management, yet they are reassuring for IBD patients, and shed light on biological agents as feasible therapeutic agents in COVID-19 treatment. In fact, there are several ongoing clinical trials that assess the efficacy and safety of these drugs in this setting (NCT-04344249 and NCT04425538).

Between the IBD subgroups, in all of the aforementioned reports[35,36,47,58,68], patients with UC had markedly worse outcomes than patients with CD. Singh *et al*[36] attribute this risk incrementation to the fact that patients with UC are more likely to be older and undergo different therapeutic modalities between the two groups[36,80]. However, since Singh *et al*[36] did not provide the age-adjusted comparison of outcomes, whether the poor outcomes of UC in contrast to CD are related to old age remains unclear. Regarding the difference in therapeutic modalities, patients with UC are more likely to be treated with 5-ASA, a treatment shown to pose a risk for more severe outcomes, whereas patients with CD are more likely to be treated with biological agents, treatment that seem to have a protective role in COVID-19 infection [81,82]. In addition, it is unclear if the observed disparity is due to the pathobiological differences between the two types of IBD, including the variability in expression of ACE2 and TMPRSS2.

## THE IMPACT OF THE COVID-19 PANDEMIC ON IBD MANAGEMENT: PRESENT AND FUTURE PERSPECTIVES

### **Current guidelines for IBD treatment with respect to COVID-19**

Two major organizations that cover the issues regarding IBD, the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) and European Crohn's and Colitis Organization (ECCO) have partnered and provided a set of guidelines regarding the management of IBD in relation to COVID-19[83]. However, there are two important notions to accentuate regarding the present guidelines. Firstly, as currently there is no adequate evidence-based data, the recommendations are based on a consensus between a group of international IBD and infectious disease experts. Secondly, since the speed of publishing is slower than the amount of emerging data, organizations urged physicians to continue to check the IOIBD or the ECCO websites for the most up-to-date information.

The most important question that was raised in the guidelines concerns the IBD immunosuppressive therapies, *i.e.*, whether the infected patients should discontinue these therapies and if should, for how long. The current consensus is that recommencing these therapies should be influenced by the clinical severity of both IBD and COVID-19. Conceptually speaking, the greater the severity of IBD and the lesser the severity of COVID-19, the discontinuation of therapy should be shorter and vice versa. Experts suggest that for most patients, a symptom-based strategy is suitable [84]. According to this strategy, COVID-19 resolution is evaluated according to symptom onset ( $\geq 10$  d) and clinical improvement. Current expert recommendations regarding immunosuppressive therapies are summarized in Table 1. Other aspects regarding recommendations, such as care for patients with IBD requiring hospitalization, priority for endoscopy, guidance for the infusion centers, management of pregnant IBD patients and a very practical set of ten "Do's" and "Don'ts" for IBD management during the COVID-19 outbreak were further discussed in the aforementioned IOIBD/ECCO guidelines[85-89]. Following the approval of several COVID-19 vaccines, the IOIBD experts have recently issued a statement regarding vaccination [90]. The expert group advised vaccinating all patients with IBD as soon as they are able to receive a vaccine, regardless of their immune-modifying therapies.

### **Impact of COVID-19 and lockdown on the management of IBD patients**

There is a scarcity of data regarding the post-lockdown phase in terms of health-care procedures[91,92], let alone in the IBD population[93-96]. Early into the pandemic, hospitals were urged to restructure their daily activities to meet the needs of health care practitioners and to provide the facilities to treat COVID-19 patients. The restructuring of the health care system did not circumvent IBD management. Consequently, the risks of secondary harm emerged, as the latter resulted in reduced access to diagnostic endoscopy, lack of face-to-face clinics, difficulties in continuing day-case infusions, issues in performing routine blood and/or stool monitoring as well as patients' fears which may have reduced their attendance in hospitals[93]. Particular problems emerged in the pediatric population, since a delay in diagnosis and delayed treatment has the potential to result in serious repercussions, such as an impact on children's growth[97,98]. Recent Italian and Spanish surveys both demonstrated that the management of urgent activities and administration of biological therapies in both the lockdown and post-lockdown periods substantially maintained the pre-pandemic standards of care[93,94]. However, the surveys also highlighted that the reduction in number of visits, endoscopies and gastrointestinal ultrasounds observed in the lockdown but also in the post-lockdown phase could result in worse long-term outcomes[93,94]. A study in the pediatric population had similar conclusions regarding the quality of care[93]. This study accentuated concerns with respect to newly diagnosed IBD patients as this subgroup was diagnosed without a histological confirmation of the disease, which is a controversial exception that had to be adopted given the present special circumstances[93]. These patients were diagnosed *via* a combination of blood tests, radiological imaging, fecal calprotectin and exclusion of infectious causes, followed by multidisciplinary discussion. The commencement of the systemic immunosuppression in children without endoscopic or histological diagnosis was an additional concern, yet physicians could adapt in the beginning exclusive enteral nutrition as a first-line therapy as an induction strategy with multiple benefits [99]. Although a delay in exposing patients to systemic immunosuppression for 4-8 weeks is beneficial, after this time patients enter a period where immunomodulatory and biological therapy should commence, while simultaneously, the ability to conduct a full disease assessment beforehand may continue to be limited. Overall, experts

