The Impact of COVID-19 in Gastroenterology and Hepatology

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Abstract: The 2019 coronavirus disease (COVID-19), an airborne infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in a global pandemic. SARS-CoV-2 relies on the angiotensin-converting enzyme 2 receptor for cellular entry and the abundance of this receptor in the gastrointestinal (GI) tract may help explain the GI manifestations, including dysgeusia, nausea, vomiting, diarrhea, and abdominal pain, present in over 40% of infected patients. GI tract involvement also raises the concern for oral-fecal transmission which is poorly understood. Outcome studies in COVID-19 patients with preexisting liver disease and inflammatory bowel disease show predominantly mild transaminase elevations and no increased risk from the use of biological agents in inflammatory bowel disease patients. High-dose corticosteroids, however, should be avoided. As endoscopic procedures are aerosol-generating, modifications to clinical practice is necessary to minimize the spread of COVID-19. We have reviewed current literature to describe the impact of COVID-19 in gastroenterology and hepatology as well as targets of future research.

Key Words: COVID-19, gastroenterology, hepatology, inflammatory bowel disease, endoscopy practice

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On March 11, 2020, the World Health Organization (WHO) declared the 2019 coronavirus disease (COVID-19) outbreak a global pandemic.[1] The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) likely entered the human population via animal exposure at a live food market in Wuhan, China. After 1 year since emergence, there have been >77 million cases of COVID-19 worldwide, including 18 million in the United States.[2] SARS-CoV-2 infections can result in a mild to severe respiratory disease, termed COVID-19, and can lead to a cytokine storm. COVID-19 affects all age groups with an estimated mortality of 1.5% to 3%, totaling 1.7 million deaths to date across the globe.[3]

SARS-CoV-2, like the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV), belongs to the β-coronavirus lineage and has a 70% and 40% genetic overlap with the SARS-CoV and MERS-CoV, respectively.[4] The angiotensin-converting enzyme 2 (ACE2) has been identified as the functional receptor necessary for SARS-CoV and SARS-CoV-2 cellular entry.[5] ACE2 expression is widespread throughout the human body including the oral and nasopharyngeal mucosa, lungs, kidney, spleen, small intestine, colon, liver, and cerebrum, with a 100-fold higher expression in the colon compared with the lungs.[6] Therefore, it is not surprising that an initially reported 40% to 70% of patients with COVID-19 have gastrointestinal (GI) symptoms, with 6% to 21% of SARS-CoV-2 infections presenting with GI symptoms only.[6–9]

COVID-19 is now a public health emergency, and understanding of its impact directly and indirectly on our patients is highly relevant to GI clinical practice. We conducted an online literature search between October to December 2020 and created this review that seeks to describe the GI manifestations of SARS-CoV-2 infections, impact on liver disease and transplant, inflammatory bowel disease (IBD) and endoscopic practice, as well as future research directions.

GENERAL GASTROENTEROLOGY

Symptoms of COVID-19 Infections in the GI Tract

GI symptoms of SARS-CoV-2 infections have been reported since the initial outbreak of the SARS-CoV-2 virus in Wuhan, China in December 2019 (Table 1). Epidemiological studies in China found 41.6% of COVID-19 patients suffered from nausea and vomiting, and 17.2% suffered diarrhea,[10] with similar rates reported in later retrospective and prospective studies.[7,11,13] However, a meta-analysis of 47 studies comprising >10,000 patients conducted by the American Gastroenterology Association (AGA) reports the prevalence of GI symptoms (diarrhea, nausea, vomiting, and abdominal pain) to be <10% in COVID-19 patients outside of China. Isolated GI symptoms can be the initial presentation in individuals with SARS-CoV-2 infections and occurs in an estimated 6% to 21% of cases.[10,13] Diarrhea

TABLE 1. The Prevalence of Gastrointestinal Symptoms and Complications in Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Infections

Symptom/Complication	Prevalence (%)	References
Nausea	7.8-41.6	7,10,11
Emesis	7.8-10	7,11
Anorexia	51	7
Dysgeusia/ageusia	30-49.8	7,12
Diarrhea	7.7-37.9	7,10,11,13
Abdominal pain	2.7-3.1	7,11
Isolated gastrointestinal symptoms	6-21	10,13
Elevated liver enzymes	14-53	11,14–16
Acute liver failure	0	17
Small bowel stenosis	Single case report	18
Hemorrhagic colitis	Single case report	19
Esophageal mucosal disruption	Single case report	12

