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Review Article

Impact of COVID-19 on Patients with Inflammatory Bowel Disease

Paula A. Ambrose and Wendy A. Goodman*

Department of Pathology, Case Western Reserve University School of Medicine, OH, USA

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in Wuhan, China, in late 2019. Responsible for the ongoing coronavirus disease 2019 (COVID-19) pandemic, SARS-CoV-2 is one of three structurally similar beta-coronaviruses that can cause a strong upregulation of cytokines referred to as cytokine release syndrome (CRS). Unresolved CRS leads to respiratory symptoms, including pneumonia, and in more severe cases, acute respiratory distress syndrome (ARDS). Although COVID-19 is widely known for these hallmark respiratory symptoms, it also impacts the gut, causing gastrointestinal (GI) tract inflammation and diarrhea. COVID-19's GI symptoms may be due to the high intestinal expression of angiotensin converting enzyme-2 receptors, which are for the binding of SARS-CoV-2 viral particles. Reports have shown that SARS-CoV-2 can be passed through fecal matter, with one study finding that 48.1% of COVID-19 patients expressed viral SARS-CoV-2 mRNA in their stool. Given that the GI tract is a target tissue affected by COVID-19, this causes concern for those with underlying GI pathologies, such as inflammatory bowel disease (IBD). Regrettably, there have been only limited studies on the impact of COVID-19 on gut health, and the impact of COVID-19 on intestinal inflammation among IBD patients remains unclear. In particular, questions regarding susceptibility to SARS-CoV-2 infection, clinical impact of COVID-19 on IBD, and the potential influence of age, sex, and immunosuppressant medications are still poorly understood. An improved understanding of these issues is needed to address the unique risks of COVID-19 among IBD patients, as well as the potential impact of SARS-CoV-2 on the host intestinal microbiota.

Introduction

Coronaviruses undergo frequent mutations, leading to increased genetic diversity and recombination capabilities, frequent human-animal host interactions, and relatively high rates of human infectivity.[1–3] Severe acute respiratory syndrome coronavirus 2, or SARS-CoV-2, is a novel beta-coronavirus that was first identified in Wuhan, China, in late December of 2019 and subsequently caused a worldwide pandemic.[4] The World Health Organization (WHO) officially designated the new coronavirus strain for a pandemic on March 11, 2020. As of August 1, 2021, this pandemic has reached approximately 200 countries and resulted in more than 198 million cases (coronavirus disease 2019, COVID-19, dashboard).[5]

Infection with SARS-CoV-2, the virus causing COVID-19, leads to the rapid release of cytokines, chemokines, and other pro-inflammatory mediators,[6,7] a process known as cytokine release syndrome (CRS).[8] Similar to genetically-related coronaviruses, SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) 2012,[9–11] SARS-CoV-2 infection results in damaging respiratory symptoms, including cough, shortness of breath, chest tightness, sore throat, and nasal congestion, pneumonia, acute respiratory distress syndrome (ARDS). The non-respiratory symptoms include fever, fatigue, myalgia, dyspnea, abdominal pain, loss of appetite, nausea, vomiting, and diarrhea. In the most severe cases, COVID-19 can lead to sepsis, multi-organ dysfunction, and death.[7,12–14]

SARS-CoV-2 enters human host cells through interactions of its

Keywords: Inflammatory bowel disease; COVID-19; SARS-CoV-2; ACE-2; Crohn's disease; Ulcerative colitis.

Abbreviations: ACE, angiotensin converting enzyme; CD, Crohn's disease; COVID-19, coronavirus disease 2019; CRS, cytokine release syndrome; GI, gastrointestinal; IBD, inflammatory bowel disease; ICU, intensive care unit; IEC, intestinal epithelial cells; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF, tumor necrosis factor; UC, ulcerative Colitis; VDZ, vedolizumab.

