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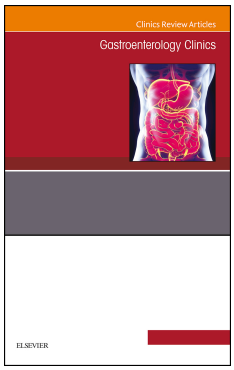

COVID-19 and Inflammatory Bowel Disease

Keith C. Summa, MD, PhD, Stephen B. Hanauer, MD, Clifford Joseph Barborka, Professor

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Authors:
Keith C. Summa MD, PhD
Email: ksumma@northwestern.edu
Instructor
Division of Gastroenterology and Hepatology, Department of Medicine
Northwestern University Feinberg School of Medicine
676 N. Saint Clair St., Suite 1400
Chicago, IL 60611
312-695-4077

Stephen B. Hanauer MD (Corresponding Author)
Email: shanauer@northwestern.edu
Clifford Joseph Barborka Professor
Division of Gastroenterology and Hepatology, Department of Medicine
Northwestern University Feinberg School of Medicine
676 N. Saint Clair St., Suite 1400
Chicago, IL 60611
312-695-8952

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Key Words: inflammatory bowel disease (IBD), ulcerative colitis, Crohn's disease, immunosuppression, COVID-19, SARS-CoV-2, COVID vaccination, SARS-CoV-2 antibodies, long COVID

Key Points: (3-5 bulleted sentences indicating main takeaways/defining elements)

- Patients with inflammatory bowel disease (IBD) are not at significantly increased risk of infection, severe disease, or death from the SARS-CoV-2 virus
- Among IBD treatments, only systemic corticosteroids have been associated with increased risk for severe COVID-19 disease and death
- COVID-19 vaccination is safe, well-tolerated, and effective in the vast majority of IBD patients
- IBD patients should undergo COVID-19 vaccination, including booster doses after the initial vaccine series, to reduce the morbidity and mortality from COVID-19
- Gastroenterologists have a role in promoting uptake of vaccination recommendations among IBD patients

Synopsis:

The COVID-19 pandemic caused by the SARS-CoV-2 virus represents an unprecedented global health crisis. Safe and effective vaccines were rapidly developed and deployed that reduced COVID-19-related severe disease, hospitalization, and death. Patients with inflammatory bowel disease (IBD) are not at increased risk of severe disease or death from COVID-19, and data from large cohorts of IBD patients demonstrate that COVID-19 vaccination is safe and effective. Ongoing research is clarifying the long-term impact of SARS-CoV-2 infection on IBD patients, long-term immune responses to COVID-19 vaccination, and optimal timing for repeated COVID-19 vaccination doses.

Introduction

In late 2019, the novel coronavirus, now known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), began circulating in Wuhan, China, and subsequently spread worldwide causing a global pandemic, with SARS-CoV-2 now likely transitioning to become a widely circulating endemic virus. SARS-CoV-2 is an RNA virus that causes infection by binding of the receptor-binding domain (RBD) from the viral spike protein to the host receptor angiotensin-converting enzyme 2 (ACE2), which triggers viral entry[1,2]. ACE2 receptors are widely expressed throughout the body, including on gastrointestinal epithelial cells[3,4]. SARS-CoV-2 infection causes the clinical syndrome of coronavirus disease-2019 (COVID-19), which is heterogeneous, ranging from asymptomatic infection, to mild and self-limited symptoms, to severe disease requiring hospitalization, and to excessive immune activation and cytokine storm leading to multiple organ failure, shock, and death[1]. Gastrointestinal symptoms such as anorexia, diarrhea, nausea, and abdominal pain are common in COVID-19, and were widely reported in the early descriptions of COVID-19[5]. Gastrointestinal symptoms of SARS-CoV-2 infection are presumably related to local effects of viral infection and host immune responses as SARS-CoV-2 viral RNA can be isolated from the stool of infected individuals[6,7].

