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CURRENT OPINION

COVID-19 and gastroenterology: clinical insights and recommendations for gastroenterology care providers.

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ABSTRACT

While the COVID-19 pandemic evolves, we are beginning to understand the role the gastrointestinal tract plays in the disease and the impact of the infection on the care of patients with gastrointestinal (GI) and liver diseases. We review the data and understanding around the virus related to the digestive tract, impact of the pandemic on delivery of GI services and daily gastroenterology clinical practice, and the effects on patients with pre-existing GI diseases.

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic has become a global threat to human health, unlike anything seen during the past century. While the COVID-19 pandemic continues to evolve, we are beginning to understand the role the gastrointestinal tract plays in the disease and the impact of the infection on the care of patients with diseases of the digestive tract. COVID-19 may have a particular effect on gastrointestinal (GI) patients on immunosuppressive agents, such as those with inflammatory bowel disease (IBD), autoimmune liver disease and post-liver transplant, and those requiring gastrointestinal procedures such as endoscopy.

We review the data and understanding around the virus related to the digestive tract, impact of the pandemic on delivery of GI services and daily gastroenterology clinical practice, and the effects on patients with pre-existing GI diseases.

Clinical manifestations

Role of GI symptoms and potential faecal-oral transmission

COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is primarily a respiratory disease. The majority of complications that contribute to mortality due to COVID-19 affect the lungs. These include severe pneumonia leading to hypoxic respiratory failure or acute respiratory disease syndrome. Initial data from China and other international centers reported subgroups of COVID-19 patients having symptoms related to the GI tract. These patients with COVID-19 experienced concurrent gastrointestinal symptoms (15–48.5%), notably anorexia and diarrhoea, and the onset of GI symptoms preceded or even occurred in the absence of respiratory symptoms [1–3]. However, in a more recent meta-analysis, GI symptoms were found to be not as common in COVID-19 as previously estimated: The overall pooled prevalence was 7.7% for diarrhoea, 7.8% for nausea/vomiting, and 3.6% for abdominal pain. Notably, in outpatients, the pooled incidence of diarrhoea is lower (4.0%) [4]. Still, the presence GI symptoms seem to relate to late presentation, the severity of COVID-19 disease, and presence and duration of viral shedding in stool, compared to those with only respiratory symptoms [2].

The duration of viral shedding in the stool ranges from the day one of onset of symptoms to day 28, even after the virus becomes negative in respiratory samples, with the potential for faecal-oral transmission [3–5]. Given the high expression of ACE2 receptor (the cellular receptor for SARS-CoV-2) in the intestinal epithelium, it is highly plausible that the gut is a site of active viral replication leading to GI involvement in COVID-19 [6].

The Centers for Disease Control and Prevention (CDC) recommends two negative respiratory tests, separated by $\geq$ 24 h, to assume non-infectivity following COVID-19. Considering the potential for continued faecal-oral transmission, some investigators recommend that real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) testing on faeces in patients with GI symptoms, before assuming non-infectivity following COVID-19 [7].

Clinicians should recognize the possibility that GI symptoms, such as diarrhoea, maybe a presenting feature of COVID-19. A high index of suspicion of the infection is needed in patients presenting with GI symptoms, rather than waiting for respiratory symptoms to develop. The general

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public should also be advised of the possibility of faecal-oral transmission, and attention to handwashing as a preventive measure should be further emphasized.

Liver injury

Liver injury was reported to be between 14 and 53% of cases with COVID-19 from the initial studies [1,8–12]. According to a recent meta-analysis, the pooled prevalence of liver test abnormalities seen in COVID-19 was approximately 15% [4]. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are elevated, usually to 1–2 times the upper limit of normal (ULN), with normal to modestly elevated total bilirubin levels, early in the disease process.

In a recently published study by Phipps et al., describing more than 3000 patients, out of those who tested positive for SARS-CoV-2, 45% had mild (ALT 1–2 times ULN), 21% had moderate (ALT 2–5 times ULN), and 6.4% had severe (ALT > 5 times ULN) liver injury. Among patients with severe liver injury, a severe disease course with higher rates of ICU admission (69%), intubation (65%), renal replacement therapy (33%), and mortality (42%) was observed [13].