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associated with COVID-19 infection has a median duration of 4 days,[20,21] with patients having up to 5 to 8 bowel movements per day.[22] Diarrhea appears to be ameliorated with antiviral therapy (oral lopinavir and ritonavir), supporting the connection between symptoms and SARS-CoV-2 infection of the GI tract.[23] The presence of diarrhea appears to be associated with increased severity of COVID-19 disease.[8,10,17] Treatment of diarrhea from SARS-CoV-2 infections is primarily supportive; hydration as well as electrolyte repletion are recommend.[20] Although treating COVID-19 with oral lopinavir and ritonavir improves diarrhea, there is no literature to support their use for the treatment of diarrhea alone.[23] There is also no literature to support the efficacy of antidiarrheal medications nor its effect on the duration of viral shedding.

Dysgeusia and ageusia (abnormal and absent sense of taste) are known symptoms of common viral illnesses as the nares and oral cavity are known points of viral inoculation. A pooled analysis of 5 studies, including 817 patients, reported a dysgeusia and ageusia prevalence of 49.8% in COVID-19 patients.[12] While patient reporting of gustatory and olfactory symptoms is subjective, the high prevalence of these symptoms has led to their use as screening tools to determine the need for testing and quarantine.

The mechanism by which SARS-CoV-2 infects the GI tract is related to the high expression of ACE2, required for SARS-CoV-2 cellular injury, in the mucosa of the oral cavity to the colon.[24] Analyses of transcriptome and proteome databases demonstrate more frequent expression of ACE2 in the ileum and colon compared with the lung. High ACE2 expression is seen in absorptive enterocytes, the destruction of which may lead to diarrheal symptoms seen in COVID-19.[6] Furthermore, ACE2 expression is upregulated following an infection by SARS-CoV-2 via interferon-γ (IFN-γ), implicating a positive feedback loop that enhances viral cell entry over the disease course.[9]

Intestinal microbial dysbiosis is another proposed mechanism of GI manifestations in COVID-19 infection. SARS-CoV-2 may interfere with tryptophan absorption and decreased antimicrobial peptide release, resulting in altered gut microbiota and increased risk for intestinal inflammation.[8] Animal studies support this hypothesis as colitis induced in ACE2-deficient mice was reversed by administering absorbable amino acids, including tryptophan. When mTOR inhibitors were administered, which downregulate antimicrobial peptide expression and alter the gut microbiome, intestinal inflammation persisted.[9]

Viral infections are a known cause of acute pancreatitis. There is evidence to suggest SARS-CoV-2 infections may cause acute pancreatitis. Case reports have been published showing isolated SARS-CoV-2 from pancreatic pseudocyst fluid. The SARS-CoV-2 virus has also been isolated from pancreata in postmortem studies. Molecular studies have demonstrated the expression of ACE2 by pancreatic ductal cells, islet cells, and acinar cells. This offers a mode of entry of SARS-CoV-2 into the pancreas, causing direct cellular injury and inflammation. A possible route of entry could be through the duodenal epithelium and the pancreatic duct. Other possible causes of inflammation could be ischemic related to microthrombi and vasculitis.[18]

Acute pancreatitis that is caused by SARS-CoV-2 is rare. Reports of acute idiopathic pancreatitis have been published since the pandemic began in China, and more have been published worldwide. A cohort study performed in the United States, consisting of 11,883 patients, found 32 cases of pancreatitis (0.27%). A similar study in Spain found an incidence of acute pancreatitis in their cohort to be 0.07%. The definitions of acute pancreatitis are heterogenous in these studies and other published literature. Furthermore, the temporal relationship to the onset of infection also varices; abdominal pain may present at the onset of infection or later in the course of infection.[18] A direct association has not been established between acute or chronic pancreatitis with SARS-CoV-2 infection, and more studies are needed to establish a relationship.

GI Complications of SARS-CoV-2 Infections

The intestinal damage caused by SARS-CoV-2 is confirmed on intestinal biopsies and autopsies of infected patients. Alternating segments of stenosis and dilatation of the small bowel have been described on autopsy,[19] and a case report has described hemorrhagic colitis attributed to a COVID-19.[25] Endoscopic biopsies performed on a patient with COVID-19 demonstrated mucosal injury to the esophagus as well as plasmacytic and lymphocytic infiltration of the lamina propria of the stomach, duodenum and rectum, with viral capsid proteins detected in the cytoplasm by immunofluorescence at locations of damage.[12]