The emergence of the COVID-19 pandemic generated widespread uncertainty and concern for patients with inflammatory bowel diseases (IBD), as the risks of SARS-CoV-2 infection for IBD patients, many of whom are treated with immunosuppressive therapies associated with increased risk of infection[8,9], were initially unknown. In addition, the dramatic societal responses to the pandemic presented challenges to IBD patients, who had to quickly adapt to a new environment characterized by changing public health recommendations, reduced opportunity for in-person clinical visits with providers, and shifts to utilization of telemedicine

technologies. Furthermore, the rapid development and deployment of COVID-19 vaccines, including the use of novel messenger RNA (mRNA)-based vaccine technology, led to new questions and uncertainties for IBD patients who were excluded from initial clinical trials leading to the Emergency Use Authorization (EUA) and subsequent approval by the Food and Drug Administration (FDA) in the United States. It was not initially known whether these vaccines would be safe and/or effective, nor whether vaccination would adversely impact their IBD. Finally, the development of persistent symptoms after SARS-CoV-2 infection, known as "long Covid" or post-acute COVID-19 syndrome (PACS), represented another unknown for IBD patients who struggled to discern the potential long-term consequences of infection.

This chapter addresses the incidence of COVID-19 and the risk for severe disease from COVID-19 in patients with IBD, gleaned mainly from large-scale IBD patient databases. The impact of IBD treatments on COVID-19 risk is reviewed. The sequelae and aftereffects of SARS-CoV-2 infection are discussed, including the concept of "long Covid", also known as post-acute COVID-19 syndrome (PACS). COVID-19 vaccination in IBD patients will then be discussed, including humoral and cell-mediated immune responses to vaccination in patients, and the effects of various IBD medications on vaccine responses. This review concludes with clinical recommendations regarding COVID-19 vaccination in IBD patients.

Discussion

COVID-19 Incidence in IBD Patients.

An immediate concern present at the onset of the pandemic was whether IBD patients were at increased risk of COVID-19 given the underlying immune dysregulation driving their IBD as well as their IBD treatment(s), the majority of which are immunosuppressive or immunomodulatory in nature. A total of 8 initial studies were summarized and combined in a

rapid review and meta-analysis published in the fall of 2020, which described an overall incidence of COVID-19 in IBD patients of 0.3%[10]. Six of these studies included patient numbers sufficient to combine in a meta-analysis of 9,177 primarily European IBD patients (two studies from Italy, two studies from Spain, one study from France and Italy, and one study from China). From this pooled patient cohort, a total of 32 confirmed cases of COVID-19 were identified during the study period (ranging from January 2020 in the Chinese study to early April 2020 in the Spanish studies). This rate of 0.3% was comparable to the rate in the general population, with similar demographics at that time (0.2-0.4%)[10].

Shortly thereafter, the results of an analysis of COVID-19 infection rates in a large multinational cohort of IBD patients (n=23,879) from 12 centers in Europe and Israel was published[11]. This study, which evaluated the time period from February 21 to June 30, 2020, identified a cumulative incidence of 0.406% (97 IBD patients with confirmed SARS-CoV-2 infection), which nearly matched the incidence observed in a matched general population without IBD (0.402%)[11].

An important caveat of this and much of the early research on COVID-19 is the substantial heterogeneity in the early phases of the pandemic, as different parts of the world were affected by waves of COVID-19 infections at different times, and different parts of the world had substantially variable COVID test availability as well as patterns of public health and societal responses to the pandemic that shifted over time and in relation to one another. It is thus difficult to interpret, understand, and compare reported rates of incidence given these temporal dynamics of the pandemic and responses to it. For example, individual IBD patients, given their concerns about potential increased disease susceptibility and/or severity, may have more carefully adhered to recommendations for social distancing, isolation, and masking than the general population. If

such behavioral patterns were adopted by large numbers of IBD patients, these behaviors may have reduced the reported incidence of COVID-19 in IBD patients compared to what would have been observed in a hypothetical environment characterized by similar behaviors for IBD patients and controls.

Despite these potential limitations and theoretical concerns related to initial studies, the conclusion that patients with IBD are not at significantly increased risk for SARS-CoV-2 infection has been borne out and confirmed over time. As SARS-CoV-2 transitions from a global pandemic to an endemic virus, ongoing research and monitoring should continue to evaluate whether IBD patients are at increased risk over time.

COVID-19 Severity in IBD Patients.

