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OPINION REVIEW

Review of inflammatory bowel disease and COVID-19

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Abstract

The first cases of a novel corona virus infection were reported in Wuhan China in December of 2019, followed by the declaration of an international pandemic by the World Health Organization in March 2020. Early reports of the virus, now known as severe acute respiratory syndrome coronavirus 2, and its clinical disease coronavirus disease 2019 (COVID-19), has shown higher rates of morbidity and mortality in the elderly and those with pre-existing medical conditions. Of particular concern is the safety of those with compromised immune systems. Inflammatory Bowel disease (IBD) is itself caused by a disordered immune response, with the most effective medical therapies being immune suppressing or modifying. As such, the risk of COVID-19, virus related outcomes, and appropriate management of IBD patients during the global pandemic is of immediate concern to gastroenterologists worldwide. There has been a rapid accumulation of clinical data and expert opinion on the topic. This review will highlight the latest source information on clinical observation/outcomes of the IBD population and provide a concise summary of the most up to date perspectives on IBD management in the age of COVID-19.

Key Words: Inflammatory bowel disease; COVID-19; SARS-CoV-2; Corona virus; Pandemic

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Core Tip: The rapid spread of coronavirus disease 2019 (COVID-19) has impacted patients and medical practice across the globe. While all individuals are at risk for COVID-19, this risk is of particular concern to those with compromised immune systems. Inflammatory bowel disease (IBD) patients are presumed to be particularly vulnerable, particularly those on immune suppressing/modifying medications. There has been rapid publication of peer reviewed source material and expert opinion addressing IBD experience, outcomes, and management in the age of COVID-19. This review provides a concise summary to help facilitate safe and effective patient management.

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INTRODUCTION

The first cases of a novel coronavirus infection were reported in Wuhan, China in December of 2019[1]. Since that time the virus has spread to all continents except Antarctica, with the World Health Organization declaring a global pandemic on March 11, 2020. As with other, similar coronaviruses, such as those associated with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), the primary manifestations of active infection are respiratory. Patients typically develop fever, cough, and shortness of breath, with a significant minority progressing to severe lung injury requiring the use of supplemental oxygen, and the need for mechanical ventilation with a high associated mortality rate[2-4]. Since its identification, the virus has been assigned the formal nomenclature of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with the associated clinical illness designated as 2019 novel coronavirus (2019-nCoV) or coronavirus disease 2019 (COVID-19)[5].

As was observed during the initial outbreak in China, and then even more dramatically in Italy, those at highest risk were noted to be the elderly and those with preexisting medical conditions, particularly cardiovascular, respiratory, endocrine, and oncologic[6,7]. As with most communicable infectious diseases, particular concern has also been raised for the safety of those with coexisting immune mediated disease, and/or those on immune compromising therapies. For the gastroenterology community (providers, patients and caregivers) this has obviously sparked particular concern for those individuals with inflammatory bowel disease (IBD). IBD is regarded as a disease of immune dysregulation, and with the exception of some limited use of diet, antibiotic and topical anti-inflammatory therapies, the vast majority of effective IBD medications for moderate to severe disease are immune suppressing/modifying[8-10]. While IBD itself is not regarded to increase non-gastrointestinal (GI) infectious disease risk[11], there is ample evidence demonstrating an increased risk of non-GI, opportunistic infections associated with IBD therapies[12-16]. Given the need for clinical evidence and expert guidance, the past weeks have seen the rapid growth of information specifically geared towards answering the core questions faced by IBD patients and providers. This work falls into two main categories, each of which we will briefly review: (1) Clinical observation of the IBD patient experience during the COVID-19 pandemic; and (2) Expert opinion on the management of IBD in an environment of COVID-19.

IBD AND COVID-19 CLINICAL EXPERIENCE

Though there is currently no evidence of SARS-CoV-2 exacerbating underlying IBD, it is now well recognized that many patients with COVID-19 will develop GI complaints. The SARS-CoV-2 invades human cells by interactions with angiotensin-converting enzyme 2 (ACE2). The ACE2 receptor is found in different tissues throughout the body, including those of enterocytes[17-19]. Studies have shown the presence of SARS-

CoV-2 in stool with persistence of viral shedding in the stool even after the resolution of respiratory complaints[20,21]. Notably, recent basic scientific evidence has observed an up-regulation of ACE2 in the inflamed mucosa of IBD patients, suggesting how IBD patients might be at increased risk for COVID-19[22,23]. However, it is also worth noting that a soluble form of ACE2 circulating in the blood is also up-regulated in IBD, which may provide an alternate binding site for SARS-CoV-2 that could limit viral binding to cell surfaces[24]. Further studies on viral load and viral dynamics are required to clarify the clinical significance of these findings.