Intestinal perforation is a rare complication of COVID-19 described in the literature. Tocilizumab is a monoclonal anti-IL-6 antibody that has been studied for the treatment of cytokine storm associated with COVID-19. Interestingly, intestinal perforation is also a rare side effect of tocilizumab. Individuals with a high-risk of perforation are those with prior diverticulitis, intestinal perforation, as well as critical illness attributed to altered hemodynamics.[26] A case reports described intestinal perforation in a patient following colectomy for colon adenocarcinoma. Imaging also detected a concurrent pulmonary embolism. Although the histology of the removed colon did not demonstrate thrombosis or vasculitis, the authors surmised that microthrombi could be the underlying cause of perforation. The inflammatory response from COVID-19 mobilizes macrophages and monocytes to release inflammatory cytokines. These cytokines induce the formation of thrombin and disrupt anticoagulation mechanisms.[27]

The measurement of fecal calprotectin has some utility in patients with COVID-19. A prospective study demonstrated the strong association between fecal calprotectin and serum D-dimer. This supports the theory that thrombosis could play a role in intestinal ischemia and perforation.[28] Furthermore, fecal calprotectin may be elevated in patients without GI symptoms indicating that the GI tract is a route of COVID-19 infection.[29]

Transmission of COVID-19 Through the GI Tract

Detection of live SARS-CoV-2 in stool samples indicate the virus exists and replicates within the GI tract,[8,30] raising the concern for fecal-oral transmission. The positivity rate of stool specimens for COVID-19 range from 29% to 54% in various clinical settings[12,31] and the positivity rate can be up to 73% in individuals with diarrhea.[13] Patients with COVID-19 can continue to have the viral nucleic acid detected in their stool despite having a negative nasopharyngeal swab[32,33]; cohort studies detected SARS-CoV-2 in feces on an average of 27.9 days after symptom onset, an average 11.2 days longer than in respiratory samples.[30] The viability of the virus and potential for transmission, however, is unclear at the end of this duration.

A rising concern is the detection of SARS-CoV-2 in wastewater, which may predict local surges in COVID-19 cases. Local environmental monitoring has detected SARS-CoV-2 RNA in water samples from treatment plants in northern Italy,[14] France,[34] and Spain[15] at 2 weeks before local COVID-19 surges. According to the WHO, SARS-CoV-2 has poor stability in wastewater and is susceptible to chlorination, however, complete eradication by this alkalinizing process has not been confirmed and validated.[16] Studies in these 3 geographic regions were performed using a real time polymerase chain reaction diagnostic panel validated by the US Centers for Disease Control and Prevention (CDC) which targets 3 regions of the virus nucleocapsid gene.[35] It is unclear if these samples truly contained live, infective viral particles as water samples were pretreated with a viral inactivation protocol to protect laboratory personnel and the surrounding environment. This protocol, however, did not affect RNA detection.[14] There is an urgent need for optimized detection and quantification of SARS-CoV-2 in wastewater. Monitoring wastewater treatment plants may provide a valuable tool for public health officials to predict imminent surges of COVID-19 cases.

The understanding that SARS-CoV-2 infections can present with isolated GI symptoms has resulted in amended protocols for screening, testing, and quarantining of patients under investigation. The presence of new GI symptoms has been included in testing algorithms, which will prevent delays in diagnosis and further transmission of SARS-CoV-2—an important factor in containing the virus. Future research into the testing and transmissibility of SARS-CoV-2 from stool and emesis are needed.

LIVER DISEASE

The Incidence and Risk Factors for Elevated Liver Enzymes in COVID-19 Infections

Elevated liver biochemical markers have been observed in patients with COVID-19 since the beginning of the pandemic.[36–38] Elevations in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) are usually mild-moderate in severity, with mean peak values for ALT and AST <150 and <300 U/L, respectively, based on a large multicenter US study.[17] Alkaline phosphatase elevations are less commonly seen compared with ALT and AST[39] (Table 2). There is no literature on therapies directed at elevated liver enzymes in COVID-19. Given that this sequela is mild, transient, and rarely results in acute liver failure (ALF), monitoring and observation is common practice.

A retrospective, cross-sectional analysis found the incidence of elevated transaminases was 28.2% in 788 patients with COVID-19 infections,[43] defined as >35 U/L for men and >25 U/L for women, at hospital admission. This finding was supported by similar studies that examined the clinical characteristics of COVID-19 infections[38,40] who report an incidence between 14% and 53%. Male sex, overweight (mean body mass index $= 24.3$ kg/m^2), smoking, and chronic liver disease (CLD) were historical features that were associated with elevated transaminases. Patients with diarrhea were more likely to have elevated transaminases, while those with pharyngalgia were less likely. Furthermore, patients with transaminase elevation also had elevated total bilirubin (mean $= 10.5$ U/L).[43] Elevated transaminases in COVID-19 were independent of septic shock, continuous renal replacement therapy, or extracorporeal membrane oxygenation requirements. Among the 222 patients with elevated transaminases, only 5 (2.3%) patients were taking medications associated with drug-induced liver injury.