The most recent systematic analysis of acute liver injury (ALI) during SARS-CoV-2 infection included studies originated in China [14]. In this study, approximately a quarter of subjects presenting with COVID-19 infection requiring hospitalization have ALI. Liver injury was mainly represented by minimal elevation of ALT and AST with normal values of total bilirubin. Cholestatic enzymes remained normal, contradicting the hypothetical notion that angiotensin-converting enzyme-2 (ACE-2) receptors present in cholangiocytes, but not hepatocytes could be involved in the physiology underlying liver injury. There was no association between GI symptoms and the presence of liver injury. There was no correlation between the presence of underlying liver disease and elevated liver enzymes. There was an association between a higher degree of liver injury, expressed by levels of ALT or AST, and admission to the ICU.

Liver dysfunction and deranged liver biochemistry in patients with COVID-19 may be multifactorial. It may be caused directly by the viral infection of liver cells. It is also possible that liver injury is due to drug hepatotoxicity, related to the medications used in the treatment of the infection. This might explain the variations in reported liver injury in different cohorts. Altered liver biochemistry may also be due to muscle injury, ischemia and cardiomyopathy associated with COVID-19. In critically ill patients, immune-mediated inflammation, such as cytokine storm and pneumonia-associated hypoxia, might also contribute to liver injury. Most recent available data support that these abnormalities are more commonly attributable to secondary effects from severe disease, rather than primary virus-mediated liver injury [4,14].

Liver injury is more commonly seen within severe COVID-19 infections than in mild cases. Liver dysfunction in milder cases of COVID-19 is often transient and returns to normal without specific treatment. However, in cases of severe liver dysfunction, liver protective drugs may have to be considered. The presence of mild to moderate liver injury should not be a contraindication for the use of investigational or off-label therapies for COVID-19 (e.g., remdesivir, tocilizumab, chloroquine, hydroxychloroquine). However, AST or ALT levels >5xULN may exclude these patients from receiving some of these investigational agents [15].

Raised serum amylase and lipase

A retrospective study involving 52 patients from Wuhan, China described the incidence of pancreatic injury in patients with COVID-19, defined only as any abnormality in amylase or lipase [16]. Based on this study, 17% of patients with COVID-19 met criteria for pancreatic injury with only mild elevations of pancreatic enzymes (PE). A mild increase in blood levels of PE can be explained by many factors other than pancreatic damage in patients with COVID-19 [17]. Therefore, clinically relevant pancreatitis or even elevation of PE does not seem to be common in COVID-19 infection. However, studies investigating the incidence of pancreatic inflammation in patients with COVID-19, based on imaging (preferably CT scan or MRI), and elevated blood levels of PE, are needed before firm conclusions can be made [17].

Another study published recently described COVID-19 among patients with a history of acute (85.3%) or chronic pancreatitis (14.7%) [18]. This study suggested patients with a history of pancreatitis may be more susceptible to COVID-19 (7.8% vs. 2.8% among controls). However, the infection may not lead to increased risk of SARS-CoV-2 pancreatic inflammation as none of the patients with prior pancreatitis developed acute pancreatitis.

Delivery of GI services

COVID-19 illness and infection risk

The main route of SARS-CoV-2 transmission is *via* aerosolized droplets from the posterior pharynx and bronchioles of infected individuals; the possibility of faecal-oral transmission also exists [19]. The risk of viral transmission is highest within two meters of a patient with COVID-19. Cough-generated aerosol clouds can extend up to two meters from the patient [20]. SARS-CoV-2 virus particles can be deposited on surfaces where they may remain detectable for up to 72 h [21], but the precise infection risk from surface contamination has not been determined. All endoscopic procedures are considered high-risk aerosol-generating procedures (AGP). This is due to the possibility of generating aerosol from coughing and retching during upper endoscopy and the passage of flatus during colonoscopy [22]. In addition, by the very design, function and leakage of the endoscopic instruments, valves, ports, and air pressures during inflation and suction, all endoscopic procedures risk generating aerosol and micro-droplets.