***Correspondence to:** Wendy A. Goodman, Department of Pathology, Case Western Reserve University School of Medicine, OH 44106, USA. ORCID: https://orcid.org/0000-0002-6864-0384. Tel: +1 216368-3920, Fax: +1 216-368-0494, E-mail: wag@case.edu

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surface spike glycoprotein ("S" protein) with the binding domain of the host-expressed angiotensin converting enzyme 2 (ACE)-2 receptor,[15–17] a broadly expressed metallopeptidase. In particular, ACE-2 is highly expressed by airway epithelial cells and intestinal enterocytes,[18,19] leading to high rates of SARS-CoV-2 infection in the respiratory tract and intestine.[20–23] Because of this, a significant number of patients experience gastrointestinal (GI) symptoms.[24–27]

Because SARS-CoV-2 directly infects intestinal enterocytes in the gut, it is critical to understand how it may influence the clinical course of chronic intestinal diseases, such as inflammatory bowel disease (IBD). IBD is comprised of two primary diseases, Crohn's disease (CD) and ulcerative colitis (UC), with distinct pathophysiologies, as well as other, non-classified forms.[28] Inflammation from UC affects the superficial mucosa of the large intestine, generally occurs in a continuous pattern from the rectum to proximal colon, and is characterized by erythema, altered vascularization, bleeding, granularity, erosions, and ulcerations.[29,30] In contrast, CD can impact any portion of the GI tract, leading to chronic, discontinuous, transmural inflammation that can reach the muscularis.[31,32] Both UC and CD are mixed autoimmune/autoinflammatory conditions with strong genetic and environmental susceptibilities. They can both cause chronic, relapsing and remitting inflammation in the GI tract, ultimately leading to irreversible tissue damage.[28] It is estimated that 6.8 million people are affected by IBD worldwide.[33] Medications for IBD include several classes of immunosuppressants, which can lead to increased susceptibility to opportunistic infections.[34,35]

How COVID-19 affects those with IBD is still unclear, but several studies have detected SARS-CoV2 viral RNA in stool samples obtained from COVID-19 infected patients (from 55 to 67%).[36–38] This further supports SARS-CoV-2 infection of cells in the GI tract, which are often damaged in IBD patients. Thus, COVID-19 infection in IBD patients is likely to exacerbate pre-existing intestinal inflammation and GI symptoms.

This review will explore the interactions between SARS-CoV-2 infection and intestinal inflammation in the IBD population, including issues of how age, sex, pregnancy, medication status, and concomitant comorbidities may impact the clinical course of COVID-19 in IBD patients.

Interaction of SARS-CoV-2 with intestinal ACE-2

A significant proportion of COVID-19 patients experience digestive symptoms, suggesting that SARS-CoV-2 may directly affect the GI tract.[39] Under homeostatic conditions, the ACE-2 receptor and its interactions with components of the renin/angiotensin system are responsible for maintaining gut homeostasis and the physical integrity of the intestinal mucosa.[40] In healthy individuals, ACE-2 is most highly expressed in the intestinal epithelial cells (IECs) of the small intestine,[41] and it is moderately expressed in the submucosal layers of the colon.[23,42–44]

The ability of SARS-CoV-2 to infect and replicate within ACE-2-expressing intestinal enterocytes has been observed in multiple human and animal studies (reviewed in[20]). Among the experimental evidence supporting viral infection of IECs, *in vitro* studies have shown that SARS-CoV-2 can effectively enter and replicate in colonic epithelial cell lines.[45,46] Several studies have also confirmed SARS-CoV-2 replication in primary IECs using small intestinal organoid models.[44,47,48] Collectively, these studies indicate that there is efficient and direct interaction of SARS-CoV-2 with ACE-2-expressing cells in the GI tract.