Cheung *et al*[25] in their systematic review and meta-analysis of 69 studies (53 from China) including 4243 COVID-19 patients, demonstrated a pooled prevalence of all gastrointestinal symptoms of 16.1% [95% Confidence Interval (CI): 10.9-23.0] from China, and 33.4% (95%CI: 15.2-58.3) in studies from all other countries. The most common complaint was anorexia 26.8% (95%CI: 16.2-40.8), followed by nausea/vomiting 10.2% (95%CI: 6.6-15.3), diarrhea 12.5% (95%CI: 9.6-16.0), and abdominal pain/discomfort 9.2% (95%CI: 5.7-14.5). It is unknown however how many of these patients had a prior IBD diagnosis or other GI condition. Goyal *et al*[26] in a more recent analysis of 393 consecutive patients admitted to 2 New York City hospitals also showed GI complaints were prominent, including diarrhea (23.7%) and nausea with vomiting (19.1%).

Despite these high rates of GI complaints, Mao *et al*[27] in their report of COVID-19's impact on those with preexisting GI conditions, noted that there had been no reports of IBD patients infected with SARS-CoV-2 in the IBD Elite Union, a consortium of the seven largest Chinese IBD referral centers, caring for over 20000 patients. The authors also reported that there had been no cases of IBD/SARS-CoV-2 infected patients in the three largest tertiary IBD centers in Wuhan (Tongji Hospital, Union Hospital, and Zhongnan Hospital) at the time their manuscript was prepared, March 8, 2020. While these results are encouraging, the methodology of case identification/reporting, and thus the true rate of IBD/SARS-CoV-2, remains unclear. Also, as rates of IBD and utilization of IBD medication may differ in China from those in other countries, these results may not be applicable to other populations.

Low rates of IBD/SARS-CoV-2 have also been reported in Lombardy, Italy, the next major COVID-19 hot spot. Norsa *et al*[28] acknowledging that the pandemic is still ongoing, reported on their region's experience (including their IBD center) up to the time of publication. At that time they observed the highest rates reported in the world: 6471 cases of COVID-19 out of a population of 1.1 million. Of the 522 IBD patients followed at their center (11% pediatric, 22% on immunomodulators (IMM), and 16% on biologics) there had been no cases of COVID-19 reported. Based on Wuhan population modeling, the authors had anticipated 21 IBD infected patients by that time point. The authors do acknowledge that their results are not definitive, as only patients with severe symptoms and/or those receiving a nasopharyngeal swab were counted. The case reporting methodology, which was at least partially dependent upon patient self-reporting, again may have been biased towards an underestimate of true cases.

More recently, case series and observational cohort data has emerged reporting on identified IBD/COVID-19 patients. Rodriguez-Lago *et al*[29] reported on 40 cases of IBD (21 hospitalized) with confirmed positive tests for SARS-CoV-2 from 5 sites in the Basque Country (Spain), median age 59 years, 60% male, 32% Crohn's disease (CD), with 28% on immune therapy, 18% biologic, and 10% systemic corticosteroids. Two deaths (5%) were reported, including an 86 years old male, on mesalamine, with prostate adenocarcinoma, and a 77 years old male on mesalamine and methotrexate. Taxonera *et al*[30] reporting from the Madrid region of Spain, observed 12 IBD cases with laboratory confirmed COVID-19 from 1912 IBD patients followed in their database. Their patients' mean age was 52 years, with 75% female, and 58.3% CD. Seven patients (58.3%) were on immune and/or biologic therapy. There was no reporting of rates of corticosteroid use. Eight patients required hospitalization, 1 required mechanical ventilation and 2 died; a 76 years old male with UC and a 72 years old female with UC, neither of whom was receiving immune or biologic therapy. The authors additionally compared their findings in the IBD cohort to the observed rates and mortality of COVID-19 in the general population of Madrid. They found a significantly lower risk of COVID-19 for IBD [Odds ratio (OR) 0.74, 95%CI: 0.70-0.77; P < 001], with no significant difference in the case fatality rate for COVID-19 for IBD patients of 16.7% *vs* 13.2% for the general population (OR 1.31, 95%CI: 0.29-6.00, P = 0.72). An additional 15 IBD patients with COVID-19 have been reported by the combined centers of Nancy University Hospital in France and Humanitas, Milan, Italy[31] from their combined cohorts of over 6000 IBD patients, they identified 15 patients who tested positive for COVID-19 via routine tele-medicine and infusion center visits. Thirteen patients were on immune and/or biologic therapy, and there