Mechanism and Pattern of Liver Injury

The expression of ACE2 in the liver is central to the pathogenesis of elevated liver enzymes in COVID-19.[44] A recent analysis of cell-specific ACE2 expression in healthy livers, using single-cell RNA sequencing, found nearly 60% of cholangiocytes and 2.6% of hepatocytes expressed ACE2.[45] Cholangiocytes are important for liver regeneration and immune responses, providing a cellular mechanism for liver injury in COVID-19. This is supported by postmortem studies identifying microvascular fatty degeneration and active lobular, portal region inflammation of the liver, suggesting hypoxemic liver injury.[46] In vitro studies demonstrated sharp increases in ACE2 expression and activity in hepatocytes and cholangiocytes in response to hypoxemia[44]; this may facilitate further invasion of SARS-CoV-2 into hepatocytes and cholangiocytes, propagating liver injury.

Other proposed mechanisms of liver injury include drug toxicity[8] as medications used to treat COVID-19, including lopinavir, ritonavir, ribavirin, oseltamivir, hydroxychloroquine sulfate, and chloroquine phosphate, can be hepatotoxic.[47] The liver injury appears to be more common in patients who received lopinavir and/or ritonavir compared with those who did not.[48] Immune-mediated inflammation of the liver caused by a cytokine storm is another mechanism proposed in severe COVID-19. After infection with SARS-CoV-2, CD4$^+$ T lymphocytes are activated and become pathogenic T helper-1 cells. Increased inflammatory cytokines, such as interleukin (IL)-2, IL-7, IFN-γ, and tumor necrosis factor (TNF)-α, induce

TABLE 2. Associations and Outcomes With Coronavirus Disease 2019 (COVID-19)

Variables	Association With COVID-19	References
Diarrhea	Increased severity	8,10,17
	Increase incidence of elevated liver enzymes	15
Elevated liver enzymes	Increased severity	16,17,34
	Worse prognosis	16,17,34
Cirrhosis	Higher all-cause mortality	17,40
	Increased risk of hepatic decompensation (ie, ascites, variceal bleed, hepatic encephalopathy)	17
Hepatocellular carcinoma	>50% mortality	17
Alcohol-related liver disease	Higher mortality than non–alcohol-related liver disease	17
Inflammatory bowel disease	No increased risk of contracting COVID-19	41
Ulcerative colitis	Higher rates of hospital admission and emergency room encounters	42

$CD14^+/CD16^+$ monocytes that highly express IL-6, which accelerate inflammation.[49] These circulating lymphocytes then migrate to the liver, potentially causing and/or propagating liver injury.

ALF, Cirrhosis, and Liver-related Outcomes

Cases of liver injury related to COVID-19 are typically mild and transient, resolving without any needed intervention.[40] Liver injury is more common in patients with severe COVID-19, and the presence of liver injury portends a worse prognosis.[17,40,48] ALF caused by COVID-19 has not been documented in available literature. In a large multicenter study in the United States, comprising nearly 1000 patients, there were 2 deaths from ALF that were both attributed to alcoholic hepatitis and not COVID-19.[17] There was a higher all-cause mortality (14%) with COVID-19 in patients with CLD. Another cohort study in the United States describes similar all-cause mortality rate of 12%.[50] Of 121 deaths in this multicenter study, 16 were non–COVID-19-related deaths that included heart failure, coagulopathy-related bleeding, and septic shock. Furthermore, there was new or worsening hepatic decompensation in 67 patients (7.7%); mostly from hepatic encephalopathy, but also severe ascites and variceal bleeding.[17]

In patients with CLD and COVID-19, factors that predict a higher mortality include alcohol-related liver disease (ALD), decompensated cirrhosis, and hepatocellular carcinoma (HCC). Other significant predictors of mortality were advancing age, diabetes mellitus, chronic obstructive pulmonary disease, cardiovascular disease, active tobacco use, and Hispanic ethnicity.[17] Patients with ALD are at higher risk for infections due to immune system impairment. Furthermore, ALD creates a *sterile* inflammatory state caused by increased systemic production of proinflammatory cytokines. The cytokine storm generated by SARS-CoV-2 can exacerbate this systemic inflammation in ALD, leading to worse outcomes. Patients with decompensated cirrhosis, from any cause, also have immune system dysfunction and very limited ability to adapt to stress.[17] Strikingly, patients with HCC who suffer from COVID-19 have a mortality rate $>50\%$, likely due to the presence of cirrhosis, active malignancy, and immune system dysfunction.[17] There are no studies that indicate HCC has a higher mortality than other cancers of similar stage. Furthermore, there is no available literature to suggest the ethology of HCC effects patient outcomes. Mortality from COVID-19 is more dependent on age, gender, and medical comorbidities rather than active chemotherapy or the ethology of malignancy.[51]