SARS-CoV-2 infection of the intestine causes injury to host cells, including epithelial enterocytes, and exacerbates the epithelial damage and inflammation already present in patients with active forms of IBD. In particular, recent studies have shown COVID19-associated damage to colonic enterocytes, which leads to infiltration of antibody-secreting plasma cells and interstitial edema.[22,49] Other studies have shown increased levels of calprotectin, a biomarker of intestinal inflammation,[50] in fecal samples from COVID-19 patients who experience diarrhea compared to those who do not.[51–53] Interleukin 18 (IL-18), a pro-inflammatory cytokine usually upregulated in human and experimental IBD,[54–57] is elevated in feces and serum samples from COVID-19 infected individuals compared to the general population.[58] This further suggests that SARS-CoV-2 infection can worsen pre-existing intestinal inflammation if the individual is experiencing an active form of IBD when infected.[59,60]

Several studies have suggested that increased expression of ACE-2 may be correlated with worse clinical outcomes of COVID-19, as well as increased risk of infection.[61–63] However, the potential regulation of ACE-2 expression and function in response to chronic intestinal inflammation is not well-understood.

Recent studies have examined potential alterations in the levels of intestinal ACE-2 expression in patients with IBD. One of them, a large, multi-center study of >800 IBD patients and >100 non-IBD controls, found that intestinal ACE-2 mRNA expression increased in colonic samples from patients with active UC, but decreased in small intestinal samples from patients with active CD.[64] In both cases, ACE-2 expression was normalized in patients responding to cytokine-directed therapies. These data suggest that cytokine-driven intestinal inflammation may impact ACE-2 expression, and that ACE-2 may be differentially regulated and have distinct functions in the small intestine versus the colon.[64] A separate study comprising 129 IBD patients in Germany supported these findings, as mRNA and protein levels of ACE-2 were reduced in inflamed CD patient ilea.[65] Intriguingly, this study also found that toll-like receptor (TLR)-dependent signaling regulated intestinal ACE-2 expression, suggesting that microbes, such as *Citrobacter rodentium* may regulate ACE-2 expression in the GI tract.[65] Increasing evidence indicates that SARS-CoV-2 infection is associated with alterations in the intestinal microbiome.[58,66] As an example, *Coprobacillus*, a gut bacterium that has been associated with severe COVID-19, was recently shown to increase ACE-2 expression in the intestine of mice, potentially contributing to the worsening of inflammation in the GI tract.[67] Collectively, these studies suggest the potential for reciprocal viral/microbial regulatory networks in SARS-CoV-2-infected intestinal tissues.

Interestingly, IBD patients have increased levels of soluble ACE-2, a competitor for SARS-CoV-2 binding,[68] in their peripheral blood;[69] this may confer some levels of protection from direct SARS-CoV-2 infection of the GI tract. Taken together, these findings suggest that ACE-2 expression may be regulated by SARS-CoV-2 viral entry, and that the up-regulated expression of ACE-2 is an important contributor to COVID-19 clinical outcomes. More studies are needed to further investigate the potential for IEC damage in both types of primary IBD patients as well as the general population in response to COVID-19 infection.

Direct and indirect effects of COVID-19 in IBD patients

Immunomodulatory agents, including targeted biologics, are commonly used for the long-term management of IBD. Clinical guidance for IBD patients during the COVID-19 pandemic includes remaining on existing therapies to avoid disease flares (crohnscolitisfoundation.org); however, long-term use of immunosuppressant medications may lead to an increased susceptibility to infections from fungal, parasitic, viral, and bacterial pathogens.[34,35,70] These factors raise concern regarding potentially increased susceptibility to SARS-CoV-2 within the IBD population.[71] However, most studies to date have observed comparable risk of COVID-19 among the IBD and non-IBD populations,[72–75] suggesting that IBD itself does not confer an increased risk of COVID-19 infection.

Multiple studies have identified male sex and advanced age (>60 years of age) as independent risk factors for COVID-19 infection, as well as severe morbidity and high mortality in both the general population and IBD patients.[76–79] To determine the potential effects of sex and age on the risk of COVID-19 among the IBD population, a retrospective cohort study was performed using analytic data from 30,911 IBD patients enrolled in the Veterans Affairs Healthcare System.[78] The majority of the cohort was male (90.9%), with a median age of 65, and 78.6% Caucasian. There were 58% of the cohort with UC and 42% with CD. There were also 649 patients (2.1% of the total IBD cohort) diagnosed with SARS-CoV-2 infection during a median follow-up period of 10.7 months.[78] The study found that the majority of SARS-CoV-2-infected IBD patients were above the age of 65 and male; however, this was most likely due to the demographic breakdown of this cohort.