A related early concern among IBD patients and providers was whether SARS-CoV-2 infection was more severe in IBD patients compared to matched individuals without IBD. Similar limitations impacted early research into risks for severe COVID-19 in IBD patients. In addition, the initial phases of the pandemic likely exhibited significant selection bias as severe cases were scrutinized closely whereas the relatively high rate of asymptomatic infection was not initially appreciated. An early case-control study involving COVID-19 positive patients (confirmed or highly suspected) at two New York City hospitals compared disease severity in 80 IBD patients versus 160 matched non-IBD control patients, finding similar overall rates of a composite endpoint of severe disease, consisting of intensive care unit (ICU) admission, endotracheal intubation, or death (24% for IBD patients *vs* 35% for non-IBD patients, p=0.352).[12] This study demonstrated that the most significant risk factor for severe COVID-19 in IBD patients was *increased age*, the same risk factor for those without IBD[12]. Older age was

associated with increased risk for severe disease in both the IBD and non-IBD cohorts, highlighting the theme that the risk factors for severe COVID-19-related disease, such as age and co-morbidities, are not unique to IBD and are instead similar between IBD patients and those without IBD. An intriguing additional finding from this study was that rates of several GI symptoms in the setting of SARS-CoV-2 infection were significantly higher in IBD patients compared to those without IBD: diarrhea (45% *vs* 19%, $p<0.001$) and abdominal pain (20% *vs* 5%, $p<0.001$)[12].

A longitudinal component of this early study described an association between moderate-to-severe IBD disease and SARS-CoV-2 infection rate, as IBD patients with COVID-19 were significantly more likely to have clinically active disease, endoscopic disease activity, and baseline elevation of the inflammatory biomarkers C-reactive protein (CRP) and fecal calprotectin[12]. In addition, an increased risk for COVID-19 was seen in IBD patients receiving corticosteroids[12]. A subsequent retrospective observational study of an Italian cohort of IBD patients (n=122; the Sicilian Network for IBD, or SN-IBD, cohort) infected with SARS-CoV-2 during the second pandemic wave in the fall of 2020 found, on multivariate analysis, that severe IBD activity was the only independent predictor of severe COVID-19, as defined by a composite end point consisting of the need for respiratory support or death[13].

One of the best resources for comprehensive, longitudinal research on COVID-19 in IBD patients has been the SECURE-IBD database (Surveillance Epidemiology of Coronavirus (COVID-19) Under Research Exclusion for Inflammatory Bowel Disease; covidibd.org). The initial report of data from the SECURE-IBD database consisting of 525 cases of COVID-19 in IBD patients from 33 countries during the early phases of the pandemic indicated that increasing age, increasing number of co-morbidities (2 or more), and use of corticosteroids were associated

with an increased risk of severe disease[14]. Interestingly, the use of 5-aminosalicylate or sulfasalazine was associated with increased risk of severe disease whereas the use of TNF-alpha antagonist therapy was not associated with an increased risk of severe disease. Among these cases of COVID-19, 161 patients were hospitalized (31%), 37 patients had severe COVID-19 (7%), and 16 patients died (case fatality rate of 3%).

The overall mortality in this IBD patient database did not differ significantly from mortality reported in the United States, Europe, and China, strengthening the conclusion that there was not an increased risk of death from COVID-19 in IBD patients compared to the general population. Overall, these findings reinforce the notion that the most significant risk factors for severe COVID-19 in IBD patients are shared with those individuals without IBD, namely increased age and medical co-morbidities. Indeed, a subsequent, updated analysis of the SECURE-IBD database reported that the majority of severe COVID-19 and COVID-19-related deaths occurred in older IBD patients[15].

IBD Treatment(s) and COVID-19.

