MINIREVIEWS

Impact of COVID-19 on inflammatory bowel disease practice and perspectives for the future

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Abstract

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); since its first description in December 2019, it has rapidly spread to a global pandemic. Specific concerns have been raised concerning patients with inflammatory bowel diseases (IBD), which are chronic autoimmune inflammatory disorders of the gut that frequently require immunosuppressive and biological therapies to control their activity. Accumulating evidence has so far demonstrated that patients with IBD are not at increased risk of contracting severe acute respiratory syndrome coronavirus 2 infection. As for the general population, the identified risk factors for severe COVID-19 course among IBD patients have been established to be advanced age and the presence of comorbidities. Treatment with high-dose corticosteroids has also been associated with an increased risk of death in IBD patients with COVID-19. Information on COVID-19 is constantly evolving, with data growing at a rapid pace. This will guarantee better knowledge and stronger evidence to help physicians in the choice of the best therapeutic approach for each patient, concurrently controlling for the risk of IBD disease under treatment and the risk of COVID-19 adverse outcomes and balancing the two. Moreover, the impact of the enormous number of severe respiratory patients on healthcare systems and facilities has led to an unprecedented redeployment of healthcare resources, significantly impacting the care of patients with chronic diseases. In

this newly changed environment, the primary aim is to avoid harm whilst still providing adequate management. Telemedicine has been applied and is strongly encouraged for patients without the necessity of infusion therapy and whose conditions are stable. The severe acute respiratory syndrome coronavirus 2 pandemic has already revolutionized the management of patients with chronic immune-mediated diseases such as IBD. Direct and indirect effects of the COVID-19 pandemic will be present for some time. This is the reason why continuous research, rapid solutions and constantly updated guidelines are of utmost importance. The aim of the present review is, therefore, to point out what has been learned so far as well as to pinpoint the unanswered questions and perspectives for the future.

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

Core Tip: The Severe acute respiratory syndrome coronavirus 2 pandemic has abruptly impacted the management of patients with chronic immune-mediated diseases such as inflammatory bowel diseases. In a setting of general uncertainty, gastroenterologists have faced the need to rapidly reorganize facilities and redefine priorities in inflammatory bowel disease clinical management. With an enormous research effort, accumulating evidence is deepening our understanding of the multifaceted interaction of inflammatory bowel disease care and coronavirus disease 2019. Direct and indirect effects of the pandemic will be present for some time; it is, therefore, necessary to keep recommendations constantly updated.

INTRODUCTION

Until the beginning of this century, coronaviruses were known to cause common colds in humans. However, in 2002 and 2013, respectively, the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome-CoV emerged. Both viruses caused severe respiratory syndromes and were highly pathogenic for humans, with more than 8000 people infected and 919 death caused by SARS-CoV and 2494 cases and 858 death by Middle East Respiratory Syndrome-CoV [1,2]. The third coronavirus epidemic was first reported in December 2019 in Wuhan, China. A new coronavirus, firstly named 2019-nCov and then severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was isolated[3]. The World Health Organization then proceeded to name the disease produced by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). COVID-19 has rapidly spread to become a global pandemic, affecting populations in nearly all areas of the world, with high morbidity and mortality rates especially in elderly patients and those affected by chronic illnesses[4]. So far, COVID-19 has infected more than one hundred million people worldwide, causing more than two million deaths[5].

Inflammatory bowel diseases (IBD) encompass ulcerative colitis and Crohn's disease. They are chronic, relapsing, autoimmune inflammatory disorders of the gut, frequently requiring immunosuppressive and biological therapies to control disease activity. Patients with IBD, treated with immune suppressants, are at an increased risk of opportunistic and serious infections[6], including viral infection[7,8]. Hence, particular concerns have been raised for patients suffering from IBD throughout the SARS-CoV-2 pandemic[8], leading the medical community to rapidly generate research in this field and international organizations to release timely recommendations under constant and frequent review.

The gastroenterological community has faced an unprecedented challenge, requiring not only to adapt the therapeutic management of IBD patients and redefine medical priorities but also to reorganize health care facilities.

