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JCIMCR OPEN ACCESS Journal of Clinical Images and Medical Case Reports

ISSN 2766-7820

Review Article

Open Access, Volume 2

Inflammatory bowel disease and COVID-19: A review

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Received: Jul 09, 2021
Accepted: Sep 17, 2021
Published: Sep 24, 2021
Archived: www.jcimcr.org

Introduction

The World Health Organization officially declared infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), leading to coronavirus disease 2019 (COVID-19) as a Public Health Emergency of International Concern (PHEIC) on 30 January 2020 and then as a pandemic on March 11, 2020 with reports of infection from most of the countries of the world [1]. COVID-19 has severely disrupted prevention and treatment for noncommunicable diseases. Severe illness can occur in otherwise healthy individuals of any age, but it predominantly occurs in adults with advanced age or certain underlying medical comorbidities [2]. Since the beginning of the health emergency, particular attention has been paid to the management of patients with chronic Inflammatory Bowel Diseases (IBDs) because they frequently are treated with immunosuppressive drugs and therefore potentially are exposed to a greater infectious risk than the general population [3].

Risk of SARS-CoV-2 infection in IBD

It is important for clinicians and patients to be aware if there is a heightened risk of COVID-19 infection in IBD and if it affects the outcomes. The GI tract may be susceptible to SARS-CoV-2 infection because of widely expressed angiotensin-converting enzyme 2 (ACE2) receptors in the intestine [4]. ACE2 is a receptor for SARS-CoV-2 virus, and digestive symptoms associated with SARS-CoV-2 infection may be caused by direct viral attack as well as tissue and organ damage due to the immune response [5]. Staining of tissue specimens from patients with COVID-19 demonstrated that the positive areas were mainly distributed in the cytoplasm of gastric and intestinal epithelial cells and the cilia of glandular epithelial cells [5]. ACE2 receptor appears to be differentially expressed in inflamed IBD mucosa with upregulation in the colon but downregulation in the small intestine [6,7]. SARS-CoV-2 receptor expression also appears to be impacted by IBD medications, with infliximab notably being associated with decreased ACE2 [8].

Burgueño et al recently demonstrated no significant difference in ACE2 or TMPRSS2 expression in colonic organoids derived from patients with ulcerative colitis as compared with controls, supporting that ulcerative colitis alone may not impact risk of COVID-19 infection [9]. However, expression of ACE2 was lower in patients on antitumor necrosis factor drugs, vedolizumab, ustekinumab, and steroids as compared with patients on no immunosuppression [9], which may limit viral entry and subsequent severity. With the current data, there does not appear to be an increased risk of COVID-19 or a more severe evolution of SARS-CoV-2 infection in patients with IBD.

IBD patients with SARS-CoV-2 infection

Initially case series and observational cohort data emerged which reported on identified IBD/COVID-19 patients. A case series from 5 sites in the Basque Country (Spain) reported on 40 cases of IBD (21 hospitalized) with confirmed positive tests for SARS-CoV-2 with median age 59 years, 60% male, 32% Crohn's disease (CD), with 28% on immune therapy, 18% biologic, and 10% systemic corticosteroids [10]. 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.

The incidence of COVID-19 in patients with IBD in the Netherlands compared to the general population was comparable (287.6 versus 330.0 per 100,000 patients, p=0.15) (Derikx et al., 2020). IBD patients in the US Veterans Affairs (VA) healthcare system had a similar incidence of confirmed SARS-CoV-2 compared to the general VA population (0.23% versus 0.20%, p=0.29) (Khan, Patel, Xie, Pernes, et al., 2020). Studies from Italy and Germany showed a similar SARS-Cov2 seroprevalence in IBD patients treated with biological therapy as in general population (Berte' et al., 2020).

In contrast with earlier reports, SARS-CoV-2 infection is not rare in patients with IBD: approximately 10% of the patients in a Spanish IBD unit were diagnosed with suspected or confirmed COVID-19 [11]. Data from 24 Italian IBD referral units found 79 patients with IBD with a diagnosis of COVID-19 through March 29, 2020, 49 of them with PCR confirmation [12]. In the Nancy (France) and Milan (Italy) cohort of 6000 patients with IBD, 15 patients who were SARS-CoV-2 PCR–positive were found with a cumulative incidence of 0.25%, similar to the cumulative incidence in France and Italy at that time (0.17%) [13].