**Table 1 Latest International Organization for the Study of Inflammatory Bowel Disease/European Crohn's and Colitis Organization recommendations for coronavirus disease 2019 infected inflammatory bowel disease-patients[101]**

COVID-19 symptomatology	SARS-CoV-2 status	Recommendation
Asymptomatic	Non-tested	Do not withhold therapy (reduce corticosteroid use if possible)
Asymptomatic	Positive	Withhold therapy for 10 days <sup>1</sup>
Symptomatic	Positive	Withhold therapy until all of the following is fulfilled <sup>1</sup> : (1) At least 10 days has passed since symptoms onset; (2) Improvement in respiratory symptoms; and (3) Days without fever (without the use of antipyretics)

<sup>1</sup>If clinical presentations imply that therapy should not be postponed, despite meeting the clinical criteria stated above, guidelines recommend moving ahead with the scheduled treatment. COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

agree that the implementation of a telemedicine approach has played an important role in maintaining the standards of quality of care in IBD management during the pandemic[93,94,100].

### **Future perspectives of IBD management**

Even though COVID-19 had a range of detrimental effects on health care systems globally, it also opened a space for improvements in clinical practice, which could be used long after the COVID-19 pandemic resolves. One of those is the use of telemedicine, *i.e.*, the implementation of virtual technologies in routine clinical practice. An expansion in technological solutions and loosening restrictions on how telemedicine can be deployed and reimbursed have opened the way for telemedicine to become an integral part of clinical practice both now and in the future. In the IBD population, virtual appointments, multidisciplinary discussions, and improvement of networks by remote collaboration all provide the opportunity for better care within specific situations, with the simultaneous reduction of the transmission of infectious diseases. Today it is COVID-19, but in the future, it could be some other virus, especially as we are now more than ever aware of our susceptibility to a viral pandemic. IOIBD/ECCO issued a summary of the best strategies for IBD management *via* telemedicine, carefully covering every aspect of the patient-physician relationship [101]. Another very important aspect of telemedicine is its inexpensiveness. As a global economic crisis is imminent, this will actually become the critical reason for widespread implementation of telemedicine. Regarding the disease itself, although for now a lot of data substantiates the fact that COVID-19 does not influence the short-term prognosis for IBD patients, the long-term effects are quite unknown. We believe that poorer long-term outcomes will be mainly due to delayed diagnostic (especially endoscopy) therapeutic procedures and not COVID-19 itself. However, Gower-Rousseau *et al*[102] argue that most of the researchers too hastily concluded that the COVID-19 pandemic is relatively safe for IBD patients. They highlighted that the recently published, underpowered studies cannot provide answers for patients with IBD, or other infrequent diseases for that matter. Further, Gower-Rousseau *et al.* asserted that low-quality studies might even prompt misguided and harmful treatment decisions. On the contrary, they argue that well-grounded answers to these questions require complex epidemiologic risk and benefit analyses with an *a priori* sample size calculation and a removal of unwanted biases.

## **CONCLUSION**

The initial fear of COVID-19 infection among patients in the IBD community that was based on available knowledge, now seems unnecessary. Accumulating data suggests that IBD is not a comorbidity that poses an increased risk for COVID-19 acquisition, except in patients treated with 5-ASA. Furthermore, although the outcomes of infected patients are largely dependent on the therapeutic modality by which they are treated, overall, IBD patients seem to have COVID-19 outcomes similar to the general population. This is in contrast to those on corticosteroids, as they currently seem to have a less favorable prognosis. Biological agents even dampen the detrimental effects of COVID-19 by inhibiting cytokine storm syndrome, according to the available data. However, preliminary data must be interpreted with caution, as the long-term effects



of both COVID-19 and IBD management during the COVID-19 outbreak are quite unknown. Finally, the COVID-19 outbreak could also change the future of IBD management, and management of the diseases in general, as telemedicine could dethrone face-to-face examinations in the following years.

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