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REVIEW ARTICLE

# Navigating the Gastrointestinal Implications of Coronavirus 19: Strategies and Lessons Learned

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## ABSTRACT

In 2019, an outbreak of COVID-19 caused by SARS-CoV2 spread worldwide, affecting millions of individuals. This was colloquially termed the "COVID-19 Pandemic." As the pandemic progressed, multiple variants of SARS-CoV2 continued to evolve, including the most recent JN1, and spread worldwide, causing a broad spectrum of symptoms affecting multiple organ systems. The purpose of this article is to comprehensively explore COVID-19 through the lens of the Gastrointestinal system (GI) and review the treatments. The prevalence of GI symptoms in COVID-affected patients ranged from 28.2% to 50% throughout the pandemic. The predominant symptoms include nausea, diarrhea, reflux, abdominal pain, and emesis. Interestingly, these symptoms persisted for an extended time, sometimes the most bothersome, even after the resolution of an active infection. Due to the nature and prevalence of these symptoms, it is imperative that we understand the mechanism of interaction of SARS CoV2 and the GI system and its pathophysiology. Despite being the less common transmission route, the fecal-oral route is to be considered when devising public health strategies. The term "Long Covid" has been coined due to the long-term symptoms after active infection, and interestingly, GI symptoms have a significant prevalence. Though unclear, the pathogenesis is thought to be due to gut dysbiosis and dysbiosis of the gut-brain connection. In this article, we have also discussed the GI symptoms and treatment of COVID infection in inflammatory bowel disease, pediatric population. We have also discussed guidelines by gastroenterology societies for care prior to, during, and after endoscopy, as well as ostomy care in COVID patients.

## Introduction

In 2019, an outbreak of COVID-19 caused by SARS-CoV2 spread across the world affecting millions of individuals and leading to hundreds and thousands of deaths. This outbreak was colloquially termed the COVID-19 pandemic. As the pandemic progressed, variants of SARS-CoV2 like omicron, delta, and alpha started to spread worldwide causing a concurrent change in the pattern of symptoms experienced by patients which ranged from a milder disease to severe form. The clinical presentation was highly variable and dependent on many factors including age and comorbidities leading to symptomatology on a wide spectrum. Gastrointestinal (GI) symptoms were reported from the onset of the pandemic and prevalent throughout. While not associated with increased mortality, there is evidence that the presence of GI symptoms is associated with longer, more complicated disease courses of COVID-19. The study of GI symptoms in the early stages of COVID and continued effects on the GI tract after COVID seemingly has been eradicated from the body continues to be important in fully understanding SARS-CoV2. Long term sequelae of COVID, colloquially termed "long COVID" is a major burden on patients and is a growing field of research as medical societies learn more about the pathogenesis of COVID-19 within different organ systems. Here we explore COVID-19 through the lens of the gastrointestinal system and the short term and long-term implications and treatments associated.

## Epidemiology:

The clinical presentation of COVID-19 infection is highly variable and dependent on many factors including age and comorbidities leading to symptomatology on a wide spectrum. The GI system has been shown to be a significant first line defense against COVID leading to interactions with the virus causing GI symptoms. These symptoms ranged from abdominal pain to nausea, vomiting to diarrhea which made up close to 28.2% of the GI related complaints of COVID patients.[1] While SARS-CoV2 is seen as predominantly affecting the respiratory system, studies show that over one-third of patients had some observed GI tract symptoms. These symptoms sometimes preceded the respiratory symptoms. As the pandemic reached its peak, reports found that two-thirds of COVID-19 patients had nausea/vomiting, 40% had appetite loss, and 50% had diarrhea.[2] However, unlike most other symptoms, some GI effects lasted well beyond the acute phase of infection. After COVID-19 infection, GI symptoms are becoming more common with some of the more serious GI affects being diseases like ulcerative lesions of the GI tract, GI bleeds, and GI thrombotic lesions. In one study, GI thrombotic lesions were found in 36.9% of patients and GI inflammatory lesions in 41.3%.[3] Other studies show that GI symptoms can persist 6 months after COVID infection in 10-25% of patients with these symptoms being rated as the worst issue in 11% of patients.[4] Due to the nature and prevalence of these GI symptoms, understanding the mechanism of the interaction of SARS-CoV2 and the Gastrointestinal system becomes that much more important.