COVID-19 IN IBD PATIENTS

Accumulating evidence has demonstrated that angiotensin-converting enzyme 2 (ACE2) can mediate SARS-CoV-2 entry into cells[9]. Briefly, the spike protein of SARS-CoV-2 binds to the extracellular portion of ACE2, resulting in the internalization of the complex receptor-virus. This internalization process is favored by the presence of another protein, *i.e.* TMPRSS2, a protease that cleaves the intracellular portion of ACE2. Conversely, another transmembrane protein, called ADAM17, can cleave ACE2 generating its soluble form that could in turn act as a decoy receptor for the virus[10].

ACE2 and TMPRSS2 are physiologically expressed by different cells within the human body, including in the gastrointestinal tract, with peaking concentrations in the terminal ileum and colon. Various single nucleotide polymorphisms have been detected in both genes, but the data so far obtained studying different populations are controversial, not demonstrating a clear genetic predisposition to SARS-CoV-2 infection[11,12]. Nonetheless, in IBD-affected patients, levels of ACE2 are higher than in the general population[13], being the latter independently and differently regulated in the large and small intestines upon inflammation[14,15]. This feature could represent a significantly increased risk of contracting SARS-CoV-2 for IBD patients, even though inflammation also triggers the expression of ADAM17[16], which could have an opposite effect.

Another protein with an increased expression in both IBD and COVID-19 is interleukin 17 (IL-17)[17,18]. It is a cytokine produced and released by T helper 17 lymphocytes, displaying complex and variegate immune functions, and involved in the immune pathogenesis of IBD. In acute respiratory distress syndrome induced both by SARS-CoV-2 infection and other betacoronaviruses, IL-17 levels have been reported to be significantly elevated, and preliminary evidence supports its contribution to immunopathology[19]. Furthermore, it seems that synergism between IL-17 and other cytokines, *i.e.* IL-6, can promote viral replication[20]. The exact role of IL-17 expression and the risk of SARS-CoV-2 infection or COVID-19 disease course is still to be determined; however, agents endowed with anti-IL-17 function, among which probiotic strains of *Bifidobacteria*, have already been proposed as an adjunct therapeutic approach[21,22].

Based on these findings, it was initially hypothesized that patients with IBD could have an increased risk to become infected with SARS-CoV-2. However, the evidence collected so far suggests that the cumulative incidence of the infection [assessed through nasopharyngeal swab (NPS) tests] in IBD patients is similar or even lower to that observed in the general background population during the same pandemic period [23-26]. In a recent Danish nationwide population-based study on IBD-affected patients, the latter displayed a significantly lower prevalence than the general population (2.55% *vs* 3.7%; *P* < 0.01). Whether this occurred secondarily to a more stringent self-isolation and shielding of IBD patients as compared to healthy subjects is yet to be understood.

Furthermore, it seems that immunosuppressive treatments do not increase the risk of contracting SARS-CoV-2[27,28]. This aspect was also confirmed by seroprevalence studies, which showed similar seroprevalence in IBD patients treated with biological agents to the one determined in the general population from the same geographical region[29,30].

Regarding the clinical presentation of COVID-19 in IBD patients, the most frequent symptoms were fever and cough[31]. Yet, diarrhea was more commonly reported in IBD patients with SARS-CoV-2 compared to non-IBD patients, with a prevalence ranging from 8% to 49% in different studies[25,31-36] and a pooled estimate of 20%, which was twice as high as the cumulative prevalence of diarrhea in the general population of COVID-19 patients[31]. This could be attributed to the inflammatory disease itself, but it could also occur as a consequence of exacerbation of intestinal inflammation through a direct viral action on the intestinal epithelium, as suggested by the higher concentration of fecal calprotectin in infected patients with diarrhea[33]. Indeed, a recent cohort study reported a higher prevalence of diarrhea among IBD patients with COVID-19 as compared to non-infected patients, independently from baseline disease activity at multiple regression analyses[32].

Moreover, gastrointestinal (GI) symptoms, including diarrhea, have been described as the sole manifestations of COVID-19 in about 10% of patients[25,37], which is of particular relevance in patients with IBD since the infection could be misinterpreted as disease reactivation. It is therefore of paramount importance to raise awareness among clinicians on these specific clinical features of COVID-19 in patients with IBD and on the need for testing patients accordingly.