Endoscopy

The COVID-19 pandemic is disrupting health care delivery systems around the world. Patient care in gastroenterology practice is no different. In addition to taking extra care to screen patients for the virus, GI societies around the world have made recommendations, the changes required in clinical practice. The potential of transmission of SARS-CoV-2 in endoscopy units, directly by aerosol and micro-droplets generation, and indirectly by objects or surfaces and by the faecal-oral route is a significant concern.

Recently, The American Association for the Study of Liver Diseases, The American College of Gastroenterology, The American Gastroenterological Association and the American Society for Gastrointestinal Endoscopy made a 'strong recommendation' to reschedule elective, non-urgent endoscopic procedures during the pandemic [23]. Similar recommendations have been made by the European Society of Gastrointestinal Endoscopy (ESGE) and Asian Pacific Society for Digestive Endoscopy (APSDE) [24,25]. The urgent and emergent procedures that should not be delayed include those for acute upper and lower GI bleeding, foreign body ingestion, oesophageal food impaction, dysphagia with concern for oesophageal obstruction, cholangitis, stenting for palliation of GI/biliary obstruction and inflammatory bowel disease (IBD), new diagnosis or exacerbation, where lower GI endoscopy will alter patient management.

Further classification of non-urgent procedures into non-urgent/perform, and non-urgent/postpone, is also useful. Some non-urgent procedures (examples include cancer evaluations, prosthesis removals, evaluation of significant symptoms) may need to be performed as a higher priority. For the non-urgent/perform indication, factors including patient age and comorbidities, symptom severity, and risk for disease/symptom progression should all be considered when making decisions. In general, endoscopic procedures that will change management significantly may be pursued.

Changing street clothes prior to entering or leaving the facility and the use of scrubs for endoscopy should be routine practice. The recommendations have also urged proper use of personal protective equipment (PPEs) for endoscopists who have to perform urgent and emergent procedures [23,26]. All endoscopic procedures should be carried out adhering to universal precautions, making sure appropriate PPEs is available and worn by all members of the endoscopy team: double gloves, caps, appropriate face mask, face shield/eye goggles, and water-resistant surgical gowns and shoe covers. It is critical that endoscopy staff should understand and practice the correct sequence to put on and take off PPE ('donning' and 'doffing') appropriately [27]. These predate the coronavirus, but it is even more important now than before because of the concern of droplet spread [28]. Independent of these protective measures, general measures such as physical distancing and frequent hand hygiene is of critical importance and need to be practiced routinely.

Special considerations should be made, as to whether or not the endoscopist should wear additional respiratory equipment. For any patients diagnosed with COVID-19 or are under investigation for high-risk exposure where endoscopy is necessary, an N95 mask should be used in addition to the other gear. Manning of endoscopy suites should be reduced to the minimum number of essential individuals, in order to conserve the use of PPE and other resources. Shortages may require to reuse some of the PPEs; considering extended use or reuse of N95 masks and eye protection should be in accordance with hospital policies.

All patients presenting for endoscopy should be screened for high-risk exposure or the presence of symptoms. A symptom questionnaire and temperature check should be administered to all patients on the day of the endoscopy procedure. The physical distancing of patients and visitors (6 feet is recommended) should be maintained throughout the entire time in the endoscopy unit. For COVID-19 positive patients, or those awaiting test results, isolation precautions should be taken with procedures are performed, if possible, in negative pressure rooms [29].

As new COVID-19 cases, plateau and authorities permit the reopening of health care facilities, resumption of elective endoscopy activity is appropriate [30]. Even then, scheduled endoscopies should continue to be prioritized based upon the level of urgency, individual patient considerations and the physician's professional judgement. Wherever possible, all patients should receive PCR-based testing, performed within 48 h of the procedure. If pre-procedure COVID-19 testing not feasible, patients should be advised to maintain a daily temperature log for ten days prior to the procedure. Endoscopy staff should also be surveyed for COVID-19 exposure and symptoms and screened daily with temperature checks. Implementing PPE requirements, as described above for urgent procedures, should continue to be practiced.

