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Gastrointestinal manifestations of COVID-19

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ABSTRACT

Gastrointestinal (GI) symptoms are seen in patients with COVID-19. The prevalence could be as high as 50%, but most studies show ranges from 16% to 33%. Presenting with GI symptoms increases the risk of testing positive for SARs-CoV-2. Approximately 50% of patients with COVID-19 have detectable virus in their stool. Having GI symptoms has been associated with more severe disease. Management of GI symptoms is mainly supportive. Healthcare providers should be aware of the GI manifestations of COVID-19 and perform SARS-CoV-2 testing for patients presenting with digestive changes, especially in those with respiratory symptoms.

SARS-COV-2 IN THE GASTROINTESTINAL TRACT

Several studies have shown the presence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the digestive tract and stools. Approximately 50% of patients with coronavirus disease 2019 (COVID-19) have detectable viral RNA in the stool.[1–3] SARS-CoV-2 nucleocapsid protein has been found in gastric, duodenal, and rectal glandular epithelial cells.[1] Viral RNA also has been found in esophageal, gastric, duodenal, and rectal biopsies particularly in patients with severe disease, suggesting that the presence of SARS-CoV-2 in gastrointestinal (GI) tissue is associated with a more severe disease course.[2]

Interestingly, SARS-CoV-2 RNA also has been incidentally found in GI and liver tissue from recovered COVID-19 patients 1 to 3 months after the initial infection.[4,5] In addition to RNA, a recent preprint demonstrated the presence of N protein and intact virions in GI tract biopsies of recovered patients up to 5.5 months after COVID-19 infection.[6] The significance and clinical implications of these findings remain to be determined.

Live virus has also been detected in the stool of patients with COVID-19 by electron microscopy.[7] Although these findings raise the possibility of fecal-oral transmission, this mode of transmission has not been confirmed. Using epidemiologic and environmental data, a study showed fecal aerosols generated during flushing may have been responsible for a cluster of cases in a high-rise building in China, suggesting the possibility of fecal-aerosol transmission of SARS-CoV-2.[8]

Infectious SARS-CoV-2 has been isolated from stool samples of COVID-19 patients and shown to infect human intestinal organoids.[9] There is also a clinical study from Austria that showed evidence for intestinal inflammation induced by SARS-CoV-2 in which patients with current or resolved diarrhea had higher concentrations of fecal calprotectin than patients without diarrhea.[10] Interestingly, fecal calprotectin levels significantly correlated with serum interleukin 6.

The pathophysiology of digestive symptoms associated with COVID-19 remains unclear. SARS-CoV-2 appears to enter host cells by binding to the angiotensin-converting enzyme-2 (ACE2) receptor and using the transmembrane serine protease 2 for spike protein priming.[11] ACE2 is highly expressed in the small bowel and colon.[6] Data have shown co-expression of ACE2 and transmembrane serine protease 2 in esophageal cells and absorptive enterocytes from both the ileum and colon.[12] Another study reported the infection of enterocytes by SARS-CoV-2 in small intestinal organoids.[13] These findings support the possibility of viral invasion of enterocytes and provide a potential mechanism for SARS-CoV-2–associated GI symptoms.

Although the presence of SARS-CoV-2 RNA in the stool was not initially thought to be associated with digestive symptoms, recent data indicate that patients with GI symptoms may be more likely to have detectable fecal RNA than patients with respi-

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ratory symptoms only.[14,15] In a study out of Wuhan, China, 69% of patients with diarrhea had detectable RNA in the stool as opposed to only 17% of patients without diarrhea.[16]

Interestingly, viral RNA can be detected in stool several weeks after symptom onset. Another study from China found that respiratory samples remained positive for an average of 16.7 days after symptom onset, whereas fecal samples remained positive for about 27.9 days.[17] In addition, patients with diarrhea may have more prolonged fecal shedding than patients without diarrhea.[16] What is unknown is whether these patients are infective and if there is a fecal-oral spread to coronavirus.