In contrast to frequent infections among older adults, COVID-19 has been known to affect children and adolescent populations the least of all age groups.[80] In a cohort study by Ludvigsson et al., less than 1 in 1,000 pediatric IBD patients (<18 years old) was admitted to the hospital for COVID-19.[79] However, pediatric IBD still led to an increased risk for COVID-19 hospitalization by a factor of 2.93 (incidence rate [95% CI] per 1,000 person-years (PY): 1.8 [0.4–3.3]) when matched with the general population (incidence rate [95% CI] per 1,000 PY: 0.6 [0.2–1.0]).[79]

In addition to advanced age, male sex, and medication-associated immunosuppression, conditions including obesity, diabetes, peripheral vascular disease, chronic kidney disease, and chronic obstructive pulmonary disease are also significant risk factors for SARS-CoV-2 infection.[81–86] Many of these conditions are common comorbidities in IBD patients,[72,87] potentially increasing these individuals' risk of contracting COVID-19 or developing a more severe clinical course. A recent study of 79 IBD patients with confirmed SARS-CoV-2 infections identified IBD-associated hypertension as a significant risk factor for COVID-19, in addition to age >65 years and the presence of active disease.[76]

Although most studies have found that individuals with IBD are not at increased risk of contracting COVID-19, IBD does likely increase the severity of COVID-19, particularly in terms of hospitalization and pneumonia.[76,77,79] However, the risk for especially severe outcomes, such as admission to the intensive care unit (ICU), ventilation, and death, appears to be similar to that of the general population.[76,77,79] The largest study to date of IBD patients with COVID-19, the SECURE-IBD cohort study, reported that one-third of the total patient cohort (476 out of 1,760 individuals) was hospitalized due to COVID-19 complications, and that 63 patients died.[77] In a smaller cohort study, 46% of IBD patients infected with SARS-CoV-2 developed pneumonia; 44% of these individuals required respiratory assistance, 28% had to be hospitalized, and 16% died.[76] Hospitalization and the need for respiratory assistance were observed mostly among patients with active disease (16% of the overall cohort) compared to those whose IBD was in remission ($p<0.001$ for both).[76] In addition to hospital reporting and testing, one point that Khan et al. mentions is that at the time of the SECURE-IBD studies, hospitals may have only reported their most severe cases (ICU, ventilation, death). All of these factors could have influenced potentially inaccurate numbers of cases amongst the IBD population.

Since primary IBD encompasses both CD and UC, it is reasonable to ask whether one or the other affects COVID-19 differently in terms of severity. Ludvigsson et al. observed a similar risk of hospitalization as well as the risk of developing severe COVID-19 among UC and CD patients.[79] In contrast, Bezzio et al. found that UC was associated with worse outcomes, particularly for COVID-19-related pneumonia, compared to CD.[76] A potential explanation for differing results between these studies could be that the majority of CD patients, but not UC patients, in the Ludvigsson study had an additional autoimmune co-morbidity, potentially contributing to an even greater risk of SARS-CoV-2 infection as well as significantly worse clinical outcomes. Interestingly, the study by Bezzio et al. found that 100% of UC patients enrolled in treatment for severe acute colitis flares tested positive for COVID-19 prior to treatment, and that all of these individuals eventually developed COVID-19 pneumonia.[76] These findings, although representing only a small sample size, suggest that COVID-19 may worsen intestinal inflammation in UC patients.

In conclusion, studies have not consistently revealed any significant differences in the prevalence of SARS-CoV-2 infection among individuals in the IBD patient population compared to the general population. However, IBD patients may be at increased risk for hospitalization and severe COVID-19, particularly if they have active disease at the time of SARS-CoV-2 infection. There is a clear need for additional studies that include more diverse patient cohorts before any definitive conclusions can be drawn.

