

COVID-19 AND THE DIGESTIVE TRACT

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INTRODUCTION

Although the most lethal effects of COVID-19 involve the respiratory tract, most clinicians have seen patients with gastrointestinal manifestations. But though we know these can be significant, it's still unclear how prevalent they are and how severe they can be. Because this pandemic is caused by a relatively new disease, high quality data are limited, and the information we do have is continuously evolving.

PREVALENCE

Initial studies suggested that as many as 60% of patients diagnosed with COVID-19 reported GI symptoms, with the most common being anorexia, diarrhea, nausea, and loss of smell and taste.¹ Subsequent data, however, including meta analyses and guidelines from the American Gastroenterological Association (AGA), found the prevalence to be closer to 8%.²

Patients occasionally present with isolated GI symptoms prior to the onset of respiratory symptoms. In one study of more than 1,000 patients, 16% had GI symptoms without respiratory complaints,³ which suggests we should be vigilant for these symptoms as a harbinger of what may come. Some data suggest there may be an association between diarrhea and measurable viral RNA in the stool,⁴ and there is a case report of one patient with positive fecal RNA and repeatedly negative pharyngeal and sputum tests.⁵ However, at the time of this writing there is no conclusive proof or expert consensus that fecal-oral transmission plays a significant role.

The AGA recommends testing for COVID-19 if respiratory symptoms develop after the onset of GI symptoms, but also to consider testing hospitalized patients with new onset GI symptoms, outpatients with new onset GI symptoms for more than 48 hours, and patients with established GI diagnoses such as inflammatory bowel disease (IBD) who present with symptoms suggestive of a disease flare.²

PATHOPHYSIOLOGY

It has been established that angiotensin-converting

enzyme 2 (ACE2) is a receptor for the SARS-CoV-2 virus. Since ACE2 receptors are widely expressed in the digestive tract, their presence may help explain the pathogenesis of digestive symptoms.⁶

ACE inhibitors and angiotensin II receptor blockers are not direct inhibitors of ACE2 and therefore don't prevent SARS-CoV-2 from binding. In fact, those agents may actually increase expression of ACE2 proteins, leading some to think early on that they could be associated with more severe disease and worse outcomes. However, there's been no evidence to date to support this association.

THE LIVER AND COVID-19

Abnormalities in liver enzymes are seen frequently, with an incidence ranging from 15% to 40%. It's thought that this phenomenon is attributable to secondary effects from severe disease rather than to direct virus-mediated liver injury,^{2,7} but the exact mechanism remains unknown, so it's important to exclude other causes of liver disease when aminotransferases are elevated.

Notably, this pattern of liver injury can be seen in COVID-19 patients with or without underlying liver disease, but studies have demonstrated that those with underlying liver disease have worse outcomes and higher mortality.⁸ As a result, it's recommended that clinicians consider patients with chronic liver disease to be in a high-risk category and to be mindful of timely diagnosis and early isolation.

Patients with chronic liver disease, cirrhosis, or cholestatic liver conditions, as well as liver transplant recipients, may be at higher risk for contracting COVID-19, as well as having a more severe illness.⁹

INFLAMMATORY BOWEL DISEASE

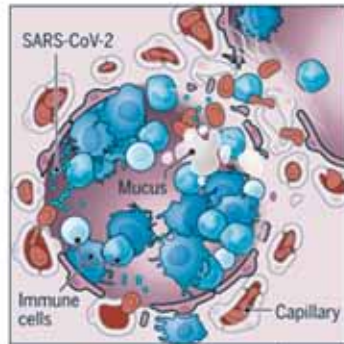
Based on current data, it appears that patients with IBD do not have a higher prevalence of COVID-19 than the general population,¹⁰ but they do pose specific management challenges. For instance, it may be difficult to determine if an increase in symptoms such as diarrhea

Pathogen's impact

Although the best known effects of SARS-CoV-2 involve the respiratory system, many other organs can be affected.

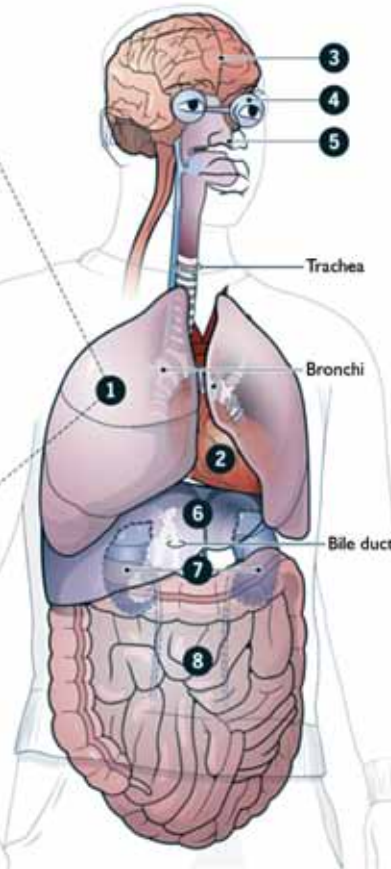
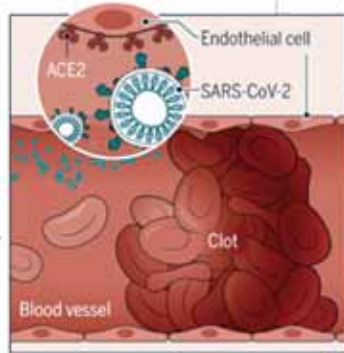
1 Lungs

A representation of immune cells filling an alveolus, impairing gas exchange.