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 [14]. 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 4,958 cases from 67 countries (48.7% men). The primary outcome of interest was severe COVID-19, defined as a composite of ICU admission, ventilator use, and/or death. Overall, two hundred and eight patients (4%) had severe COVID-19 (as determined by physician global assessment), 814 (16%) were hospitalized, and 81 patients died (2% case fatality rate). There were 2842 cases of SARS-CoV-2 infection in Crohn's disease patients and 2084 Ulcerative colitis patients. Similarly, data from the international SECURE-IBD registry for COVID-19 infections reported that only 19% of patients on antitumor necrosis factor monotherapy required hospitalization and 1% died, rates which were lower than those observed for patients on aminosalicylate therapy (46% hospitalized, 7% died).

Table 1: Symptoms of IBD Patients with a Confirmed diagnosis of COVID-19 in the Overall Population [15].

Symptoms	N (%)
Fever	217/449 (48.3)
Cough	209/449 (46.5)
Diarrhea	92/449 (20.5)
Dyspnea	55/449 (10.5)
Nausea	40/449 (8.9)
Abdominal pain	39/449 (8.7)
Vomiting	39/449 (8.7)
Fatigue	39/449 (8.7)
Myalgia	35/449 (7.8)
Dysgeusia	23/449 (5.1)
Sore throat	21/449 (4.7)
Rhinopharyngitis	17/449 (3.8)
Anosmia	12/449 (2.7)
Hypoxemia	12/449 (2.7)
Anorexia	8/449 (1.8)
Ageusia	6/449 (1.3)
Headache	3/449 (0.7)
Chest pain	2/449 (0.4)

COVID-19 symptoms in IBD patients

A recent systematic review reporting the prevalence, clinical characteristics, diagnostic/therapeutic management, and risk factors of IBD patients with a confirmed diagnosis of COVID-19 showed a COVID-19 prevalence of 0.4% in the IBD cohort as shown in Table 1 [15]. COVID-19 was found in more men than women (56.5% vs 39.7%), and patients of all ages, from children to the elderly, were involved, as highlighted in the first reports from China on non-IBD individuals [4]. The most frequent symptoms were fever (217 of 449 [48.3%]), cough (209 [46.5%]), and diarrhea (92 [20.5%]), followed by dyspnea (55 [12.2%]), nausea (40 [8.9%]), and abdominal pain (39 [8.7%]) [55]. In line with general population data, fever (48.3%) and cough (46.5%) were the most frequent symptoms in infected patients with IBD. Interestingly, approximately a fifth of the patients experienced diarrhea. This high prevalence could be related to the influence of the underlying disease on the number of evacuations, justi-

fying the greater percentage of diarrhea in CD and UC patients than in the general population. On the other hand, SARS-CoV-2 has been isolated in the duodenum and rectum, [16] and a higher concentration of fecal calprotectin, a known inflammatory marker, has been found in infected patients with diarrhea compared with those without diarrhea (123.2 vs 17.3 mg/g; P < .001), [17] suggesting that viral gut tropism could worsen inflammatory status and symptoms of IBD patients.

Gubatan et al found 5 of 168 patients with IBD (3%) with positive SARS-CoV-2 testing in Northern California and found that advanced age (>age 66 years) is independently associated with an increased risk of contracting COVID-19 [18]. The most common symptom in the whole cohort, including 1160 individuals with or without IBD who were SARS-CoV-2-positive, was coughing (63%), followed by sore throat (41%), dyspnea (37.5%), fever (36%), and body pain (32%), with 19% of patients presenting with gastrointestinal symptoms (diarrhea 15.5%, abdominal pain 13%, and nausea/vomiting 9%). In the review of Mao et al combining data from 29 studies (N=6064), the prevalence of digestive symptoms in patients with COVID-19 was 15% (95% CI, 10%-21%), with symptoms such as loss of appetite found in 21% of patients, diarrhea in 9%, nausea or vomiting in 7%, and abdominal pain in 3% [19]. They also found that patients with gastrointestinal symptoms had an increased risk of severe COVID-19 compared with those without gastrointestinal symptoms (OR, 4.0; 95% CI, 1.5-10.6), although the risk of severe COVID-19 was not increased in patients with digestive comorbidities compared with patients without digestive comorbidities (OR, 0.6; 95% CI, 0.15-2.2).