## Viral structure:

Coronaviruses are large, spherical, and enveloped with a single stranded, large positive sense RNA genome. They consist of 4 key structural components: the spike (S), membrane (M), envelope (E) and the nucleocapsid (N) protein encoded within the 3' end of the genome. The S protein is the component that is the focus of research and immense interest within the scientific and medical communities due to it being the prime target for autoantibodies and the development of potential vaccines. The virus uses the S protein to bind the host cell with specific receptors and thus allows for the virus to enter

the host cell and initiate the translation of the viral genome. Random mutations and recombinations makes the coronavirus highly infective across species and lead to cross-species infection.[5] The newest strain, JN1, is currently causing a surge of infections in the US with almost a 10% rise in COVID hospital admission since December 2023 and accounting for over 85% of COVID infections by January 2024.[6] The JN1 strain's unique feature is the presence of an additional spike protein mutation. This mutation increases its infectivity and its potential to evade immune response seen with the COVID-19 vaccine. Breathlessness is one of the key signs of severe disease in this new strain but other symptoms include other respiratory symptoms as well as GI issues like severe diarrhea.[7] However, it does not seem like the JN1 strain affects the GI tract as severely as the respiratory tract. As surveillance of symptoms by the WHO and national governments continues for each strain, this will be an area of interest going forward.

## Pathophysiology:

The pathophysiology of COVID-19 has been integral to understanding how the virus targets the body, the clinical manifestations of this process, and viral treatment and clearance. The ACE2 is a target receptor found on cells that has been implicated as part of the major pathogenesis of COVID-19 infection. ACE 2 is commonly associated with the RAAS system but in the intestine, ACE2 is important for the regulation of amino acid homeostasis, intestinal inflammation, and the gut microbiome. The attachment of the SARS-COVID spike protein to this target receptor leads to viral entry into the cells and is seen as the possible root of infection of COVID in the GI system as ACE 2 receptors are highly expressed in epithelial cells of the GI tract.[8] This was revealed via immunofluorescence showing staining of ACE 2 receptors in the cytoplasm of GI epithelial cells while being seen much less in parts of the body that express more glandular epithelial cells like the esophagus. The ACE 2 receptor is then internalized after being attached to by the viral spike protein and subsequently newly synthesized viral specific RNA and proteins assemble new virions and release into the GI tract. The subsequent accumulation of ACE2 levels is seen and corresponds to more severe disease. PCR is used to detect virions in the feces which has been found to be positive for viral shedding in 20% of patients who have successfully cleared the virus from the respiratory tract. This viral shedding can last up to 7 months. The fecal-oral route of transmission is an important measure when devising public health strategies and can be useful in stopping the spread of COVID-19.

The term "long COVID" has been coined as more research and attention is being drawn towards long term effects of COVID-19 on the body. In one study, up to 30% of patients reported long-term symptoms long after resolution of the infection and undetectable viral loads.[9] The CDC has estimated that 1/13 adults in the US suffer from long COVID-19 with an ICD code for Post-Acute Sequelae of COVID-19 being approved. The most common symptoms with long COVID include diarrhea, nausea, vomiting, abdominal pain, with some patients having significant elevations in LFTs. In a meta-analysis, the pooled prevalence of stool samples positive for viral load was 48.1% and of those, 70.3% remained positive after testing negative from respiratory specimens. The pathogenesis is still unclear, but the underlying mechanisms are thought to be from gut dysbiosis and dysbiosis of the gut-brain connection. Coronavirus 19 decreases microbial production of butyrate which is important in maintenance of colon mucosal health and leads to systemic pro-inflammatory states long after infection.[10] The long-term presence of these pro-inflammatory compounds can

affect the cerebrovascular system via the compromised blood brain barrier causing a cycle that is not easily corrected.