Mortality and outcomes related to other disease-specific causes of cirrhosis and COVID-19 are unknown. Patients with autoimmune hepatitis (AIH) are often treated with corticosteroids and azathioprine. Investigations on the use of high-dose corticosteroids for COVID-19 proved ineffective and lead to delayed viral clearance.[51] However, the lower doses used in AIH may provide a protective effect from the cellular mechanisms that result in cytokine storm but may worsen the immune system dysfunction related to cirrhosis. Patients with primary biliary cirrhosis or primary sclerosing cholangitis may have increased vulnerability to liver injury from COVID-19, possibly due to the high expression of ACE2 by cholangiocytes. Further research is needed to determine the optimal prevention, treatment, and outcomes of patients with AIH, primary biliary cirrhosis, and primary sclerosing cholangitis who suffer from COVID-19.

The Prevalence of Alcohol Use in the COVID-19 Pandemic

The COVID-19 pandemic has resulted in tremendous social, economic, and health implications for the global population, both from direct infection and from widespread mitigation efforts. Populations that are especially vulnerable include those who suffer from alcohol use disorder and ALD due to a dramatic rise in the consumption of alcohol since the onset of isolation measures. Studies from China indicate a >2-fold increase in the incidence of "hazardous drinking" since the start of the pandemic.[52] In the United States, alcohol sales increased by 55% within the first month of the pandemic.[53] A cohort study of patients with COVID-19 found that up to 30% of patients with CLD, and 50% of patients with ALD, reported daily alcohol consumption.[17]

Quarantine guidelines may have negative psychological impacts, with a study from China reported markedly increased anxiety, unmanageable stress, and depression in over half their study population after similar measures.[54] Unemployment, loss of outdoor or group activity, and deprivation from social support can result in relapses in alcohol use disorder. Group counseling, such as alcoholics anonymous, has a protective effect from relapse but in-person meetings have been canceled due to mitigation efforts. Patients may turn to alcohol to self-medicate for these stressors, even patients who have years of abstinence or those who are listed for liver transplantation.[55]

In addition, the American Associated for the Study of Liver Diseases (AASLD) has stated the COVID-19 pandemic created an environment that encourages Americans to imbibe. Restaurants, considered essential services, now offer alcoholic beverages for takeout and delivery, social media platforms highlight alcohol consumption, and virtual platforms facilitate online "happy hours" from home to maintain social contacts. A Wisconsin brewery has even named a beer after COVID-19.[55,56] Medical societies, like the AASLD warn of a potential public health crisis related to excess alcohol consumption.[57]

Liver Transplantation During the COVID-19 Pandemic

Deferring liver transplantation during the COVID-19 pandemic has been proposed for a variety of reasons. In anticipation of hospital surges, efforts have been made to reserve intensive care unit (ICU) beds and resources for COVID-19 patients. There is a strikingly high mortality (20.5%) and morbidity associated with elective surgeries during the incubation period of COVID-19.[41] In addition, starting potent immunosuppression on vulnerable patients may increase the risk of severe COVID-19.[58] As a result of these precautions, the number of liver transplantations in the United States has declined during the COVID-19 pandemic, and living-donor transplants have completely stopped at many US transplant centers.[58] While the intent is to protect patients, there are long-term consequences to be considered. There will be an initial period of focused, high-acuity care resource utilization for emergency situations and delayed elective care due to physical distancing. With the end of physical distancing, a "return to normal" phase will ensue, potentially with increased decompensations and disease progression, overwhelmed hospital systems due to a backlog of deferred elective care and previously missed diagnoses, increased wait-list time, and mortality.[42]

Strategies to mitigate the predicted poor outcomes are an interesting area of research as it will impact patients and hospital systems on many levels.