GI manifestations may actually help to spot SARS-CoV-2 infection in patients with negative NPS tests, through the assessment of stool samples. PCR testing for SARS-CoV-2 infection with NPS is the currently recommended diagnostic approach, yet false-negative results have occurred[38-43]. Explanations for this have included, besides poor specimen collection, absent or intermittent viral shedding from the upper airways and viral recovery in the oropharyngeal mucosa, whilst the virus may still be present in other tissues. Solid data demonstrated that fecal viral shedding may persist for up to nearly 5 wk following the negativity of NPS[44-48], being more prevalent in patients with GI symptoms in comparison to those with respiratory symptoms alone (73.3% *vs* 14.3%; P = 0.033)[49]. This may indicate that the virus can continue to replicate in the gut after being cleared from the respiratory tract, thus implying the possibility of fecal-oral transmission[45]. Although no clear evidence on the diagnostic performances of PCR testing on stools is available to date, patients with negative NPS and PCR positive stool samples were reported[46,50], and research in this field is rapidly evolving. The current knowledge allows us to speculate that testing for fecal SARS-CoV-2 RNA may be helpful as a complementary tool to the NPS, at least in patients presenting GI alterations and particularly in patients with IBD to distinguish infection from disease reactivation.

On the other hand, it is currently unknown if SARS-CoV-2 infection can interfere with IBD natural history, possibly inducing a disease reactivation. Very preliminary data from a Danish population study demonstrated no risk of relapse in a very small number of patients at 35 d of follow-up[51]; ongoing studies will help to clarify this point.

It has been very recently reported that patients with COVID-19 exhibit significant alterations in fecal microbiota composition, including an increase in opportunistic pathogens and the depletion of commensals. These alterations correlated both with fecal levels of SARS-CoV-2 and COVID-19 severity, irrespective of the medications received, and persisted up to 30 d after disease resolution[52,53]. Whether this persistent dysbiosis could have a role in the development of de novo IBD or in the progression of a pre-existing disease remains to be investigated.

When compared to non-IBD patients, the clinical course and severity of COVID-19 might be somewhat more severe, although definitive evidence is lacking. Data from the SECURE-IBD registry demonstrated, at the earlier stages of the pandemic, a trend toward increased age and sex-standardized mortality ratios compared to the general population in China, the United States and Italy, indicating up to 50% higher mortality in patients with IBD[54]. Though the data were originally not statistically significant, a more recent analysis, based on a total of 3493 reported cases, confirmed earlier findings and reached statistical significance[55]. However, this finding must be interpreted with caution due to the voluntary nature of reporting in the registry, which is therefore affected by several biases. Indeed, a recent population-based retrospective cohort study with propensity score matching for demographic and comorbidities found no difference in hospitalization and mortality for COVID-19 in IBD patients[36].

As in the case of the general population, identified risk factors for severe SARS-CoV-2 infection among IBD patients are advanced age and the presence of comorbidities[26,36,51,54,56].

When considering the risk connected with IBD medications at the time of viral infection, in the SECURE-IBD registry data analysis, systemic corticosteroid administration was positively associated with an increased risk of death (adjusted odds ratio (OR) = 11.62, 95% confidence interval (CI): 2.1-64.7); conversely, the use of anti-tumor necrosis factor (TNF) was associated with a lower rate of hospitalization or death (adjusted OR = 0.60, 95%CI: 0.38-0.96)[57]. A recently published retrospective multicenter study has also confirmed the negative impact of corticosteroids in IBD patients with COVID-19[36]. Similar data emerged from an analysis of 600 patients with rheumatic diseases in which glucocorticoid exposure correlated with a higher odds of hospitalization (OR = 2.05, 95%CI: 1.06-3.96), while the opposite occurred for anti-TNF agents (OR = 0.40, 95%CI: 0.19-0.81)[58].

This might be explained by a selective action of targeted therapies in contrasting some key mediators of the cytokine storm, a major factor in the occurrence of acute respiratory distress syndrome[59], which could counterpart the hypothetic risk of reduced viral clearance.

Conversely, the results from the RECOVERY Trial, the largest randomized controlled trial examining corticosteroids in the treatment of COVID-19 to date, demonstrated that treatment with dexamethasone in dose equivalents similar to those used for IBD treatment are indeed protective against adverse outcomes and mortality for patients hospitalized with COVID-19[60]. These data were confirmed by a recent meta-analysis considering a large number of SARS-CoV-2 infected patients included in seven clinical trials[61].