Impact of therapeutics on IBD patients with COVID-19

Pharmacological agents used in the treatment of IBD are immunomodulatory and include biologics, such as vedolizumab (VDZ, targeting the α4β7 integrin), ustekinumab and tofacitinib; cyclosporine; 5-aminosalicylic acid (5-ASA, i.e. mesalazine); corticosteroids; thiopurines; and methotrexate (MTX).[88–90] These agents are broadly immunosuppressive, leaving IBD patients at risk for adverse outcomes of infection.[34,35,78] Nevertheless, most studies have found that the rate of SARS-CoV-2 infection is comparable between the general population, the IBD population, and IBD patients receiving biologics, corticosteroids, or combination therapies.[76,91]

Several studies have asked if common IBD medications, including biologics, may affect the clinical course of COVID-19. In the large-scale VAHS study, COVID-19-associated hospitalization was highest among patients co-treated with anti-TNF and MTX (incidence rate of 7.42 per 10,000 person-years, 95% CI 2.79 to 19.77).[78] The majority of IBD patients who were administered VDZ were also co-administered corticosteroids[78] and therefore it is difficult to interpret if the risk of infection increased due to corticosteroids or due to VDZ independently. In a separate study, corticosteroid use among IBD patients increased the risk of COVID-19-associated pneumonia, especially when the patient had active inflammation.[76] Interestingly, Khan et al. also determined that IBD patients who were not on medication were surprisingly more prone to severe COVID-19 compared to those on mesalazine.[78] This finding contradicts the SECURE-IBD study that determined that those on mesalazine were more prone to severe COVID-19 outcomes,[77] highlighting the need for larger-scale studies with expanded demographic data.

Interestingly, a recent study found that anti-TNF therapeutics as well as VDZ are associated with lower antibody levels following either Pfizer-BioNTech or NIH-Moderna COVID-19 vaccination. This suggests that IBD patients receiving these therapies may exhibit reduced vaccine efficiency.[92] In this study, sero-prevalence tests for antibodies against SARS-CoV-2 S and RBD proteins were compared among healthy controls and IBD patients receiving either COVID-19 mRNA vaccine. There were 84.6% of the IBD cohort with sufficient levels of both anti-RBD and anti-S antibodies, indicating that for the majority of IBD patients, vaccine efficacy was not significantly affected by their medications.[92] However, lower sero-prevalence index levels were observed in IBD patients who were taking anti-TNF (anti-RBD total Ig: p=0.0299) and VDZ (anti-RBD total Ig: p=0.0069, anti-RBD IgG: p=0.045, and anti-S IgG: p=0.0043), compared to controls.

Recently, the American Gastroenterological Association and the European Crohn's and Colitis Organization highly advise that IBD patients stop or reduce their use of corticosteroids during the pandemic as more research has been eluding to their association with severe COVID-19 clinical outcomes, such as ventilation, ICU, and death.[93,94] In contrast, the WHO recommends corticosteroid use only for patients with severe COVID-19, as steroid use in non-severe disease increases the risk of developing severe disease (reviewed in[95]). More studies need to be conducted on the effects of immunosuppressant use at different time points in COVID-19 before, during, and after treatment in order to better understand how IBD medication can affect COVID-19 severity in IBD patients.

Interestingly, a recent clinical trial sponsored by the University of Oxford (RECOVERY trial, NCT04381936) found that low dosages of the glucocorticoid receptor-activating corticosteroid, dexamethasone (DEX), reduced death from COVID-19 in up to 1/3 of hospitalized patients experiencing severe respiratory symptoms.[96] However, corticosteroids are the medication class most often associated with greater disease severity among IBD patients with COVID-19.[76–78] Few studies have compared the outcomes for patients who were given corticosteroids *before* versus *after* contracting COVID-19, or at different time points in COVID-19 treatment, potentially accounting for disparate results between the RECOVERY trial and other published studies.[77,78]