IBD

Natural History of COVID-19 Infections in Patients With IBD

Since the beginning of the COVID-19 pandemic, special consideration has been given to individuals who are immunosuppressed, especially patients with IBD. Despite the concern for increased risk of infection, from disease or immunosuppressive therapy, large studies show that IBD patients do not have an increased risk for COVID-19.[59] In a systematic review of > 200,000 IBD patients, 0.4% suffered from a COVID-19 infection with a slight male predominance (56.5% vs. 39.7%), 30.8% of whom were on a TNF-α inhibitor, which was the most common therapy.[60] This review reported that 11.2% of hospitalized patients required ICU level care with a 3.8% mortality rate. Interestingly, 2 studies in the systematic review reported a lower, cumulative ICU admission, and death rate in IBD patients compared with controls[60] that was not statistically significant ($P = 0.352$). Patients with a diagnosis of ulcerative colitis had higher rates of emergency visits or admissions. Patients older than 65 years and active IBD had higher COVID-related mortality.[60]

The most common chief complaints of COVID-19 in IBD patients were fever and cough. Diarrhea was the chief complaint in 20.5% of patients,[60] which is over twice as high compared with the general population. It is often difficult to differentiate diarrhea caused by an exacerbation of IBD symptoms versus diarrhea caused by SARS-CoV-2. While the sensitivity of stool virus polymerase chain reaction for COVID-19 has not been established, this test may be useful in making the distinction between an exacerbation of IBD versus a SARS-CoV-2 infection going forward.

Pathogenesis of COVID-19 Infections in IBD Patients

The ACE2 receptor is highly expressed in the terminal ileum and colon, routine targets of Crohn's disease and ulcerative colitis.[61] Individuals with IBD have elevated ACE2 expression and activity in the colon[61] driven by overexpression of IFN-γ, and other cytokines.[61] In addition, IBD upregulates the trypsin-like proteases necessary for S-protein, the activation of which facilitates SARS-CoV-2 cellular entry via the ACE2 receptor.[62]

These findings supported the initial hypothesis that IBD patients are more susceptible to COVID-19. However, prospective studies following IBD patients in Wuhan report zero cases of COVID-19.[63] An explanation of these findings was the early warning and preventative measures instituted for this patient cohort. Also, there is an existing, heightened awareness of the risk of opportunistic infections by patients as they tend to adopt stricter hygiene practices for infection prevention. These findings from Wuhan were similar to other prospective studies from northern Italy that found no increased risk of acquiring COVID-19 compared with the general population.[64]

Treatment Considerations for IBD in the COVID-19 Pandemic

There is a broad overlap of therapies for IBD that have been considered for COVID-19.[59] Corticosteroids are frequently used to treat IBD, however, their use in COVID-19 has not demonstrated clinical benefit and is associated with delayed viral clearance, psychosis, hyperglycemia, osteoporosis, and avascular necrosis of bone. The mean doses of corticosteroids in these studies were 75 mg of prednisone equivalent per day, much higher than doses used to treat IBD.[51]

Thiopurines, such as 6-mercaptopurine and 6-thioguanine, have demonstrated inhibitory activity against MERS-CoV and SARS-CoV in vitro[65] but have not been evaluated in vivo. In addition, a common side effect of thiopurines is lymphopenia, which is associated with a poor prognosis and increased mortality from COVID-19.[66] Methotrexate is another disease-modifying antirheumatic drug for IBD whose side effects include bone marrow suppression and pulmonary toxicity. The effects may have implications on disease severity of COVID-19[59] and could be an area of future research.

Patients with IBD may also be treated with biological agents such as TNF-α inhibitors. TNF-α inhibitors can reduce viral immunity as evidenced by the established risk of hepatitis B virus reactivation.[59] However, increased IFN-γ and TNF-α production is associated with severe COVID-19 and TNF-α inhibitors have been a proposed treatment for cytokine storm in COVID-19.[67] Postmarketing surveillance of patients on vedolizumab and ustekinumab show a low incidence of viral infections.[68,69] Tofacitinib is another agent used to treat IBD which may reduce viral immunity and is known to increase the risk of herpes zoster reactivation.[59] However, available prospective studies have not shown increased risk of COVID-19 in patients receiving tofacitinib. Interestingly, several studies demonstrate IFN inhibition by tofacitinib, which may abate the cytokine storm in COVID-19.[59]

Currently, there is no existing evidence that supports the discontinuation of biological therapies in IBD patients in remission. In fact, prospective studies of IBD patients found that concomitant IBD therapy was not associated with a higher risk of COVID-related pneumonia or death. The most recent recommendations from the International organization for the Study of Inflammatory Bowel Disease (IOIBD) include continuing maintenance therapy for IBD and reassess the use of high-dose corticosteroids (> 20 mg prednisone equivalents per day).[3]