A possible explanation for such contrasting results may be related to the differential timing of steroid treatment, perhaps leading to diverse clinical scenarios. Indeed, we can speculate that the use of systemic steroids before contraction of a viral infection hampers the immune-system response, thus fostering viral replication. Conversely, treatment at later stages may quench the cytokine storm responsible for the onset of acute respiratory distress syndrome, positively impacting overall survival.

In the most recent analysis of the SECURE-IBD registry collecting 1439 cases and specifically analyzing the effect of IBD medications on COVID-19 course, thiopurine therapy, both alone and in combination with anti-TNF, has emerged as an independent risk factor for severe COVID-19 (aOR of 4.08 and 4.01, respectively) when compared with TNFα antagonist monotherapy[62]. Thiopurines have indeed previously been associated with increased risk of viral infection compared to anti-TNF agents [6]. However, data from the SECURE-IBD, though extremely helpful, need to be interpreted with caution since they are subject to reporting bias, and considering the high proportion of patients treated with anti-TNF agents, they might have overestimated the effect of thiopurines. Recently collected data from a nationwide population-based study of IBD patients with COVID-19, for instance, revealed no impact of immune modulators or biological therapies on the risk of hospitalization or death[51].

For what concerns anti-interleukin-12/23 and anti-integrins, limited data are available on their impact on the course of COVID-19, though general safety data suggests that they are not associated with a significant increased infectious risk. To date, the SECURE-IBD analysis demonstrated no differences compared to anti-TNF drugs[54].

Some concerns have been raised for tofacitinib since it may blunt the innate immune response to viral infection, including inhibition of interferon-gamma activity. Tofacitinib has so far been associated, both in clinical trials and in post-marketing monitoring, with an increased risk of infection, particularly of herpes zoster reactivation [63]. However preliminary data from the SECURE-IBD registry, though focused on a very small number of patients, showed no significant differences between tofacitinib-treated patients and other IBD patients in the occurrence of hospitalization, intensive care unit admission and severe COVID-19[64]. Moreover, recent preclinical evidence is emerging that tofacitinib treatment might in fact reduce ACE2 upregulation and ACE2-mediated intestinal viral uptake[65], and randomized clinical trials for the treatment of COVID-19 pneumonia are ongoing.

Last but not least, it should be kept in mind that the treatment-related risk of infection should be balanced against the disease activity related risk of infection. It has been previously demonstrated that the risk for systemic viral infections (cytomegalovirus and Epstein-Barr virus primary infections and reactivations) in IBD is significantly higher in patients with a clinically active disease[7]. Moreover, active disease is a known risk factor for malnutrition and may lead to hospitalization, thus again raising the infectious risk.

As for SARS-CoV-2 infection, preliminary data coming from two Italian studies identified a correlation between IBD activity and COVID-19 negative outcome[32,56], including a higher risk for pneumonia (OR = 10.25, P = 0.003) and death (OR = 8.45, P = 0.02)[56].

CONCEPT OF FRAILTY FOR IBD PATIENTS

Intensive efforts have been made by the scientific community to identify frail patients requiring more stringent social distancing and further precautions taken to limit the risk for SARS-CoV-2 infection. Since the presence of comorbidities correlates with a higher risk of severe COVID-19, most patients with chronic disorders are considered frail. Specifically regarding IBD patients, while initial data seem reassuring, they should also be regarded as frail. This has been recently supported by the data emerging from the SECURE-IBD registry, pointing towards increased sex-standardized mortality ratios in patients with IBD infected with COVID-19[55].

With these regards, early in the pandemic, the British Society of Gastroenterology categorized IBD patients into three risk groups, each associated with different necessities of social isolation (Table 1)[66]. This risk profiling remains substantially valid, also bearing in mind the newly accumulated evidence. Yet, since the pandemic diffusion varies greatly between countries and constantly fluctuates in severity across time, it is necessary to adapt preventive measures applied to each category accordingly. This would allow tailored preventive measures, according to individual fragility, risk of viral exposure and subsequent negative outcomes upon infection, avoiding on the other hand unnecessary limitations that can negatively impact patient quality of life.

GENERAL RECOMMENDATIONS AND CLINIC REORGANIZATION

Strict social distancing, regular use of face masks and meticulous sanitization of hands and frequently used surfaces, such as phones, tablets, desks, *etc*., with alcohol-based solutions remain the most important recommendations for the general population and should therefore apply to IBD patients as well.