## Viral loads:

In viral infections like COVID-19, assessing viral load is important in assessing disease severity as the amount of viral load correlates with the number of viral particles in the body. This can be measured using rRT-PCR. The viral load in the respiratory tract peaks around symptom onset and gradually decreases 1-3 weeks after. However, the same cannot be said for viral load measured in stool as this can last weeks to months after clearance from the respiratory tract.[11] 5 years into COVID, the use of viral loads has been implemented in public health policy. One of these ways is through the CDC's use of wastewater surveillance to infer COVID-19 cases and the peaks and troughs that a population can expect. This can be used as an early warning sign so that early action can be taken. The positives of implementing this surveillance as early detection for rising COVID cases includes inclusion of individuals without access to healthcare, nearly universal implementation as over 80% of US households are included in this surveillance and does not require access to COVID testing. The cons include the inability to capture homes on a septic system, inability to capture facilities that treat their own waste like jails and hospitals, and overall cannot accurately assess the number infected as people move in and out of cities.[12] Overall, it is a good tool to see the trends of a community's rate of infection but cannot be used to accurately predict the number infected.

## Gastrointestinal clinical presentation:

SARS-CoV-2 is a respiratory virus spread through droplets but GI symptoms are a prominent feature of acute infection. A multinational study done shortly after the start of the COVID-19 pandemic showed that nearly 60% of patients hospitalized for COVID had one or more GI symptoms. These symptoms include:

- Nausea
- Diarrhea
- Reflux
- Abdominal pain
- Emesis

With studies being done throughout the 5 years of COVID-19, new findings show that long term GI symptoms are frequently reported after resolution of all other symptoms of COVID-19. A more recent study now shows that 10-25% of patients reported new, persistent symptoms related to the gastrointestinal system. Risk factors for persistent GI symptoms include:

- GI symptoms during acute COVID infection
- More severe COVID infection
- Mental health issues like depression or anxiety

Clinically worse disease does correlate to gut microbiome changes and increased inflammatory markers but these mechanisms are unclear. Studies show that COVID-19 can cause liver injury with mild to moderate LFT elevations but at lower rates than respiratory coronaviruses (5-37% vs 60% respectively). However, the greater the extent of GI symptoms and liver injury, the more severe the disease with these patients often needing ICU level care.[13] The liver exposure is also VIA ACE-2 receptors in cholangiocytes with a retrograde mode of liver damage from the biliary tract. Both disease via pro-inflammatory cytokines and treatment can exacerbate underlying liver injury during the course of SARS-CoV2 infection. The presence of chronic liver disease like those with cirrhosis or pre-existing hepatitis B is considered a risk for worse prognosis and more severe disease course.[14] However, this is an area that needs more investigation.

Gastrointestinal symptoms from COVID infection has many overlapping symptoms with IBD including diarrhea and abdominal pain. The same receptor (ACE-2) which is implicated in the pathogenesis of COVID in the GI system is upregulated in those with IBD.[13] Recent studies show that those with IBD are more prone to higher incidence of GI symptoms when infected with SARS-CoV2 than those without IBD. Determining when to test in this subgroup of patients can be difficult to determine, but a good rule of thumb remains to test individuals who have increased GI symptoms with other symptoms, mainly the respiratory tract, being involved. In patients who are already diagnosed with IBD, the continuation of their immunomodulators and biologics is a controversial topic. There is growing consensus that continuation of treatment does lead to decreased risk of severe infection and hospitalizations in this patient population.[15] However, the international Organization for the Study of IBD did release a guide for treatment of IBD and COVID and supported the discontinuation of TNF or ustekinumab in those who develop COVID. These medications should be held until symptoms of COVID-19 resolve which usually takes around 2 weeks and can be restarted after the course of infection resolves.[16] The testing of asymptomatic individuals with IBD for COVID before initiation of biologics is not recommended at this time.