A particular benefit of the SECURE-IBD database has been to evaluate the impact of different IBD treatments on COVID-19 disease risk; an important challenge given the number of medications and the different mechanisms of action currently utilized by IBD patients. This comprehensive registry was used in a recently published evaluation of different IBD medication classes on COVID-19 risk using 6,144 individual reports of SARS-CoV-2 infection in IBD patients since the inception of the SECURE-IBD database on March 13, 2020, until May 21, 2021[16]. Confirming prior reports, including a previous publication from the SECURE-IBD registry[15], systemic corticosteroids were associated with an increased risk of hospitalization or

death (from any cause) or both (adjusted odd's ratio (aOR) 2.45; 95% confidence interval (CI) 1.81-3.31), an increased risk of severe COVID-19 (aOR 3.49, 95% CI 2.62-4.65), and an increased risk of death due to COVID-19 (aOR 4.77, 95% CI 3.36-6.77). Methotrexate was marginally associated with an increased risk of hospitalization or death or both (aOR 1.26, 95% CI 1.00-1.57), which did not persist in models evaluating associations between methotrexate and severe COVID-19 (aOR 1.04, 95% CI 0.39-2.81) or between methotrexate and death due to COVID-19 (aOR 0.79, 95% CI 0.20-3.08).

Biologic therapy with monoclonal antibodies targeting TNF, IL12/23, or $\alpha 4\beta 7$ integrins was associated with *decreased* risk of hospitalization, death or both [aORs 0.58 (95% CI 0.50-0.69), 0.44 (95% CI 0.36-0.54), and 0.66 (95% CI 0.56-0.78)], respectively. Combination therapy using a TNF antagonist plus thiopurine was associated with significantly *increased* risk for hospitalization or death, but not with severe COVID-19. In contrast, combination therapy using a TNF antagonist plus methotrexate was not associated with significantly elevated risk for adverse COVID-19-related outcomes (hospitalization, death, or severe disease). No statistically significant differences in risk of adverse COVID-19 outcomes were observed when comparing patients on different classes of biologic medications (TNF antagonist, IL12/23 antagonist, or integrin antagonist)[16].

In contrast to prior reporting from the SECURE-IBD database[14], in this analysis, no significant increase in risk of adverse COVID-19 outcomes was observed in patients on aminosalicylates or sulfasalazine therapy[16]. The larger body of evidence utilized in this most recent publication, as well as evidence from an independent cohort of IBD patients[17], supports the conclusion that neither aminosalicylate nor sulfasalazine therapy is associated with increased risk of severe COVID-19 or COVID-19-related complications. It may be that the unexpected

association between 5-aminosalicylate or sulfasalazine therapy and adverse COVID-19 outcomes that was initially reported was actually driven by delays in reporting and/or reporting bias due to early pandemic associated factors discussed above.

A potentially *protective* effect was seen with the Janus Kinase (JAK) inhibitor, tofacitinib (aOR 0.48, 95% CI 0.30-0.76), though the sample size was small, consisting of only 9 infections[16]. A dedicated analysis of SECURE-IBD database patients treated with tofacitinib did not identify significantly increased risks for COVID-19-related adverse events or venous thromboembolism in patients receiving tofacitinib[18]. Furthermore, a recent meta-analysis of six studies including 11,145 patients receiving systemic JAK inhibitor therapy (for any indication) with moderate-to-severe COVID-19 infection found a probable *decrease* in all-cause mortality at 28- and at 60- days post-infection (relative risk (RR) 0.72, 95% CI 0.57-0.91; RR 0.69, 95% CI 0.56-0.82; respectively), without an increase in adverse effects[19]. Patients on newer agents from medication classes including sphinogosine 1 phosphate receptor modulators, IL23 antagonists, and selective JAK inhibitors were not part of the SECURE-IBD database at the time of the data collection period and thus were not included in this analysis.

Taken together, the totality of evidence at present indicates that systemic corticosteroid use is unequivocally associated with increased risk for adverse outcomes from SARS-CoV-2 infection, and that advanced therapies for IBD, with the possible exception of combination therapy using a TNF antagonist and thiopurine, are not associated with an increased risk of COVID-19-related adverse events. Thus, in concordance with international guidelines for treating IBD, corticosteroid-sparing therapies should be used to wean patients off corticosteroids as soon as possible to reduce the risk of corticosteroid-related (including adverse COVID-19-related) risks. Likewise, patients should be informed of the safety of other IBD medications in

the setting of COVID-19 infections to provide reassurance and enhance adherence to therapy. The SECURE-IBD database has been an invaluable resource for the field to facilitate practical research to inform clinical care in the setting of a rapidly evolving global pandemic. Ongoing utilization and maintenance of SECURE, as well as similar disease-related internet databases, offer unique and powerful opportunities to advance clinical research for global IBD, immune-related inflammatory diseases, transplant, and cancer communities.