was no mention of corticosteroid use. Five patients required hospitalization, but no deaths were reported. The authors observed an incidence of COVID-19 positive IBD patients in the cohort of 0.0025, which was similar to the current cumulative incidence of 0.0017 in France and Italy at that time.

To date, the largest national case reporting has come from a combined 24 IBD referral centers in Italy, affiliated with the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD)[32]. Patients either had laboratory testing confirming Sars-CoV-2 or a known infected contact and a combination of suspicious clinical complaints and/or lung CT findings of COVID-19. In total 79 patients were described, median age 45 years, 44.3% female, 32 CD, of whom 8% were on thiopurines, 37% anti-TNF, 20% vedolizumab, 4% ustekinumab and 11% systemic corticosteroids. Additionally, 28% of patients (12% of CD and 35% of UC) were determined to have active disease based upon chart abstraction of the Harvey-Bradshaw index for CD and partial Mayo score for UC. Overall 36 patients (46%) had COVID-19 related pneumonia, 22 (28%) were hospitalized, 2 (3%) required mechanical ventilation, and 6 (8%) died. Important observations included a significant association between active IBD and COVID-19 related pneumonia (OR 10.25, 95%CI 2.11-49.73, P = 0.003), and active IBD and COVID-19 related death (OR 8.45, 95%CI: 1.26-56.56, P = 0.02). There was no association between either corticosteroid use or anti-TNF use and COVID-19 related death. Age > 65 years was the strongest predictor of COVID-19 related death (OR 19.6, 95%CI 2.95-130.6, P = 0.002).

Also, in keeping with the observed low rates of clinically significant disease in the young, low rates have also been reported from a sample of the 102 pediatric IBD (PIBD) centers (mostly in Europe), part of the Porto group of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)[33]. A voluntary reporting system was constructed to include those with virologically confirmed SARS-CoV-2, as well as cases with strong clinical suspicion in those without access to testing. Reporting required a 7-d follow-up to ensure documentation of disease severity. The Chinese pediatric centers (84% from Wuhan) reported 917 confirmed or suspected cases of COVID-19, none in the IBD patients. The South Korean cohort reported no cases of COVID-19 out of the 272 children with IBD followed at four tertiary care centers. Reporting from a combined 32 centers in Europe, Canada, and Israel up through March 26, 2020 resulted in a total of 7 cases of PIBD and COVID-19, all with mild disease despite ongoing treatment with immunomodulators, corticosteroids and/or biologics. Notably, despite reporting no cases of IBD patients contracting COVID-19 at the Chinese centers, the crisis created by COVID-19 resulted in delays of scheduled infusions. There were 233 PIBD patients scheduled to receive infliximab during the pandemic. Of these, 66 (28%) had their infusions delayed, resulting in 14 disease exacerbations and 10 hospitalizations.