## COVID-19 in the pediatric population

While COVID -19 is predominantly known for the respiratory manifestations in children, it can also have a significant impact on the gastrointestinal (GI) system. Surprisingly, GI symptoms can be some of the earliest presenting symptoms or they may manifest very late in the disease course and in up to 10% of children may be the only presentation of the disease.[17] Diarrhea was the most common manifestation and most often occurred between 1-8 days after the disease onset.[18] These symptoms can be seen below in figure 1. There have been many studies looking at the presentation of MIS-C (multisystem inflammatory syndrome in children), which is a condition characterized by systemic inflammation and multisystem organ dysfunction, which includes the GI system. However, few studies have narrowed in on how the GI tract is specifically affected and how that may even play a role in the spread of this illness.[18] The SARS-COV-2 enters cells via the ACE-2 receptor that is commonly found on lung cells, but it can also be found on enterocytes. Around 50% of all covid-19 patients have detectable viral RNA in their stools and viral shedding can be seen almost five weeks beyond the first negative nasopharyngeal aspirate in children. [18] COVID-19 has made a significant impact on health care service and has affected children in various ways. Clinical practice within the GI system has had a significant impact as it has raised the risk of delaying assessment of chronic GI issues such as IBD due to the risk of performing endoscopic procedures during acute illnesses. By having a better understanding of the impact COVID-19 has on the GI system, we can optimize the treatment and equity of care provided to children.

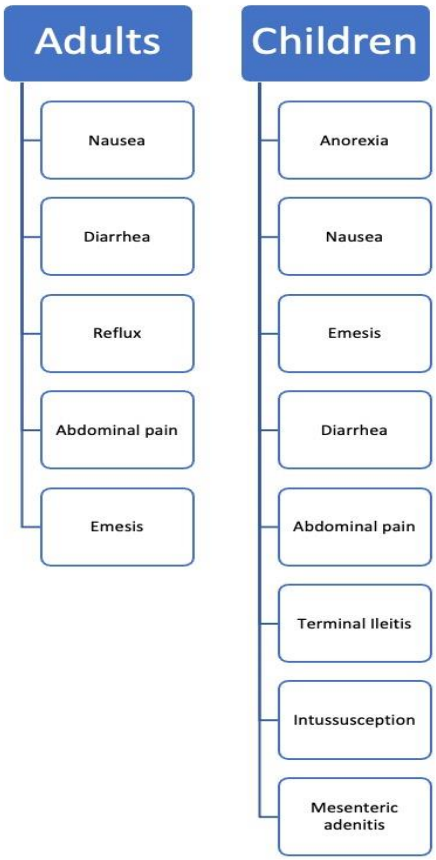


*Figure 1: Described above showing common GI symptoms in patients with known COVID infection delineated between adults (Age >18) and children (Age <18).*

## GI specific treatment:

Management of COVID-19 is largely preventative with reduction in risk factors and implementation of screening protocols as well as supportive in the hospital with oxygen. COVID treatment guidelines fall into 3 classes: Class A (strong recommendation), Class B (moderate recommendation), and Class C (weak recommendation). There is a class A rating for symptomatic management of COVID symptoms in all patients, however, it recommends against the use of systemic corticosteroids or dexamethasone in all non-hospitalized patients or hospitalized patients without oxygen needs unless treating an underlying condition. In non-hospitalized patients who are at high risk for severe COVID infection without the use of oxygen, the use of Paxlovid within 5 days of symptom onset (Class A) is recommended over remdesivir (Class B) and molnupiravir (Class C). In hospitalized patients needing minimal supplemental oxygen, remdesivir without dexamethasone is recommended but if needing increasing oxygen requirement the addition of dexamethasone is recommended.[19]