Post-Acute COVID-19 Syndrome (PACS) or "Long COVID".

An important development from the COVID-19 pandemic has been the recognition of persistent symptoms lasting at least four weeks or longer after SARS-CoV-2 infection. This phenomenon has been labeled as post-acute COVID-19 syndrome (PACS), commonly referred to as "long COVID". For this review, these two terms (PACS and "long COVID") will be considered synonymous, and PACS will be used for consistency. PACS involves many different and often non-specific symptoms such as chronic fatigue, headache, "brain fog," cognitive dysfunction, chronic pain, shortness of breath, and chest pain[20]. Manifestations of PACS may range from relatively mild and self-limited to severe and debilitating symptoms[20].

Gastrointestinal symptoms are present in about half of patients with acute COVID-19 infection and persist at 6 months in approximately 10-25% COVID-19 patients [21,22]. A recently published systematic review and meta-analysis estimated the prevalence of persistent gastrointestinal symptoms in the setting of PACS to be 22%, though the underlying studies included in this meta-analysis were limited by small size and heterogeneity[23]. Gastrointestinal symptoms of PACS include diarrhea, constipation, nausea/vomiting, dyspepsia, anorexia, abdominal pain, and heartburn, among others[21-23]. They are often associated with symptoms of

anxiety and depression, which usually precede SARS-CoV-2 infection, and they tend to gradually wane over time. The underlying etiology of long-term and persistent gastrointestinal symptoms of PACS is unknown. Potential mechanisms may include persistent viral antigen presence in mucosal tissues triggering ongoing host responses, changes in the microbiome induced by SARS-CoV-2 infection, aftereffects or sequelae of host immune responses to the SARS-CoV-2 virus, persistent activation or alteration of immune cells and inflammatory signaling pathways, or post-infectious irritable bowel syndrome. These are not mutually exclusive processes and may interact in different ways in different patients to contribute to the reported symptoms.

A study of 46 European patients with IBD that underwent upper endoscopy and colonoscopy at a median of 7 months after SARS-CoV-2 infection (range ~3-8.5 months) demonstrated that SARS-CoV-2 RNA expression was present in mucosal tissue of most patients (69.5%), and that SARS-CoV-2 viral antigen was present in intestinal epithelial tissue and CD8+ T cells in over half of patients (52.1%)[24]. Despite these viral (or remnant) markers persisting in many patients, infectious virions of SARS-CoV-2 were unable to be retrieved from mucosal tissues and live virus was not able to be cultured from any of the patients; suggesting that patients were experiencing inadequate or incomplete viral clearance as opposed to active subclinical, latent, or recurrent viral infection. Importantly, only those patients with persistence of viral antigens experienced post-COVID symptoms, whereas no symptoms were reported in patients without detectable viral antigens. Viral antigen persistence was not related to the severity of COVID-19 infection, underlying endoscopic inflammatory activity at the time of endoscopy, or IBD-related immunosuppressive treatment[24].

This finding of SARS-CoV-2 viral antigen persistence has been explored in individuals without IBD as well. In a small study of 14 individuals evaluated at an average of 4 months (range 2.8-5.7 months) after acute SARS-CoV-2 infection, five patients (35.7%) had detectable viral antigen (SARS-CoV-2 N protein) in intestinal enterocytes[25]. Although these individuals did not have PACS, this establishes that viral antigen persistence occurs in the intestine in a subset of patients after acute SARS-CoV-2 infection. Taken together, these findings demonstrate that SARS-CoV-2 viral antigens can persist within the gastrointestinal tract after acute infection with SARS-CoV-2, raising the intriguing possibility that viral antigen persistence may induce a chronic inflammatory response or host immune perturbation that contributes to ongoing symptoms of PACS. Further research with validation and replication of these findings in independent cohorts in conjunction with longer-term monitoring of patients with PACS, including those with IBD, may help clarify the natural history of this entity as well as its underlying mechanisms.

COVID Vaccination in IBD Patients.