2 Circulatory system

The virus (blue) invades vascular endothelium via the ACE-2 receptors. Adverse consequences include abnormalities of perfusion, intravascular thrombosis, MI, and myocarditis.



3 Brain

Some patients develop strokes, seizures, confusion, and encephalitis. It is not yet certain which are direct viral effects, and which are secondary to intravascular thrombosis.

4 Eyes

Conjunctivitis is more common in the sickest patients.

5 Nose

Anosmia is often an early symptom, with or without dysgeusia. It is most likely due to temporary dysfunction of supporting cells in the olfactory epithelium, which affects function of olfactory neurons.

6 Liver

Liver enzymes are often elevated, with or without pre-existing liver disease (see text).

7 Kidneys

Renal injury is common, either from direct viral damage, or labile BP with inadequate renal perfusion.

8 Intestines

Intestinal injury is common because the gut is rich in ACE-2 receptors (see text).

Fig. 1. A rampage through the body. Adapted from Wadman M et al. *Science* Apr 24, 2020. Reprinted with permission from AAAS.

is due to a flare of IBD or to COVID-19; inflammatory markers may not be reliable because they can be elevated in either case. Also, access to endoscopic evaluation could potentially be limited.

For IBD patients in remission it is recommended that no changes be made to their existing medication regimen.¹¹ For IBD patients in an active disease flare, most experts recommend avoiding or minimizing use of systemic corticosteroids. Safe alternative options include aminosalicylates, topical/rectal therapies, budesonide, and biological therapies like anti-tumor necrosis factor, anti-integrin, and anti-interleukin agents.² For IBD patients with known or suspected COVID-19 infection, it may be necessary to adjust their medication regimen to reduce immunosuppression and lower their risk of COVID-19 related complications. In these situations, aminosalicylates, topical therapy, budesonide, and antibiotics can be safely continued; systemic corticosteroids should be tapered and if possible transitioned to oral budesonide; and immunomodulators like azathioprine and biologics like infliximab should be stopped.²

Nonetheless, for active IBD in the setting of mild COVID-19 disease, preliminary data suggest that induction therapy with a biologic agent is not likely to result in progression to more serious infection. Small European case studies have demonstrated that COVID-19 patients with chronic inflammatory diseases on chronic immunosuppression have outcomes similar to the general population.¹² There is debate about when to resume therapeutic agents that have been temporarily stopped, but most experts agree that patients should be observed for a 14-day period after testing is negative and/or symptoms are absent.

THE PANCREAS AND COVID-19

We know that SARS-CoV-2 affects multiple organ systems (Fig.1), and the pancreas may also be susceptible. One study showed that approximately one patient in six with pneumonia from COVID-19 had serologic evidence of pancreatic injury.¹³ It remains unclear if this finding results from direct infection of the pancreas itself, or from an inflammatory response to a severe

systemic illness and its treatments. It's also unclear if elevated pancreatic enzymes portend a more serious clinical course or worse outcomes, just as inflammatory markers, kidney injury, lymphopenia, and abnormal liver enzymes do.⁶

IMPACT ON OTHER GI SERVICES

The pandemic has impacted all of our lives as health care providers in many ways. The restriction of services to only the most essential has potentially far-reaching implications. A study in two New York hospitals showed that patients admitted with active GI bleeding during the pandemic had significantly lower hemoglobins and platelet counts, and higher INRs, than GI bleeders admitted prior to the outbreak. They also were more likely to receive a blood transfusion, had longer hospital stays, and were 70% less likely to undergo endoscopy.¹⁴

It's too soon to know how cancer detection will be impacted by the reduction in elective procedures like screening and surveillance colonoscopies, but a study

in Hong Kong demonstrated a 50%-60% reduction in upper and lower endoscopies beginning at their turning point in January 2020, and a 30%-40% reduction in diagnoses of gastric and colon cancer.¹⁵

Predictive modeling suggested that a significant percentage of patients would present at a more advanced stage of cancer 6 months after the turning point. Additional reductions in endoscopic procedures were predicted to lead to larger drops in gastric and colorectal cancer diagnoses.

This phenomenon means that deferment of elective endoscopic procedures cannot continue indefinitely. If we are successful in containing the spread of the virus, it won't have to. As the nation gradually reopens and attempts to return to some degree of normalcy, our practice at Regional GI is slowly resuming elective endoscopies. At the time of this writing, we will have just started to take the first tentative steps. Hopefully, by publication, we'll be back up to full speed.

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