Due to there being unclear mechanisms to long term GI symptoms after resolution of COVID-19, there are two main focuses. There has been evidence of COVID-19 infection compromising the endothelium in the CNS and epithelium in the intestines which may cause dysfunction in the gut brain neurovascular system. The virus uses an ACE2 receptor which is widely present in cerebrovascular endothelium as well as the GI system. This can

lead to dysbiosis which is a shift towards pro-inflammatory and pathological shift in the gut microbiome.[18] The first is a focus on normalizing gut-brain connection at the gut level with fiber, prokinetics or antispasmodics, and diet changes based on the symptoms that are present. The other focus is on centrally acting treatment including CBT, neuromodulators, and gut directed hypnotherapy. These therapies focus on mitigating the effects of dysbiosis, improving the gut-brain system, and towards decreasing long term GI symptoms related to SARS-CoV2 infection. Some of these therapies are also being explored in relation to IBD and is growing field of research.[20]

Dysregulation of the bidirectional gut-brain barrier is posited as a mechanism for long COVID and the prolongation of GI symptoms after resolution of COVID. The interplay between this pathway needs continued study and could unlock treatment options to target specific parts of the pathways leading to these prolonged symptoms. Currently, there are no guidelines on management of these symptoms with medications, recommendations to improve chronic inflammation in the gut includes: multivitamins with extra vitamin D, increasing Omega-3 levels, increasing fiber intake, and increasing probiotic foods in one's diet.[21]

From a GI standpoint, there are updated recommendations from the different societies including the American Gastroenterology Association regarding COVID-19. These include rescheduling elective, non-urgent endoscopies in patients with COVID, continued use of immunosuppressive medications in patients with IBD and autoimmune hepatitis, and pre-screening all patients for risk factors. During the pandemic testing for COVID-19 prior to all procedures was standard but new guidelines do not require testing prior to procedures like colonoscopy or endoscopy. They also recommend monitoring patients with new diarrhea, nausea, or vomiting for other COVID symptoms and elevated liver enzymes, which is seen in 15% of COVID patients, should be thoroughly evaluated.[22] While the overall number of endoscopies and colonoscopies were decreased during the COVID-19 pandemic, guidelines were quickly implemented for the use of these procedures in emergent cases. Urgent endoscopies were staffed with strategically assigned staff (one endoscopist and 2 nurses) to minimize exposure and they were performed in negative pressure rooms when available. Standardized infection control was put in place including standard hand hygiene procedures before and after, the use of PPE at all times, increased care while handling all biopsies, and a 30-minute buffer between each use of the room. The disinfection and reprocessing of endoscopes and instruments was fairly unchanged and all disposable devices were not to be reused.[23]

The United Ostomy Association of America states that those with ostomy are not at increased risk of contracting COVID or at increased risk of side effects from the COVID vaccine.[22] Handwashing remains the most effective way to protect patients from getting sick while doing ostomy care. Other ways to reduce risk is social distancing and decreasing fecal transmission. Guidelines have been created to help guide patients on safe waste disposal as shedding of SARS-CoV2 can be found in fecal matter. Those with suspected COVID-19 infection should use their own toilet if able, flush with the lid down to prevent droplet splatter, and disinfecting surfaces that could be contaminated. When providing self-care for an ostomy pouch, no gloves are needed, and waste should be disposed of via garbage. Individuals helping with ostomy care of a patient should use gloves and masks whenever in contact with the pouch.[24]

## Conclusion:

The COVID-19 pandemic had a monumental effect on the world socially, economically, and

physically. Over 60% of patients infected with the SARS-CoV2 reported at least one GI symptoms ranging from nausea, vomiting, abdominal pain, and reflux. The fecal-oral transmission is an established and important mechanism of transmission with viral loads being shed via the GI tract months after respiratory symptoms have ceased. The CDC estimates that almost 1/13 of Americans suffer from long COVID symptoms and 30% of COVID patients report being symptomatic for months after viral load is no longer detectable leading to the ICD code for Post-Acute Sequelae of COVID-19. Major American gastroenterologist societies have created guidelines in terms of endoscopy care prior, during, and after procedures on COVID patients as well as how to perform safe ostomy care for patients infected with COVID. The international Organization for the Study of IBD has also released guidelines on which biologics and immunosuppressants should be discontinued in the context of COVID which had previously not been studied.

## Conflict of Interest:

The authors have no conflicts of interest to declare.

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