Younger age in patients with IBD with a lower rate of comorbidities could be associated with a lower risk of severe COVID-19. In contrast, older age in patients with IBD is associated with a higher risk of hospitalization and death (Table 2). Taxonera et al reported 12 laboratory-confirmed patients with COVID-19 found in 1918 patients with IBD in an IBD center in Madrid, without an increased risk of infection or associated mortality ratio compared with the general population [20]. Allocca et al found that 5 of 15 (33%) patients with IBD were hospitalized because of SARS-CoV-2 infection, but none of them required intensive care or died [13].

Table 2: Outcomes by age from secure IBD [2].

Characteristic	Total N	Hospitalized (n, %)	Death (n, %)
Overall	5,454	864 16%	89 2%
Age			
0-9 years	33	3 9%	0 0%
10-19 years	570	25 4%	0 0%
20-29 years	1,152	93 8%	1 1%
30-39 years	1,127	118 10%	3 0%
40-49 years	978	139 14%	3 0%
50-59 years	809	181 22%	13 2%
60-69 years	442	157 36%	24 5%
70-79 years	190	83 44%	19 10%
>=80 years	123	61 50%	25 20%

IBD medications and COVID-19 outcomes

A prospective observational cohort study on consecutive patients with an established IBD diagnosis and confirmed COVID-19 from a combined 24 IBD referral centers in Italy, affiliated with the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD) was published [12]. 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). They found no association between corticosteroid (OR, 4.94; 95% CI, 0.95–25.55), thiopurine (OR, 1.21; 95% CI, 0.22–6.40), anti-TNF (OR, 1.18; 95% CI, 0.47–2.97), or vedolizumab (OR, 0.53; 95% CI, 0.16–1.73) use and risk of COVID-related pneumonia. There was also no association between corticosteroid or anti-TNF use and death. 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).

Several studies have been published examining the impact of IBD diagnosis on outcomes after COVID-19 disease [21]. These have shown that immunosuppression is not associated with worse outcomes among those with COVID-19 disease and that outcomes in patients with IBD are comparable with those without underlying IBD. Results from the international registry showed corticosteroids, but not TNF antagonists, are associated with adverse covid-19 outcomes in patients with inflammatory bowel diseases [22].

A study to evaluate risk of disease related to drug exposure used the American Veterans affairs cohort and examined thiopurine and antitumor necrosis factor (anti-TNF) exposure [23]. The study consisted predominantly of older (mean age 63 years) male patients and it found that the use of anti-TNFs or thiopurines was not associated with the development of COVID-19 infection. Discovering the real number of infected patients remains a global challenge because of the limited availability of PCR and serology tests during the pandemic, the possibility of false results, and the still uncertain interpretation of serology results.

In a large, multi-institution cohort study immunosuppressive treatment for management of IBD was not associated with an increase in risk of COVID-19 infection [24]. Additionally, there was no effect of immunosuppression on severity of COVID-19, including need for hospitalization and mortality. In contrast, other recognized comorbidities, particularly obesity [25], increased risk of development of COVID-19 infection and severe disease in this population, consistent with prior studies [26].

It is plausible that because of the perceived higher risk, patients on systemic immunosuppression may have practiced stricter quarantine measures and self-isolated more rigorously than those not on such treatments, decreasing their risk of viral infection. COVID-19 has been associated with a cytokine storm, and patients with severe disease often demonstrate markedly elevated inflammatory cytokines such as interleukin (IL)-6 on presentation [27]. Indeed, in addition to antiviral therapy, one of the avenues being explored for COVID-19 treatment is target-

ed immunosuppression, including IL-6 antagonists [28-30] with some even proposing a role for steroids or TNF-antagonists [31].