GI clinics

Telehealth is becoming more common and more navigable as practices adapt to managing patients in the era of physical distancing. Therefore, for clinic visits, offering elective visits remotely, *via* telemedicine if possible, will decrease the clinic density of patients. Shifting outpatient visits to telehealth visits will also allow care for patients who are less willing or unable to travel. Additionally, telemedicine will keep people away from a potentially dangerous setting of crowded clinics and hospitals.

Improved telemedicine, to better deliver services, has the ability to bring not only gastroenterologists to interface with their patients but also a whole suite of services in the field, including nutritional health services and behavioural health services. This has the potential to become one of the few silver linings of this global pandemic.

Pre-screening of patients for high-risk exposure or symptoms, checking body temperature of the patient upon arrival, keeping patients at an appropriate distance from each other and providing hand sanitization facilities should be practiced in conducting GI clinics for those needing face-to-face clinic consultations.

Liver transplantation

The complex decision making involved on whether or not to proceed with transplantation is now significantly more challenging due to the COVID-19 pandemic [31–33]. It is essential that liver transplant centers continuously assess and adapt to their local situation and its impact on patients included in transplant waiting lists. There will be a reduction in organ recovery because of COVID-19-related limitations on institutional resources and the potential risk of donor-derived disease transmission. Patients with high MELD scores, risk of further decompensation, or tumour progression will need to complete their evaluation or be evaluated for transplantation, even during the COVID-19 pandemic.

Patients and their caregivers should be informed of the potential impact of the COVID-19 pandemic on their waiting time on the transplant list. Regardless of test results or availability, all potential donors should be screened for exposure and clinical features compatible with COVID-19, and the use of alternatives to PCR-based testing such as chest radiography may have to be considered. Similarly, potential recipients should be screened for features of COVID-19 before they are called in from home for transplantation. Accepting only grafts with a low risk of delayed graft dysfunction should be considered to minimize complications and length of postoperative hospital stay. Living donor liver transplant should generally be avoided during the pandemic, except for pediatric patients with acute liver failure.

Impact on patients with pre-existing GI disease

Patient on immunosuppressive therapies

One of the main concerns about COVID-19 was its impact on immunosuppressed patients, and for gastroenterologists, that brought to focus patients with inflammatory bowel disease (IBD), autoimmune liver disease and those after liver transplantation, who might be on immunosuppressive or immunomodulatory therapy.

Immunosuppressed GI patients *without* COVID-19 should not stop taking their medications because the potential drawbacks could be worse than COVID-19. Making anticipatory changes to current immunosuppressive drugs or dosages should be avoided [34–36]. By stopping or reducing their medications, exacerbation of Crohn disease or ulcerative colitis, relapse of autoimmune liver disease or acute cellular rejection in liver transplant becomes a real risk. This may result in requiring admission to over-crowded hospitals, and the need for stronger immunosuppressive therapy during the pandemic. It is, therefore, advisable for patients with these conditions to remain on their therapies (including scheduled infusions of biologics for IBD) and strictly adhere to recommended health care guidelines on hygiene and social distancing to prevent COVID-19 infection.

In immunosuppressed GI patients *with* COVID-19 infection use of high-dose steroids should be minimized, maintaining a sufficient dosage to avoid adrenal insufficiency, and stopping azathioprine, mycophenolate and calcineurin inhibitors should be considered especially in the setting of lymphopenia, fever, or worsening pneumonia [34–36]. However, immunosuppressive therapy should be initiated in patients, *with or without* COVID-19, who have strong indications for treatment (e.g., relapses of IBD and autoimmune hepatitis, graft rejection). In patients *with* COVID-19, caution should be used when initiating steroids or other immunosuppressive drugs where the potential risks outweigh the benefits (e.g., in alcohol-associated hepatitis) [34–36].

Patients with IBD

Whether IBD patients are at higher risk for acquiring COVID-19, and if they do whether they at higher risk of the more severe disease needs addressing. To help find answers to these questions and how to manage patients with IBD during the pandemic, Mount Sinai and the University of North Carolina have launched the Surveillance Epidemiology of Coronavirus Under Research Exclusion-IBD (SECURE-IBD) registry in the USA to monitor and report outcomes of COVID-19 in patients with IBD [37]. At the time of revision of this article, there were 1572 patients in the register with 29% requiring hospital admission, 5% requiring ICU care, 4% requiring ventilation and a 3% mortality. The evidence so far does not seem to suggest that IBD increases the risk of developing or the severity of COVID-19.