In an attempt to keep up with the pace of the pandemic and the need for updated data, the Surveillance Epidemiology of Coronavirus Under Research Exclusion (SECURE-IBD) database has been established[34]. It is an international, pediatric and adult database to monitor and report on outcomes of COVID-19 occurring in IBD patients. The database is open to reporting by IBD clinicians, both pediatric and adult, worldwide. Reporters are encouraged to include both symptomatic and asymptomatic patients. De-identified data points collected for analysis include age, gender, country of origin, IBD disease type and IBD medication use. The database is tracking rates of hospitalizations, ICU admission, need for mechanical ventilation and mortality. At the time of this manuscript's submission, the first published reports from the database have become available. Currently "in press," the authors report 525 cases from 33 countries (Median age 43 years, 53% men). The primary outcome of interest was severe COVID-19, defined as a composite of ICU admission, ventilator use, and/or death. Thirty seven patients (7%) had severe COVID-19 (as determined by physician global assessment), 161 (31%) were hospitalized, and 16 patients died (3% case fatality rate). Age-standardized mortality ratios for IBD patients were 1.8 (95%CI: 0.9-2.6), 1.5 (95%CI: 0.7-2.2), and 1.7 (95%CI: 0.9-2.5) relative to data from China, Italy, and the US, respectively. On multivariable analysis, risk factors for severe COVID-19 among IBD patients included increasing age [adjusted OR (aOR) 1.04, 95%CI: 1.01-1.02], ≥ 2 comorbidities (aOR 2.9, 95%CI: 1.1-7.8), systemic corticosteroids (aOR 6.9, 95%CI: 2.3-20.5), and sulfasalazine or 5-aminosalicylate use (aOR 3.1, 95%CI: 1.3-7.7). TNF antagonist treatment was not associated with severe COVID-19 (aOR 0.9, 95%CI: 0.4-2.2). Of note, only 3 cases of COVID-19 were reported in the age range of 0-9 years, and 26 patients in the range 1-19 years. Only 3 pediatric patients required hospitalization; none required ICU or ventilator support.

IBD AND COVID-19 EXPERT RECOMMENDATIONS

In the weeks and months since the initial outbreak, several GI professional societies and patient support organizations have developed recommendations for the management of IBD in the era of COVID-19[27,35-38]. Expert opinion has focused on several core questions: (1) Are IBD patients at greater risk for contracting COVID-19? (2) How should IBD be managed in an environment of COVID-19? And (3) How should IBD patients with known or suspected COVID-19 be treated? As acknowledged by the authors, much more data is still needed, with the current recommendations drawing heavily upon IBD experience with other infections, and with the mechanisms and the accumulated clinical experience with different IBD therapies. The current consensus is that IBD itself is not a risk factor for COVID-19, but that the risk lies mainly with the use of IBD medications, including corticosteroids, immunomodulators and biologic therapies. While there are active clinical trials using immune therapies to treat the inflammatory storm typical of severe COVID-19, none of the drugs involved are those currently approved for IBD management, and the results of these trials all are still pending. None of the society statements recommend discontinuing 5-ASA/mesalamine therapies. All of the recommendations support continuity of IBD therapy as long as the patient has not acquired SARS-CoV-2 or developed COVID-19, and all of the groups that address endoscopy/surgery suggest postponing any non-urgent procedures. Tables 1 and 2 summarize some key points related to disease management from the recommendations. For detailed clinical management scenarios, we recommend referring to the treatment algorithm provided in the AGA practice update or to the 76 expert consensus statements provided by the IOIBD.

CONCLUSION

Just a few months ago patients with IBD and their providers entered a new and uncertain world dominated daily by the specter of COVID-19. Added to the significant concerns of the general public, facing a highly communicable and sometimes fatal illness, the IBD community carries the additional concerns of a high-risk group. While IBD is characterized by an innate immune dysfunction, there fortunately is no evidence yet to suggest a higher risk for a severe clinical course of COVID-19 conferred by IBD alone. While it is too early to say whether the therapies used for IBD, currently centered around immune suppression/modification, place patients at higher risk of infection itself or severe outcomes of infection, we are hopeful that the rapid accumulation of collaborative data from around the world will begin to provide answers. While the rapidity of data collection is impressive, there remains a significant risk of bias in the cases submitted to "real time" registries that may prevent their generalization to specific populations. It is also not clear whether "risks" of a severe outcome from COVID-19 infection in this population is modified by country specific variables, such as severity of lockdowns, access to care, access to ventilators, threshold for admission to hospitals based on availability of beds, availability of COVID PCR testing, all of which vary by locality and cannot be adjusted for in the final analysis. This leaves a knowledge gap for concentrated data from a single location that minimizes the risk of bias during data collection and variability in outcomes resulting from country specific health care resources. Just as we are increasingly in a world where many of our patients can receive expert care without the risks of leaving their own home, so too does the almost real time collection and analysis of data from around the world offer the promise of rapidly providing answers to those most urgent questions raised by the worldwide IBD community.