It is plausible and indeed likely that the threshold for testing for COVID-19 is lower in those with immunosuppression since it may more directly impact interruption of such therapy. This lower threshold for testing would introduce a bias towards higher estimate of SARS-COV-2 infection risk in immunosuppressed population. In contrast, testing may be reserved for more severe illness in those not on immunosuppression and thus not deemed high risk. This would bias away from demonstrating harm with immunosuppressive drugs.

IBD and COVID-19 expert recommendations

After the outbreak began, several GI professional societies and patient support organizations have developed recommendations for the management of IBD in the era of COVID-19. Because of the paucity of data recommendations were initially based on expert opinion. However, as the pandemic unfolded around the world, accumulated data and clinical experience helped shape the latest recommendations form the societies. The current consensus is that IBD patients do not appear at increased risk of contracting COVID-19. The risk of severe covid-19 lies primarily with older age and comorbidities [32]. In addition, steroids and immunomodulators may be associated with higher risk for COVID-19 and consequently most of the eminent societies recommend withholding these drugs on a case-by-case basis. However anti-TNFs and other biologics appear to be low risk and the societies recommend they should be continued in the COVID-19 era.

Table 3: Summary of expert opinions and guidelines [33-35].

IBD drugs	BSG	AGA	ECCO/IOIBD
Corticosteroids	Avoid Prednisolone ≥ 20 mg. Rapid tapering (10 mg/week) should be considered where possible. Consider Budesonide for flare	Taper Corticosteroids/switch to Budesonide	Taper or discontinue Prednisolone
Immunomodulators	Don't initiate monotherapy. May be stopped in >60 years or with comorbidities in remission.	Hold thiopurines, methotrexate.	Discontinue thiopurines, methotrexate for 2 weeks. If hospitalized, consider IV Cyclosporine for UC
Anti-TNF therapy	Consider initiation with monotherapy (preferably Adalimumab)	Delay biologics at least 2 weeks to see if COVID-19 resolves.	Discontinue or delay dosing of biologics for 2 weeks
Anti-interleukin-12/23p40 therapy (ustekinumab)	No current evidence of increased risk of COVID-19 infection.	Delay biologics at least 2 weeks to see if COVID-19 resolves.	Discontinue or delay dosing of biologics for 2 weeks
Anti-α4β7 integrin therapy (vedolizumab	No current evidence of increased risk of COVID-19 infection.	Delay biologics at least 2 weeks to see if COVID-19 resolves.	Discontinue or delay dosing of biologics for 2 weeks
Janus kinase inhibitors (tofacitinib)	No current evidence of increased risk of COVID-19 infection.	Hold	Discontinue
5-Aminosalicylic acid derivatives (mesalazine)	No current evidence of increased risk of COVID-19 infection. Optimize 5-ASA or topical(rectal) therapies.	Continue 5-ASA, rectal therapies, enteral nutrition	Continue 5-ASA, rectal therapies

IBD and COVID-19 vaccine

Patients with IBD should be vaccinated against SARS-CoV-2. SARS-CoV-2 vaccines including messenger RNA vaccines, replication-incompetent vector vaccines, inactivated vaccines and recombinant vaccines are safe to administer to patients with IBD [36]. SARS-CoV-2 vaccination should not be deferred because a patient with IBD is receiving immune-modifying therapies. Patients with IBD vaccinated with SARS-CoV-2 should be counselled that vaccine efficacy may be decreased when receiving systemic corticosteroids. This includes biologics, but also thiopurines, methotrexate or steroids. Still, vaccination should not be deferred.

Conclusions

IBD patients do not appear at increased risk of contracting COVID-19. However, a subgroup of IBD patients with COVID-19 may be at increased risk of adverse events. The risk is primarily driven by older age, co-morbidities, and steroid use. Thiopurines and combination therapy may increase risk as well. Anti-TNFs and other biologics appear to be low risk and should be continued in the COVID-19 era. IBD patients who develop COVID-19 should be managed on a case-by-case basis. The general recommendation is to de-escalate combination therapy and to taper steroids. In difficult to control patients, one can consider not delaying or stopping biologics if the patient is asymptomatic or having mild COVID-19 symptoms.

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