Guidance issued by the Crohn's and Colitis Foundation and the American Gastroenterology Association recommends that IBD patients stay on their medications, such as mesalamine or other aminosalicylates during the pandemic [34,35]. Patients should continue immunomodulators and the Jak-inhibitor tofacitinib. Patients should not to stop scheduled biologics or biosimilars but should be advised to check with their health care providers if they are taking additional steroids.

If they become infected, IBD patients should seek advice from their health care provider, whether the adjustment to dosages of medications needs to be made. In this instance, stopping thiopurines, methotrexate, tofacitinib and biological therapies (including anti-TNF, ustekinumab, vedolizumab) is recommended. These therapies can be safely restarted after complete resolution of COVID-19 symptoms.

Patients with chronic liver disease, cirrhosis and HCC

It is not known whether patients with chronic liver diseases such as chronic viral hepatitis B and/or C, are more susceptible to liver injury from SARS-CoV-2 [38] It is also unknown whether COVID-19 exacerbates cholestasis in those with cirrhosis or underlying cholestatic liver diseases such as primary biliary cholangitis or primary sclerosing cholangitis [39]. Emerging data suggest that patients with nonalcoholic fatty liver disease (NAFLD) may be at higher risk of severe COVID-19 [40].

Similar to the SECURE-IBD registry, to assess the impact of patients with chronic liver disease and post-liver transplantation during the COVID-19 pandemic, Mount Sinai and the University of North Carolina has launched the Surveillance Epidemiology of Coronavirus Under Research Exclusion-

CIRRHOSIS (SECURE-CIRRHOSIS) registry [41]. This is to monitor and report outcomes of COVID-19 patients with chronic liver disease (with and without cirrhosis) and post-liver transplantation. At the time of revision of this article, there were 833 patients in the register (Cirrhosis-379, chronic liver disease (without cirrhosis)-303, Post-liver transplant-151). The reported morbidity from any form of decompensation among patients with cirrhosis was 45%. The reported mortality rates for the three groups were, cirrhosis-33%, chronic liver disease (without cirrhosis)-8%, post-liver transplant-19%, indicating high mortality in this group of patients. This high mortality rates for SARS-CoV-2 infection in patients with pre-existing chronic liver disease and cirrhosis from this international registry was reported recently [42].

Some procedures related to the management of liver disease may need to be performed on an urgent basis. These include liver biopsy to rule out post-transplant graft rejection or to diagnose autoimmune hepatitis, therapeutic paracentesis, trans-jugular intrahepatic portosystemic shunt and/or endoscopy for variceal bleeding, follow-up band ligation in those with recent variceal bleeding, urgent biliary procedures for conditions such as cholangitis with sepsis (interventional radiology or ERCP) [23]. However, primary prophylaxis with beta-blocker therapy could be considered instead of performing a screening endoscopy for cirrhotic patients with clinically significant portal hypertension or having a high risk of decompensation.

Patients on or off therapy for HCC should continue to be monitored, and surveillance should be continued for patients at risk for HCC (e.g., patients with cirrhosis, chronic hepatitis B or C) as close to schedule as circumstances allow, although an arbitrary delay of 1–2 months may be reasonable. Online reviewing of images of newly referred patients with liver masses and conducting virtual multidisciplinary meetings prior to scheduling an in-person visit may be helpful. It may also be helpful to consider virtual patient consultations to discuss the diagnosis and management of HCC and other liver tumours. Treatment for HCC should be offered when patients qualify and should not be delayed.