Table 1 Summary of expert opinions and guidelines

Organization	IBD treatment, stable disease (No known or suspected COVID-19)		Known or suspected COVID-19
Chinese IBD Society	May continue anti-TNF; May continue vedolizumab; May continue ustekinumab but avoid new IV infusion initiation (to avoid infusion center); Discourage new tofacitinib use in endemic areas; Discourage new or increased dose of immunosuppressant; Postpone elective surgery or endoscopy		Contact physician for temperature over 38 C; Hold immunosuppressant and biologic agents for suspected COVID-19
		SARS-CoV-2 positive testing (without COVID-19 disease)	SARS-CoV-2 positive testing (with COVID-19 disease)
IOIBD	Continue infusions (if center has COVID-19 testing protocol); Reduce or DC prednisone (but not other therapies); Treat moderate to severe IBD (new or relapsing disease) with same therapies as pre-COVID-19; Postpone elective procedures	Uncertain if need to stop anti-TNF; Uncertain if need to stop ustekinumab; Stop tofacitinib; (IBD medications can be restarted after 14 d if the patient has not developed COVID-19)	Stop anti-TNF, ustekinumab, tofacitinib; Stop IMM if on combination therapy; Uncertain if need to stop vedolizumab; (IBD medications stopped may be restarted after COVID-19 symptoms resolve and/or after 2 nasopharyngeal PCR tests are negative
AGA	Continue current IBD therapies; Continue infusions at appropriate infusion centers; Only perform urgent or emergent procedures	Hold thiopurines, methotrexate, and tofacitinib; Delay biologic therapy for 2 wk while monitoring for COVID-19 symptoms	Hold thiopurines, methotrexate, tofacitinib, and biological therapies; (IBD medications may be restarted after complete symptom resolution or when follow up viral testing is negative or serology demonstrates convalescent stage

IBD: Inflammatory bowel disease; COVID-19: Coronavirus disease 2019; TNF: Tumor necrosis factor; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; IOIBD: International Organization for the Study of Inflammatory Bowel Disease; DC: Discontinue; IMM: Immunomodulators; AGA: American Gastroenterological Association.

Table 2 Continued summary of expert opinions and guidelines

	General recommendations	Serious COVID-19 disease risk: Highest risk	Moderate risk	Lowest risk
BSG	Continue current medications; Avoid corticosteroids if possible Observe "shielding" while prednisone dose ≥ 20 mg daily; Initiation of IMM monotherapy not advised; Consider stopping thiopurines in older patients or those with significant comorbidity who are in sustained remission; Consider monotherapy with anti-TNF; Consider adalimumab over infliximab to promote home care; Early use of therapeutic drug monitoring; Do not recommend switching from IV to S/C	IBD and a comorbidity; Hypertension Diabetes; Age ≥ 70 yr; AND one from "Moderate Risk" column OR; Moderate to severely active disease; ≥ 20 mg prednisolone or equivalent; New biologic < 6 wk; Moderate to severely active disease NOT controlled on Moderate risk Rx; Short bowel syndrome ON nutritional support; Requirement for Parenteral nutrition	Anti-TNF monotherapy; Biologic plus immunomodulator in stable patients; Ustekinumab; Vedolizumab; Thiopurines; Methotrexate; Calcineurin inhibitors (tacrolimus or ciclosporin); Janus kinase inhibitors (tofacitinib); Immunosuppressive trial medication; Mycophenolate mofetil; Thalidomide; Prednisolone < 20 mg or equivalent per day	5-ASA users; Rectal therapies; Orally administered topically acting steroids (budesonide or beclometasone); Therapies for bile acid diarrhoea (cholestyramine, colesevelam, colestipol); Antidiarrhoeals (*e.g.*, loperamide); Antibiotics for bacterial overgrowth or perianal disease
CCF	Stay on your medications; Do not skip infusion appointments; Consider rescheduling non urgent endoscopic procedures			

COVID-19: Coronavirus disease 2019; BSG: British society of gastroenterology; IBD: Inflammatory bowel disease; TNF: Tumor Necrosis Factor; IMM: Immunomodulators; ASA: Aminosalicylic acids; CCF: Crohn's and colitis foundation.

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