The gut microbiome also appears to be affected in COVID-19. Fecal microbiomes in patients with COVID-19 are characterized by an enrichment of opportunistic pathogens and depletion of beneficial commensals, with specific patterns correlated with COVID-19 severity and SARS-CoV-2 fecal load.[18] Although this suggests a possible role for probiotics in the treatment of COVID-19, there is currently no evidence to support their use in this context.[19]

GI SYMPTOMS: PREVALENCE

Although initial data found the prevalence of GI symptoms to be 2% to 10% among patients with COVID-19,[20,21] subsequent studies have reported higher rates. In a multicenter study of 204 patients with COVID-19 in China, 50.5% reported GI symptoms at presentation to the hospital.[22] In a meta-analysis including 60 studies and 4,243 patients, the pooled prevalence of all GI symptoms was 16.1% in studies from China and 33.4% from other countries.[15] In another meta-analysis including 47 studies and 10,890 unique patients, GI symptoms were present in less than 10% of patients, but rates were higher in studies outside of China.[23] In a recent large prospective UK cohort of 20,133 patients with COVID-19, 29% had enteric symptoms on admission.[24]

Most studies included hospitalized patients, but some included outpatients. More recent studies out of California, New York, and Massachusetts reported a prevalence of GI symptoms of 31.9%[25] and 35%[26] (both inpatients and outpatients) and 61.3% (hospitalized patients).[27] Furthermore, a US case-control study found that the presence of digestive symptoms was associated with a 70% increased risk of testing positive for SARS-CoV-2 (adjusted odds ratio 1.7; 95% confidence interval 1.1–2.5).[26]

Of note, patients with COVID-19 may present with GI symptoms without respiratory symptoms. In a retrospective study of 1,141 patients with COVID-19 in China, 16% presented with GI symptoms only.[28] In addition, a recent US study reported that 14.2% of patients with COVID-19 had digestive symptoms as their main presenting complaint, regardless of age or underlying comorbidities.[27]

GI SYMPTOMS: CHARACTERISTICS

Among GI manifestations associated with SARS-CoV-2 infection, loss of appetite or anorexia is the most commonly reported symptom. Although rates vary across studies, a meta-analysis of 60 studies found a pooled prevalence of 26.8% in patients with COVID-19.[15] Diarrhea was the second most common symptom with a pooled prevalence of 12.5%. A pooled analysis of clinical studies that reported diarrhea found a prevalence of 10.4% (range 2% to 50%) in patients with COVID-19.[29] However, recent US data found higher rates ranging from 23.7%[30] to 33.7%.[27] Although some studies have described mild diarrhea,[22,31] other studies have reported severe diarrhea and acute hemorrhagic colitis associated with COVID-19.[32,33] The etiology of colitis is not known, but given the thrombotic complications associated with COVID-19, this likely represents ischemia.

Other digestive manifestations include nausea or vomiting and abdominal pain. According to US data, nausea or vomiting were found in 10.3%[25] to 26.4%[27] of patients with COVID-19, whereas abdominal pain was found in 8.8%[25] to 14.5%[27] of patients. Dysgeusia has also been reported, often in conjunction with anosmia, in up to 64% of patients with COVID-19.[34,35] Interestingly, in a US study, dysgeusia and anosmia were more common among patients with GI symptoms and were independently associated with nausea and anorexia.[27] Additional GI manifestations have been reported in the setting of COVID-19, including acute pancreatitis[36] and neutropenic enterocolitis.[37]

ARE GI SYMPTOMS ASSOCIATED WITH WORSE OUTCOMES?

Early data showed GI symptoms were associated with a worse disease course and prognosis. In one study, patients with diarrhea, nausea, or vomiting were found to have a more severe disease course, including higher rates of mechanical ventilation, than patients without GI symptoms.[31] A meta-analysis found higher rates of severe disease in patients with GI symptoms compared with patients without GI symptoms.[15]

In one of the first case series of inpatients with COVID-19, patients admitted to the intensive care unit (ICU) were more likely to have digestive

symptoms, including abdominal pain and anorexia, than non-ICU patients.[21] In addition, a recent US retrospective study found that patients with digestive symptoms had a 4-fold increased risk of hospitalization compared with patients without GI symptoms.[38] Another study out of New York City found patients with GI symptoms to be at increased risk of admission.[39] In a recent large retrospective cohort of 29,393 COVID-19 patients, the presence of GI symptoms was associated with a 50% increased risk of severe illness. Furthermore, patients with both GI symptoms and fever had an 85% increased risk of severe COVID-19.[40]

Other studies, however, including those with US data, have not found an association between GI symptoms and worse outcomes.[2,25–27] In fact, in a US case-control study, a significantly lower short-term mortality rate was found among patients with digestive symptoms.[26]

Although the reason for these differences is unclear, possible explanations may include variations in reporting, distinct patient populations, and different viral strains.[27,41,42] In addition, viral clearance among patients with digestive symptoms appears to be significantly longer compared with patients with respiratory symptoms only.[14] Interestingly, patients with COVID-19 and GI symptoms also appear to have a longer illness duration[26] and present later for medical care than patients without GI symptoms.[14,22]