A defining feature of the COVID-19 pandemic has been the rapid development, testing, and deployment of vaccinations against the SARS-CoV-2 virus, including the use of novel mRNA-based technologies. Despite the political and cultural challenges related to vaccine uptake and utilization among the population at large, the creation of highly effective and safe vaccines targeting this novel virus is a resounding success of the biomedical establishment that has resulted in significant reductions in hospitalizations, severe illness, and death from COVID-19. Although the initial mRNA vaccines granted approval for use (Pfizer-BioNTech BNT162b2 and Moderna mRNA1273) were shown to safe and effective in trials leading to emergency use

authorization (EUA), patients with IBD were excluded from these initial clinical trials. This led to initial concerns about the safety and efficacy of these vaccines in IBD patients, given their underlying disease and their potential use of immunosuppressive and/or immunomodulatory medications.

In a similar manner to the SECURE-IBD database to study COVID-related adverse outcomes in IBD patients, the PREVENT-COVID and CLARITY-IBD initiatives were launched to examine the safety and efficacy of COVID-19 vaccination for IBD patients. Initial results from the PREVENT-COVID study demonstrated that vaccination is safe, well-tolerated, and effective in IBD patients[26]. This has been confirmed in additional studies and meta-analyses[27-29]. A meta-analysis published in July 2022 including 46 studies evaluating responses to COVID-19 vaccination in IBD patients found that the vast majority of IBD patients receiving COVID-19 vaccination achieve adequate immunogenic responses, as determined by seropositivity for anti-SARS-CoV-2 spike and/or anti-SARS-CoV-2 receptor binding domain antibodies[27]. For studies with complete immunization data (n=31 studies, 9447 patients), the pooled seroconversion rate for vaccinated IBD patients was 0.96 (95% CI 0.94-0.97), which was slightly less than the rate for vaccinated control patients of 0.98 (95% CI 0.98-0.99). Among vaccinated IBD patients, the pooled positivity of neutralization assays (testing the ability of patient antibodies to neutralize the virus) was 0.80 (95% CI 0.70-0.87). Furthermore, there were no statistically significant differences in vaccine responses among IBD patients taking different medication classes. In addition, pooled rates of breakthrough infection risk after vaccination were similar in IBD patients and the vaccinated general population (RR 0.60, 95% CI 0.25-1.42)[27]. Taken together, these findings indicate that COVID-19 is highly effective, safe, and well-tolerated in IBD

patients. Furthermore, there has been no evidence that undergoing vaccination can trigger activation of underlying IBD activity or inflammation.

In addition to these large-scale studies confirming the safety and efficacy of COVID-19 vaccination in IBD patients, detailed studies have explored the immunogenic responses to vaccination in patients receiving different medication classes. Several studies have shown that antibody responses are attenuated in patients on TNF antagonist therapy[30-32], but the clinical significance of these findings is unclear, and these results should not be construed as indicating that patients on these therapies should not undergo vaccination.

As the COVID-19 pandemic transitions to an endemic virus that will likely circulate widely in a seasonal pattern common to many infections spread via respiratory droplets and aerosols, it will be important to determine how frequently IBD patients, according to IBD subtypes or therapies, should undergo vaccination with booster doses. Studies examining the durability of antibody responses in vaccinated IBD patients have shown that antibody titers begin to decline approximately 4 weeks after vaccination, and this reduction is accelerated in patients receiving a TNF antagonist therapy or combination therapy with a TNF antagonist and immunomodulator[27]. Although such reductions in titers have been described, the clinical significance of these reductions is unknown, as the underlying antibody titer has not been shown to be directly related to susceptibility to infection, and patients may generate protective cell-mediated immune responses that are independent of antibody titers. For now, it seems prudent to recommend that IBD patients, especially those at increased risk because of older age and those receiving immunosuppressive therapies, receive booster COVID-19 doses approximately every 4-6 months pending further evidence-based guidance. The continued utilization of registries and databases such as PREVENT-COVID and SECURE-IBD can be leveraged for ongoing research

on the durability and efficacy of vaccination in IBD patients, which may inform recommendations on frequency of booster doses.