Patients with IBD, still require regular medical follow-up and to some degree hospital access. In this setting, among the adopted general measures to reduce the risk of viral exposure, there has been the postponing of non-urgent outpatient visits and elective endoscopic procedures. As for the latter, the reduced distance between patients and hospital workers, and the air insufflation required by the procedure may increase the risk of SARS-CoV-2 transmission. Specific recommendations on endoscopy in IBD during the COVID-19 pandemic have been released[67].

The use of noninvasive inflammatory markers, such as C-reactive protein and fecal calprotectin for monitoring disease activity, should be encouraged during the pandemic[68]. Fecal calprotectin has been proven to correlate with endoscopic disease extension, mucosal healing and histological activity[69,70]. Home-test measurements of fecal calprotectin could be a valuable alternative, as evidence has demonstrated a good correlation with laboratory determinations[71].

Virtual clinics or online consultants are encouraged for patients without the necessity of infusion therapy and with stable disease, maintaining as much as possible the same timing as the originally scheduled visit. Several accessible and widely available digital technologies have been explored with exciting results[72]. Whenever hospital visits cannot be avoided, symptoms and fever checks at hospital entry, the social distancing of at least 2 m, the use of face masks and strict handwashing policies are highly recommended, even whenever not imposed by state laws.

Patients should ideally be provided with an emergency helpline, given the paramount importance of promptly controlling a disease flare.

Infusion units are dedicated spaces, often located within hospitals, which provide high-quality care during the administration of intravenous drugs for the treatment of several chronic disorders, including IBD. The infusion unit should be regarded as an essential service. A proper organization of the infusion unit is essential to guarantee the safety of both patients and healthcare workers, again through symptoms and fever checks at hospital entry, distancing of beds/chairs of at least 2 m, the use of face masks and strict hand and surface sanitization policies. Furthermore, the turnover of healthcare workers should be limited as much as possible to reduce the risk of viral spread[73]. A telephone screening for symptoms before the scheduled appointment time and rapid SARS-CoV-2 testing can also be considered, based on local epidemiology and resource availability.

Finally, home delivery of subcutaneous drugs should be implemented.

The stress on the healthcare system, with an extremely increased number of severe respiratory patients, has turned the spotlights on the importance to vaccinate people for common influenza virus and *Streptococcus pneumoniae*[74]. It is recommended that all patients with IBD are offered both vaccinations.

It is too early to bring conclusions; however, this pandemic might have sped up the process of a technological revolution in medicine, which will likely change the landscape for the management of patients with chronic diseases, including IBD, also with long-term benefit.

Table 1 British Society of Gastroenterology stratification of inflammatory bowel disease patients according to the risk of severe acute respiratory syndrome coronavirus 2 infection		
Highest risk patients"shielding indicated"	**Moderate risk patients"stringent social distancing"**	**Lowest risk patients"social distancing"**
Patients who either have a comorbidity (respiratory, cardiac, hypertension or diabetes mellitus) and/or age ≥ 70 yr old and are on any "moderate risk" therapy for IBD (per middle column) and/or have moderate to severely active disease. Patients of any age regardless of comorbidities and who meet one or more of the following: (1) intravenous or oral steroids ≥ 20 mg prednisolone or equivalent per day (only while on this dose); (2) began biologic plus immunomodulator or systemic steroids within previous 6 wk; (3) moderate-to-severe active disease not controlled by "moderate risk" treatments; (4) short bowel syndrome requiring nutritional support; and (5) requirement for parenteral nutrition	Patients with moderate to severely active disease who are not on any of the medications in this column. Patients on the following medications: (1) anti-TNF (infliximab, adalimumab, golimumab) monotherapy; (2) biologic plus immunomodulatory in stable patients; (3) ustekinumab; (4) vedolizumab; (5) Thiopurines (azathioprine, mercaptopurine, tioguanine); (6) methotrexate; (7) calcineurin inhibitors (tacrolimus or ciclosporin); (8) JAK inhibitors (tofacitinib); (9) immunosuppressive trial medication; (10) mycophenolate mofetil; (11) thalidomide; and (12) prednisolone > 20 mg or equivalent per day	Patients on the following medications: (1) 5ASA; (2) rectal therapies; (3) orally administered topically acting steroids (budesonide or beclometasone); (4) therapies for bile acid diarrhea (colestyramine, colesevelam, colestipol); (5) anti-diarrheals (*e.g.*, loperamide); and (6) antibiotics for bacterial overgrowth or perianal disease

5ASA: 5-aminosalicylic acid; IBD: Inflammatory bowel diseases; JAK: Janus kinase; TNF: Tumor necrosis factor.