ENDOSCOPIC PRACTICE

The Risk of COVID-19 With Aerosol-generating Procedures (AGPs)

SARS-CoV-2 is primarily spread by respiratory droplets expelled by infected individuals by talking, coughing, sneezing, or close contact. Human-to-human transmission can originate from those who are symptomatic, asymptomatic carriers and from viral shedding during the incubation period.[70] The WHO identifies health care workers as a population who are at a 3-fold higher risk of contracting COVID-19 due to high-risk exposures,[70] including endoscopic procedures which result in aerosolization of droplet particles imbued with SARS-CoV-2. These AGPs include esophagogastroduodenoscopy, enteroscopy, endoscopic retrograde cholangiopancreatography, breath testing, and esophageal manometry with highest risk during esophageal intubation and insertion and removal of instruments from the endoscope. Colonoscopies, sigmoidoscopies, and

anorectal manometry are less studied but are assumed to be aerosol-generating and confer a similar risk.[71]

Personal Protective Equipment and Endoscopic Practice Considerations in the COVID-19 Pandemic

Given the increased risk of transmission from AGPs, the AGA recommends the use of N95, N99, or powered air-purifying respirators for upper and lower endoscopic procedures to prevent COVID-19.[72] This recommendation is generalized to all patients undergoing upper endoscopies because COVID-19 is spread in the community and to avoid viral transmission from asymptomatic carriers. The AGA also recommends these precautions for lower endoscopic procedures given the risk for aerosol generation, especially during inserting and removing of instruments via the colonoscope channels and prolonged fecal shedding of the virus. The cleaning and reuse of N95 masks and powered air-purifying respirators has been suggested by the AGA however there isn't enough evidence to comment on the safety of extended (re)-use of personal protective equipment (PPE).

The AGA recommends double gloving with the first inner glove donned with the wrist of the glove covered by the distal sleeve of the gown, followed by a second outer glove that covers said sleeve. Double gloving is associated with less viral droplet contamination in prospective studies.[71]

Negative-pressure ventilation is used in airborne isolation rooms, creating an inward flow of air to prevent airborne droplets from spreading out of the room. An anteroom is an intermediary room between negative-pressure rooms and hallways that contains a sink, an area for donning and doffing PPE, and minimizes aerosol contamination.[71] Negative-pressure rooms minimize the spread of SARS-CoV-2 and are recommended by the AGA for endoscopic procedures.[71] This recommendation is based on the survival of SARS-CoV-2 on copper surfaces for 4 hours, cardboard surfaces for 24 hours, and plastic or stainless steel surfaces for up to 72 hours.[73] This recommendation was made with the understanding of the impact on workflow efficiency. In a situation where negative-pressure rooms are unavailable for use, the use of portable, high efficiency air filters is recommended for endoscopy rooms. Continued decontamination of endoscopes is essential to limiting the spread of COVID-19 between patients. Standard biocidal agents have proven effective in inactivation of coronaviruses. These agents include hydrogen peroxide, alcohols, sodium hypochlorite, or benzalkonium chloride.[74]

Triaging GI Procedures

As health systems in the United States plan for medical surge capacity that exceeds operating capacity, triaging of health care services has been proposed. Early in the pandemic, the US Surgeon General suspended all elective surgical procedures to conserve PPE and mitigate spread. Similarly, GI societies recommended rescheduling elective, nonurgent procedures with the AGA outlining strategies for triaging. A procedure is deemed nonelective by the triaging physician if the procedure is time-sensitive based on short-term impact on patient outcomes, harm in delayed intervention, or rapid progression of underlying disease. Elective procedures can be delayed for 8 weeks. Examples of nonelective procedures include the diagnosis and treatment of cholangitis, GI bleeding, food impaction, or assessment of IBD activity.[71] These recommendations are irrespective of the patient's COVID-19 status as it was made before rapid serologic testing of COVID-19 was available. Collaboration with the referring provider and/or a multidisciplinary team is encouraged if the clinical situation is unclear.[71]

DISCUSSION

GI symptoms are an important yet underrecognized component of COVID-19 disease. SARS-CoV-2 infections can present with isolated GI symptoms, the presence of which correlates with increased severity of COVID-19. Increased disease severity is also seen in COVID-19 patients with elevated liver enzymes. Targeted therapies for COVID-19 are appropriately directed toward respiratory illness as this is the primary cause of patient morbidity and mortality. Supportive measures for GI symptoms in COVID-19 is common practice, and directed treatment options may be a natural consequence of treating COVID-19 respiratory disease as seen in observational studies with oral lopinavir and ritonavir. While diarrhea typically resolves in 4 days, the long-term impact of COVID-19 on the development of functional GI disorders such as irritable bowel syndrome, which can be triggered by viral infections, remains an area of further research need.