GI SYMPTOMS IN CHILDREN

Several studies have reported digestive symptoms in pediatric patients with COVID-19. A meta-analysis found a pooled prevalence of 24.8% among children with COVID-19.[15] In one of the largest pediatric series, diarrhea was found in 8.8% of patients with COVID-19, whereas vomiting was found in 6.4%.[43] Data from the Centers for Disease Control and Prevention, as of April 2, 2020, show rates of nausea/vomiting, abdominal pain, and diarrhea of 11%, 5.8%, and 13%, respectively, among 291 pediatric patients with COVID-19.[44]

In a more recent prospective UK study of hospitalized pediatric patients, 35% had GI symptoms on admission.[45] In addition, in a large prospective seroprevalence study, GI symptoms were reported in 19% of SARS-CoV-2–positive children and were found to be independently associated with SARS-CoV-2 seropositivity on multivariable analysis.[46]

MANAGEMENT

TABLE 1

Suggested management of COVID-19–related gastrointestinal symptoms in adults

Supportive care[47,48]

Fluid and salt intake (eg, soup, broth, juice, saltine crackers, low carbohydrate sports drinks) to maintain hydration status

Oral rehydration therapy for mild dehydration

Intravenous rehydration for severe dehydration

Pharmacotherapy[47,48]

Nausea and vomiting:

- Prochlorperazine 5 to 10 mg orally 3 to 4 times daily as needed (maximum of 40 mg/day)
- Ondansetron 4 to 8 mg orally 3 times daily as needed (off-label use)

Diarrhea:

- Loperamide 4 mg orally initially, followed by 2 mg after each watery stool (maximum of 8 mg/day)

Monitoring for worsening disease course[49]

Hospitalization if alarm symptoms:

- Severe or persistent symptoms
- Gastrointestinal bleeding
- Intractable vomiting
- Dehydration
- Change in mental status

Consider consultation with a gastroenterologist for further work-up and management if worsening disease course.

Currently, management of GI symptoms in patients with COVID-19 is mainly supportive. There are no published data on the treatment of COVID-19–associated GI symptoms. The following recommendations are based on evidence from data on acute diarrhea and gastroenteritis in patients with COVID-19 (**Table 1**).[47–49]

Treatment should be individualized according to the patient's symptoms, underlying comorbidities and COVID-19–associated complications. First, other causes of GI symptoms should be considered as the treatment may differ, including *Clostridioides difficile* or medication-related adverse events.[50]

It is important to note that medications used for COVID-19 may be associated with GI symptoms as well.[23] Remdesivir appears to be associated with diarrhea in 3% to 9% of patients,[51,52] and nausea and

vomiting in 3% to 5% of patients with COVID-19.[51] Chloroquine and hydroxychloroquine are also associated with GI symptoms but are no longer approved for the treatment of COVID-19.[23] Baricitinib, which is now approved for the treatment of COVID-19, has also been associated with GI symptoms and rare GI perforations when used for rheumatoid arthritis.[53]

In most cases, patients with acute diarrhea are able to maintain their hydration status with fluid and salt intake by consuming sports drinks, juices, soups, and other fluids.[47] For patients with more significant fluid depletion, oral rehydration therapy with a balanced electrolyte solution is recommended.[47] Isotonic intravenous fluids should be used for severe dehydration or shock.[48]

In addition to supportive care, medications can generally be used for symptomatic relief in the setting of gastroenteritis or acute diarrhea. Antiemetics such as ondansetron or dimenhydrinate can be used to help with oral intake and rehydration. Antimotility drugs such as loperamide can be used to manage acute diarrhea; however, these agents have been associated with the development of toxic megacolon in certain conditions and should be used cautiously.[47,48] Probiotics have been used in China in patients with COVID-19,[54] but there is a general lack of evidence supporting their use in this setting. Patients should be monitored for worsening or persistent symptoms. Hospitalization and gastroenterology consultation may be required in more severe cases.

CONCLUSION

Among the GI symptoms associated with COVID-19 are lack of appetite, dysgeusia, anosmia, diarrhea, abdominal pain, and vomiting. Patients may present with GI symptoms alone or with respiratory symptoms. Healthcare providers should be aware of the GI manifestations of COVID-19 and perform SARS-CoV-2 testing in patients presenting with digestive changes, especially in those with respiratory symptoms.

DISCLOSURES

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