THERAPEUTIC MANAGEMENT OF IBD DURING SARS-COV-2 PANDEMIC

During this turbulent historical period, the care of chronic patients, including patients with IBD, has necessarily changed and is constantly evolving, reacting and adapting to the evolution of the pandemic.

As a general principle, we must not depart from solid evidence for the therapeutic management of IBD based solely on emergent data that, though extremely valuable, are certainly subject to many biases. Therefore, the principles of IBD management should remain largely unchanged during the pandemic, yet we certainly need to tailor patient care considering whether the patient is infected with SARS-CoV-2, has symptomatic manifestations of COVID-19 and shows underlying activity of the IBD.

Stable IBD course

Published guidelines, position statements and expert opinions agree in affirming that IBD patients with stable disease course and without SARS-CoV-2 infection should maintain the ongoing immunomodulatory treatment since the risk of disease reactivation outweighs the risk of SARS-CoV-2 infection (Table 2)[55,74-78]. As the pandemic ensued, the impossibility to reach hospitals has led to treatment discontinuation in some areas. Among 386 Chinese IBD patients on maintenance therapy during the epidemic[79], 107 (27.7%) have suspended medications, mostly biologics, with resulting disease relapses and hospitalization rates of approximately 25% and 50%, respectively.

Based on the available data, patients on high-dose corticosteroids (prednisolone dose ≥ 20 mg daily) should be informed about the higher risks they are exposed to and therefore encouraged to observe extra protective measures. It is more important than ever to minimize corticosteroid exposure and consider corticosteroid-sparing therapies where appropriate[57,62].

In patients with stable disease, a de-escalation of combination therapy with thiopurine and anti-TNF should be considered[62].

If necessary, it could also be considered to extend dose intervals of intravenous drug injection to reduce hospital visits; for instance, infliximab and vedolizumab infusions can be postponed up to every 8 wk and 10 wk, respectively[80,81]. The switch from infliximab to subcutaneous adalimumab treatment is not recommended, unless intravenous infusions cannot be performed safely; in fact, this elective shift is associated with loss of tolerance and efficacy within 1 year[82].

Patients with stable IBD and positivity for SARS-CoV-2 infection should be considered individually, simultaneously balancing the risk of inflammatory disease reactivation with the risk of severe COVID-19 course (Table 3).

Treatment with non-immunosuppressive medications (5-aminosalicylates) should be continued irrespectively of viral symptoms[74,78] , despite data from the SECURE-IBD registry indicating their association with severe COVID-19 disease course[57,62]. The unexpected nature of this finding from a biological perspective and the presence

Table 2 Summary of treatment in severe acute respiratory syndrome coronavirus-2 negative patients with stable inflammatory bowel disease disease course

Drug	Suggestions Continue therapy	Additional comments
Salicylates	Yes	Data from the SECURE-IBD of possible harm need to be confirmed.
Locally acting steroids	Yes	No specific data available
Systemic steroids	Yes	Limit use to strictly necessary and taper rapidly
Azathioprine	Yes	Data from the SECURE-IBD of possible harm need to be confirmed, the risk of reactivation seems to outweigh the risk of continued treatment
Methotrexate	Yes	Limited data available
Anti-TNF	Yes	Data from the SECURE-IBD indicate better outcomes compared to other treatments; there are ongoing trials for the treatment of COVID-19
Vedolizumab, anti-IL-12/23	Yes	Limited data available
Tofacitinib	Yes	Limited data available

COVID-19: Coronavirus disease 2019; IBD: Inflammatory bowel diseases; IL: Interleukin; TNF: Tumor necrosis factors.