Expert opinion and unanswered questions

There will likely be several stages of illness from the COVID-19 pandemic. The immediate stage will be the casualties from COVID-19 among patients with chronic GI diseases (e.g., IBD and chronic liver disease). The intermediate stage will result from delayed care or avoidant care of existing medical conditions. These patients may delay care for their conditions or delay refilling meds, or electively stop meds, and suffer subsequent complications [e.g., IBD, autoimmune hepatitis and post-transplant patients reducing, stopping or unable to continue their immunosuppressants (or biologics) will result in, a relapse of these chronic immune conditions or acute cellular rejection in LT]. The delayed stage is due to delayed care and missed new diagnoses from avoidant or substandard follow-up care. Diseases that may have been preventable or curable at early stages may progress beyond the curative stage (e.g., patients skipping or missing screening tests for colorectal cancer or HCC). The true effects of all these stages will only be known in the years to come.

Our knowledge of COVID-19 is still rapidly evolving. The response of the international Gastroenterology and Hepatology community during the COVID-19 pandemic has been commendable. Major international societies have

Table 1. Summary of the key recommendation of the major European, Asian-Pacific and American societies for Gastroenterology, Hepatology and Transplantation*.

Practice		Recommendation
Outpatient care	1.	Offer telehealth via virtual clinic consultations
	2.	Limit elective blood draws, tests, imaging
	3.	Mail order medications
	4.	Continue immunosuppression in IBD and autoimmune liver disease
	5.	Postpone cancer screening till services resume
Inpatient care	1.	Separate COVID-19 and COVID-19 patients
	2.	Minimize personal on rounds
	3.	Limit elective blood draws, tests, imaging
	4.	Treat flares of IBD and autoimmune liver disease and transplant rejections as usual
	5.	Suspect and screen for COVID-19 in acute decompensation of cirrhosis and in acute-on-chronic liver failure
	6.	Avoid transfer between units and facilities
	7.	Can reduce immunosuppression in severe COVID-19
	8.	Limit patient visitors
Endoscopy	1.	Limit to emergent indications such as severe GI bleeding, ERCP for cholangitis
	2.	Postpone screening and elective procedure
	3.	Minimize personnel during procedure
	4.	Appropriate PPE and masks for all personnel in Endoscopy room
Transplantation and surgery	1.	Avoid inpatient evaluation
	2.	Limit to urgent indication after case-by case selection
	3.	Offer bridging therapies for HCC if surgery postponed
	4.	Screen donor and recipients for COVID-19
	5.	Minimize personnel during procedure
	6.	Use of appropriate PPE and safe anesthetic practice
	7.	Do not routinely reduce immunosuppression
	8.	Can reduce immunosuppression in severe COVID-19

*AASLD: American Association for the Study of Liver Diseases.
AGA: American Gastroenterology Association; APSDE: Asian Pacific Society for Digestive Endoscopy; ASA: American Society of Anesthesiologists; ASGE: American Society of Gastrointestinal Endoscopy; ASTS: American Society of Transplant Surgeons; CCF: Crohn's and Colitis Foundation; EASL: European Association for the Study of Liver Disease; ESGE: European Society of Gastrointestinal Endoscopy; ILTS: International Liver Transplantation Society.

formulated and published recommendations on how to manage patients with gastrointestinal and liver disease during COVID-19. A summary of the key recommendation of the major American, Asian-Pacific and European societies for Gastroenterology, Hepatology and Transplantation is given in Table 1. Despite the differences in healthcare resources, COVID-19 incidence, and gastrointestinal disease prevalence, the recommendations outlined on these guidelines are relatively similar but for only minor differences. Infection control, risk stratification, prioritization, mitigation and supportive management remain universal throughout these recommendations. The authors strongly recommend gastroenterology practitioners adopt these guidelines not only to weather the presents pandemic but also 'second or subsequent' waves of COVID-19 infections or another future pandemic.

Conclusion

In this broad overview, we attempted to summarize the key findings and recommendations related to COVID-19 relevant for the Gastroenterology care providers. COVID-19 and its impact on Gastroenterology practice is a rapidly evolving area with new data and information emerging almost on a daily basis. Therefore, periodically checking for updates from leading national and international health organizations, such as the CDC, the World Health Organization, and Gastroenterology associations and societies is essential for both GI physicians and patients to stay informed. The outcome of patients with GI disease during this pandemic will become clearer only with time.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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