IBD, pregnancy, and COVID-19

Women are more prone to infection during pregnancy and unrestrained intestinal inflammation during pregnancy is highly associated with adverse fetal outcomes.[97,98] Therefore, avoidance of chronic infections, particularly intrauterine infections, is crucial for successful pregnancies.[99–101] ACE-2 receptors are not only found in the intestinal and respiratory tracts, but also in the uterine endometrium.[102] Despite the expression of endometrial ACE-2, pregnancy itself does not appear to be associated with an increased risk of contracting COVID-19.[103]

Among the general (non-IBD) population, pregnant women with COVID-19 during the third trimester have an increased risk of being hospitalized.[104] Another study found that compared to the general population, pregnant women with COVID-19 were five times more likely to be admitted to the ICU during the second half of pregnancy.[105] Collectively, these studies indicate that SARS-CoV-2 infection during pregnancy, specifically during the third trimester, is particularly deleterious for pregnant women.

Relatively few studies have been conducted on how SARS-CoV-2 infection affects IBD pregnancies. In a study by Selinger et al., a cohort of pregnant women with IBD was followed and observed to have low incidence rates of COVID-19 and low adverse pregnancy outcomes.[106] Female IBD patients at reproductive age are routinely counseled to plan pregnancies for times when their IBD symptoms are in remission, and therefore, pregnant IBD patients who contract COVID-19 are unlikely to have active disease. Regardless, low rates of SARS-CoV-2 infectivity and minimal adverse outcomes may be due to pregnant IBD patients being particularly cautious of social interaction during the pandemic, thereby limiting exposure risk.

The question of whether pregnant IBD patients should continue corticosteroid use during the COVID-19 pandemic is controversial. Cyclosporine is of particular concern since it crosses the placenta during pregnancy and is detectable in neonatal serum samples.[107] Cyclosporine is frequently considered a "last resort" therapy for pregnant COVID-19 patients since it has been long-associated with hypertension[108] and is also known to increase risk of pregnancy complications, including gestational diabetes, pre-term birth, and low birth weight.[109] In a recent case report, a 26-year-old pregnant UC patient experienced acute disease flares and was treated with intravenous cyclosporine and steroid, then later tapered to oral corticosteroids.[109] Her symptoms reemerged every time when she was put on oral corticosteroids and she was admitted to the hospital three times. On the third admission, she had severe chest pain and tested positive for COVID-19. She discontinued corticosteroids and re-started IV cyclosporine; however, by day nine of her third admission, she had a spontaneous abortion. Although larger-scale studies are clearly warranted, this case highlights the potential danger of cyclosporine use in pregnant IBD patients after COVID-19 diagnosis.[110]

Future directions

Although we understand far more about the course of COVID-19 in IBD patients than we did at the outset of the pandemic, more work needs to be done. Higher levels of serum soluble ACE-2 (i.e., IBD patients) and estrogen (i.e. in women) may have a potential protective effect against SARS-CoV-2 infection due to the ability to control viral entry and replication. Unquestionably, more research is warranted and is necessary to better understand the complicated interactions between SARS-CoV-2, intestinal ACE-2 receptor, and IBD.

Conclusions

Based on recent studies and because SARS-CoV-2 is still a novel virus, there appear to be no significant safety concerns for IBD patients taking immunomodulatory treatments. The risk of SARS-CoV-2 infection for the general IBD population without additional comorbidities is not significantly increased; however, active IBD patients with SARS-CoV-2 infection are strongly associated with severe COVID-19 pneumonia. Those with active IBD remain most at-risk for hospitalization, but there is no increased risk of death.[76,78,79] However, there appears to be an inherent risk in those patients who are particularly immunocompromised, such as those who are pregnant, of advanced age, or with significant comorbidities. Until more data is available, treatment options such as corticosteroids should be avoided for COVID-19 treatment in those populations as there is some evidence that the treatment increases the risk for severe COVID-19. As the proportion of vaccinated people increases, some of these concerns may be mitigated; however, more research is needed regarding vaccine efficacy among immunocompromised patients to better understand its safety and efficacy.

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Conflict of interest

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Author contributions

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