Table 3 Summary of treatment in severe acute respiratory syndrome coronavirus-2 positive patients with stable inflammatory bowel disease disease course

Drug	Suggestions Continue therapy	Additional comments
Salicylates	Yes	A pause can be considered since data suggest a possible association of their use and poor COVID-19 outcome
Locally acting steroids	Yes	No data available
Systemic steroids	Rapid tapering	Dosage below 40 mg/d is suggested along with rapid tapering, particularly in patients without pneumonia and need for oxygen supplementation
Azathioprine	No	Delay treatment for 2 wk and/or until COVID-19 symptoms resolve
Methotrexate	No	Delay treatment for 2 wk and/or until COVID-19 symptoms resolve
Anti-TNF	No	Delay treatment for 2 wk and/or until COVID-19 symptoms resolve. Continued therapy may be considered in selected patients since no data demonstrated adverse outcome to date.
Vedolizumab, anti-IL-12/23	No	Delay treatment for 2 wk and/or until COVID-19 symptoms resolve
Janus kinase inhibitors	No	Delay treatment for 2 wk and/or until COVID-19 symptoms resolve

COVID-19: Coronavirus disease 2019; IL: Interleukin; TNF: Tumor necrosis factors.

of potential unmeasured confounders linked to data collection make further investigations necessary to confirm this association.

Corticosteroids should ideally be rapidly tapered off to the lowest possible dose in patients without symptoms or with mild symptoms. IBD patients presenting COVID-19 symptoms and requiring oxygen supplementation should probably maintain the dose equivalent to prednisone 40 mg/d since data from the RECOVERY trial has demonstrated the beneficial role of 6 mg of dexamethasone (equal to 40 mg prednisone) for up to 10 d in reducing 28 d mortality in patients receiving either invasive mechanical ventilation or oxygen supplementation[60].

The major guidelines state that patients positive for SARS-CoV-2 should interrupt the treatment with azathioprine, 6-mercaptopurine, biologics and Janus kinase inhibitors irrespective of the presence of COVID-19 symptoms[74,76].

However, uncertainty remains on the possibility of continuation of maintenance therapy with biologics in asymptomatic patients, with data from the SECURE-IBD registry and recent evidence suggesting no harm[54,83]. Even if these findings are insufficient to drive any solid conclusion, we might consider maintaining biologic agents in those patients with a high risk of IBD reactivation.

IBD disease reactivation

Telemedicine visits are encouraged as a first approach to gain insights into type and severity of symptoms reported by a patient. The cause underlying the symptoms should be deeply addressed in order to exclude an alternative diagnosis. In particular, all patients with IBD reactivation should undergo SARS-CoV-2 testing through NPS irrespective of respiratory symptoms[84]. Standard stool testing for bacterial and parasitic infections, including test for *Clostridioides difficile* toxins, should always be performed in patients presenting with diarrhea. Functional symptoms should also be considered during this stressful period.

A rapid assessment of the severity of disease activity is advisable, coupling clinical evaluation with noninvasive tests, including blood tests and fecal calprotectin. The reason for a disease flare should be quickly addressed (*i.e.* coinfection, drug immunogenicity or drug resistance) in order to be able to rapidly adjust medical therapy.

The need for face-to-face evaluation should be considered on a case-by-case basis, evaluating both clinical and biochemical parameters. Endoscopic procedures should be limited to what is strictly necessary for treatment decision; whenever possible, it should be replaced with ultrasound examinations or cross-sectional imaging[68].

SARS-CoV-2 negative patients. The management of IBD reactivation in SARS-CoV-2 negative patients should follow the current local and international guidelines, as it occurred in the pre-COVID era[74].

As stated, it appears to be even more important to minimize steroid exposure and consider steroid-sparing maintenance treatments if appropriate. There is currently no conclusive evidence to prefer one agent over another.

Patients must follow general and specific recommendations to reduce the risk of being infected with SARS-CoV-2, considering that active disease may represent an additional risk factor (Table 1).

SARS-CoV-2 positive patients. In mildly active disease a course of locally acting steroids can be instituted, despite the lack of specific evidence on the course of COVID-19. Alternatively, a reasonable approach would be to postpone treatment for 2 wk in order to observe the clinical course of COVID-19 and/or allow resolution of infection[85].