Establishing a sensitive and specific fecal assay for SARS-CoV-2 will have high utility in clinical practice as fecal shedding can persist for up to 4 weeks. This would prove useful in determining the safe and appropriate timing for elective and nonemergent endoscopic procedures. Such a test could also prove useful for monitoring wastewater treatment plants, where the presence of SARS-CoV-2 can predict local outbreaks of COVID-19. Public health officials could use this information to act preemptively against surges and reduce the burden on local hospitals. This may also help elucidate the impact of fecal-oral transmission in the spread of COVID-19.

COVID-19 almost never causes ALF; however, patients with cirrhosis suffer a higher all-cause mortality and greater risk of hepatic decompensation associated with COVID-19. This problem is compounded by the increase in alcohol consumption in the United States and China noted during the COVID-19 pandemic with an alarming 50% of patients with ALD reporting *daily* alcohol consumption. Restricting and/or deferring liver transplantations during a pandemic likely comes with further disease progression, decompensations, and increased wait-list mortality. Given the high risk of decompensation, our cirrhotic patient population requires close monitoring and adequate social support mechanisms to reduce the increased rates of alcohol consumption.

Patients with IBD do not have a higher risk of contracting COVID-19 but have diarrhea more frequently with COVID-19 infections compared with those without IBD. However, physicians should use caution when prescribing high doses of corticosteroids, or consider dose reducing existing corticosteroid regimens, as their use may prolong SARS-CoV-2 fecal shedding. Biological therapies have garnered a lot of interest as they have potential efficacy in treating the immune activation phase of COVID-19. This is certainly an interesting topic for further investigation—whether they can be used as a treatment of COVID-19 immune reactivation and associated clinical outcomes. Close monitoring of patients on azathioprine may be needed as azathioprine-related leukopenia may be problematic in patients with COVID-19, which is associated with lymphopenia.

Many of the procedures performed by gastroenterologists generate aerosols that contain SARS-CoV-2 viral particles

from an infected host. Testing patients for COVID-19 before AGPs is now common practice in the United States and can be used to help decide on the appropriate timing of the procedure. As vaccinations becomes more widespread, guidelines on PPE use and need for COVID-19 may continue to evolve.

During this pandemic, the health care field has learned a lot about the high utility and even patient preferences for telemedicine visits. Monitoring and follow-up strategies for patients with cirrhosis and IBD could be done safely through electronic consults (e-consults) or virtual telemedicine visits which also improves access for those residing further from medical centers. Going forward, whether COVID-19 persists within the global population or not, we do envision telemedicine and virtual support systems will remain in place for effective and efficient health care delivery. Hospital emergency and surge planning has been at the forefront of discussion surrounding the COVID-19 pandemic, and hospital systems are now better prepared to handle future pandemics. New challenges will arise as the topography of the COVID-19 pandemic continues to change with the advent of vaccines, development of viral variant, and use of new treatments. Effects of novel therapies on GI function and specifically liver enzyme elevations need to be further understood. Recent publications have called attention to potential increases in the rates of functional GI disorders either from sequelae of COVID-19 infection or increased personal or financial stressors from quarantine. New strategies will be needed to specifically address elective care that has been delayed far too long. The impact of COVID-19 on the GI system has been significant and will continue to impact our care significantly going forward.

CONCLUSIONS

COVID-19 is relevant to the GI community both from patient care as well as a clinical practice standpoint. GI symptoms are prevalent in COVID-19 and may portend a worse prognosis. COVID-19 also leads to mild elevations in liver transaminases with extremely rare reports of ALF. More importantly, increased alcohol use, avoidance of routine care, and delayed liver transplantations among vulnerable patients during quarantine periods may lead to worsening outcomes. In the care of IBD patients, use of anti-TNF-α agents has not been associated with increased risk of COVID-19 infection and therapy should not be stopped. However, high-dose corticosteroid therapy should be minimized if possible. Endoscopic procedures are considered AGPs with increased risk of transmission of SARS-CoV-2 from patient to providers. Therefore, practices should follow society guidelines in establishing testing protocols before procedures and utilizing adequate PPE. As more becomes clear about this novel coronavirus infection and new therapies, including vaccines, emerge, our understanding of the impact on the field of gastroenterology and hepatology must be updated.

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