Summary

The initial global pandemic caused by the SARS-CoV-2 virus confronted patients with IBD with uncertainties, anxieties, questions, and challenges. These centered on individual personal risks for severe COVID-19-related disease and death, the impact of COVID-19 on their underlying IBD, the safety of their IBD medications in the setting of the global pandemic, the efficacy and safety of COVID-19 vaccination, and the long-term consequences of SARS-CoV-2 infection on their health and quality of life. In addition, societal changes induced by the COVD-19 pandemic exerted a significant burden related to uncertainties associated with often changing public health guidance as well as changes to healthcare access and delivery. Fortunately, a currently large and growing body of evidence from prospectively monitored cohorts of IBD patients has consistently demonstrated that patients are not at significantly increased risk of severe disease or death from COVID-19. Furthermore, COVID-19 vaccination is now known to be safe, effective, and durable for the vast majority of individuals with IBD. Although some studies have shown decreased antibody concentrations in response to vaccination in IBD patients, in particular in older patients and patients treated with anti-TNF monotherapy, combination therapy with anti-TNF and a conventional immunomodulator, tofacitinib, and systemic corticosteroids; the cumulative body of evidence indicates that COVID-19 vaccination is a powerful and proven tool to reduce morbidity and mortality from SARS-CoV-2 infection.

Gastroenterologists have an important role in promoting COVID-19 vaccination adherence and should provide reassurance for all gastroenterologic patients, including those with IBD,

regarding the safety and efficacy of COVID-19 vaccination. This guidance should be delivered clearly and consistently for IBD patients to receive vaccinations in accordance with updated professional guidelines. IBD patients should receive COVID-19 vaccination, preferably with an mRNA vaccine. Patients receiving immunosuppressive therapies should have an additional mRNA vaccine dose four weeks after completion of the two dose primary vaccine series and a booster dose about three months thereafter. Individuals not on immunosuppressive therapy should have a booster dose about five months after completion of the initial two dose vaccine series. These recommendations are in accordance with guidelines and consensus opinion from the International Organization for the Study of Inflammatory Bowel Disease (IOIBD)[33], the British Society of Gastroenterology[34], the Crohn's & Colitis Foundation, and the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP). Though the ACIP's position included individuals treated with systemic corticosteroids (at a dose of $\geq$20 mg/day), anti-TNF therapy, and immunomodulators, it did not provide specific recommendations for patients taking vedolizumab, ustekinumab, risankizumab, ozanimod, tofacitinib, or upadacitinib. Despite this limitation, it seems reasonable and prudent to also apply these recommendations to patients receiving these particular therapies.

As vaccine-induced immunity wanes over time and as new SARS-CoV-2 variants emerge, it will be incumbent upon gastroenterologists to maintain clear communication with IBD patients regarding updated COVID-19 vaccination recommendations and guidance. Ongoing prospective monitoring of clinical studies in IBD patients are expected to inform clinical practice with respect to the optimal timing of booster vaccination doses to maintain adequate immunity to prevent and minimize COVID-related morbidity and mortality. In addition, future studies offer the potential to describe and clarify longer-term effects of SARS-CoV-2 infection in IBD

patients, as an initial study has reported long-term persistence of SARS-CoV-2 viral antigens in intestinal tissue of IBD patients, a finding of unknown clinical significance. Given the growing number of IBD (and non-IBD) patients suffering from persistent GI symptoms after COVID-19 infection, such information will be critical to understand the prevalence, natural history, and progression of post-COVID-19 sequelae, as well as the impact on COVID-19 vaccination on long-term SARS-CoV-2 infection-related outcomes.

Clinics Care Points

- Patients with IBD are not at significantly increased risk for severe disease or death from COVID-19
- Systemic corticosteroid use is associated with increased risk of COVID-19-related severe disease and death, rendering weaning off and reducing use of systemic corticosteroids key priorities for gastroenterologists taking care of IBD patients
- COVID-19 vaccination is safe and effective in IBD patients, including those on immunosuppressive therapies
- Individuals with IBD should undergo COVID-19 vaccination, preferably with an mRNA vaccine, including a booster dose for those that are not immunosuppressed and an additional dose as part of the primary series as well as a booster dose for those on immunosuppressive therapy
- Ongoing work is clarifying the long-term impact of SARS-CoV-2 infection and post-acute COVID-19 syndrome in IBD patients as well as the optimal timing for booster vaccine doses

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