In a moderate to severe flare, there remain doubts about the use of systemic steroids, especially in patients without symptoms of COVID-19 or without need for oxygen supplementation. Indeed, besides the increased risk for adverse outcomes that emerged from the analysis of the SECURE-IBD registry data[54], in the RECOVERY trial patients receiving no respiratory support did not experience any benefit, but rather a trend toward harm was observed[60]. However, the role of high-dose systemic steroids in controlling the underlying IBD disease activity remains often pivotal.

Whenever necessary, a reasonable approach might be to limit the dose of prednisone to 40 mg daily, with rapid dose tapering and switch to maintenance biologic therapy[85].

When needed, biologic agents should be preferred as the first-choice treatment for the induction and maintenance of remission in IBD patients with SARS-CoV-2 since data available indicate their higher safety profile as compared to other drugs[6,54].

A strong emphasis needs to be put on the role of thromboprophylaxis for patients with both active IBD and SARS-CoV-2 infection, given the high rate of thrombotic complications observed in COVID-19 patients[85].

PSYCHOLOGICAL IMPLICATIONS OF SARS-COV-2 IN IBD PATIENTS

Since its first description in December 2019, COVID-19 has created a worldwide sense of fear, termed "coronaphobia," steeply increasing the incidence of various psychiatric manifestations[86]. Even before the pandemic onset, IBD patients were at an increased risk for mental health impairment and psychological comorbidities[87], with a reported incidence of depression and anxiety of up to four times higher than that of the general population[88,89]. During this pandemic, self-isolation, future uncertainty and lack of regular face-to-face contact with the referred physician will likely lead to

the amplification of latent psychopathological conditions or the development of new ones.

In the early phase of the pandemic, an online survey supported by the European Federation of Crohn's and Ulcerative Colitis Associations clearly demonstrated a communication gap between patients and physicians, as only 11% of patients had found relief from their worries from medical consultations[90].

Bearing all this in mind, the role of telemedicine, and perhaps of telepsychology, seems pivotal alongside a close-knit collaboration with patients' associations.

SARS-COV-2 VACCINATION

In December 2020 two mRNA vaccines and one replication-incompetent viral vector vaccine against SARS-CoV-2 have been approved, while many other candidates are currently in phase 3 testing. Vaccination campaigns have started in most countries with prioritization criteria mainly based on the risk of SARS-CoV-2 exposure and the risk of COVID-19 adverse outcomes.

Patients with IBD and other immune-mediated diseases were not included in the registration trials. Data on the safety and efficacy of SARS-CoV-2 vaccinations in these populations are therefore lacking.

The International Organization for the Study of Inflammatory Bowel Disease has recently released recommendations[91], mainly based on the extrapolation of safety and efficacy data from other vaccines.

Non-live vaccines are considered to be safe in patients with IBD, irrespective of immune-modifying treatments, though in the latter case it is acknowledged that the response may be to some degree blunted. In particular, previous studies have shown reduced response to influenza and pneumococcal vaccinations in IBD patients treated with immunosuppressant and anti-TNF agents[92-94]. Treatment with ustekinumab and vedolizumab, on the contrary, does not seem to impair response to influenza and pneumococcal vaccines[95,96].

Therefore, it is recommended that all IBD patients should be vaccinated against SARS-CoV-2, as soon as possible based on local policies, and irrespective of medications. According to the International Organization for the Study of Inflammatory Bowel Disease expert panel, the available SARS-CoV-2 vaccines are safe for patients with IBD, but patients should be informed that vaccine efficacy could be decreased when the latter are administered during corticosteroid therapy[91].

Further studies are definitively needed to assess the safety and efficacy of SARS-CoV-2 vaccines in IBD patients. Whether IBD patients on immune-modifying treatments may benefit from intensified vaccine administration regimen should also be evaluated.

CONCLUSION

Existing evidence shows that IBD patients are not at an increased risk for SARS-CoV-2 infection. As in the case of the general population, older age and presence of comorbidities are the primary risk factors for more severe COVID-19 course. Moreover, systemic steroids exposure has been consistently associated with COVID-19 negative outcomes. For what concerns the other class of IBD medications, no definite evidence of harm has emerged. In the clinical management of patients with IBD the risk of under treatment should be balanced against that of potential adverse outcomes of COVID-19, particularly in the setting of SARS-CoV-2 positive patients. Despite the lack of data, SARS-CoV-2 vaccination is recommended in IBD patients since the risk of the disease outweighs the uncertainty of potential adverse effects.

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