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## Gut Involvement by COVID-19



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The coronavirus disease 2019 (COVID-19) pandemic persists unabated over this year, and this experience with the disease has given us an appreciation that the disease may be far-ranging in the tissues involved and multisystemic in nature. As of September 7, 2020, according to the Johns Hopkins University COVID-19 tracker, there have been over 27 million estimated COVID-19 cases associated with over 890 thousand deaths worldwide. Initial reports suggested that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was a respiratory pathogen mediated by its affinity to the angiotensin-converting enzyme 2 (ACE-2) receptor. As our understanding of COVID-19 evolved, it became clear that SARS-CoV-2 leads to gastrointestinal signs and symptoms, owing to the ubiquitous presence of the ACE-2 receptor in the human gut. The gastrointestinal effects are seen due to ACE-2 expression on small intestine and colonic enterocytes, hepatocytes, and cholangiocytes.

Gastrointestinal manifestations of SARS-CoV-2, including anorexia, nausea, vomiting, diarrhea, and hepato-cellular injury (manifesting as transaminitis), have been widely reported. A recent systematic review and meta-analysis of 78 studies with 12,797 patients reported that loss of appetite with a prevalence of 22.3% was the most common gastrointestinal symptom. Other symptoms such as diarrhea were reported in 12.4%, nausea and/or vomiting were seen in 9.0%, and abdominal pain occurred in 6.2%.<sup>1</sup> Another meta-analysis demonstrated that the pooled prevalence estimates of transaminitis was 15%.<sup>2</sup> These two large reviews demonstrate that studies from China report a lower prevalence of gastrointestinal symptoms and abnormalities compared with studies from other countries. This lower prevalence could be related to lack of adequate reporting of systemic symptoms in studies from China, as SARS-CoV-2 was initially thought to be a respiratory illness. In the midst of the

beginnings of a global pandemic, gathering and reporting all data can be a legitimate challenge; indeed, significant heterogeneity exists among the studies included in these systematic reviews. Studies have demonstrated that gastrointestinal symptoms may be present before respiratory symptoms and sometimes even in the absence of respiratory symptoms. The emergence of these data has led to amendment of screening and diagnostic protocols for COVID-19, with the inclusion of gastrointestinal symptoms to testing algorithms. It is now being recommended that patients presenting with these common gastrointestinal symptoms should undergo a thorough assessment for exposure to and presence of other nongastrointestinal symptoms of COVID-19.

A bigger debate and concern center on the detection of SARS-CoV-2 in stool and the role of feco-oral transmission of COVID-19. Samples from wastewater treatment plants from Italy demonstrated that SARS-CoV-2 was present in such sources in northern Italy in December 2019, thereby predating the severe surge of cases seen in Italy.<sup>3</sup> Interestingly, the evolution of the COVID-19 pandemic in an area can be monitored through the detection of SARS-CoV-2 in sewage water. In this regard, a study from France demonstrated an increased number of new COVID-19 cases two weeks after detection of SARS-CoV-2 in waste water.<sup>4</sup> Similar observations are now reported in other parts of the world. Chlorine treatment of waste water can effectively reduce SARS-CoV-2 but does not prevent the surge of cases that occurs after the detection of the virus in sewage. This suggests an increasing presence of the virus in the environment prior to case-surge, and that feco-oral spread may play a role in the transmission of COVID-19. There is an urgent need for the development of validated and optimized protocols for SARS-CoV-2 detection and quantification in stool and sewage samples.<sup>5</sup> This has implications both for infection

control when dealing with sick individuals and for epidemiological prediction of a surge of COVID-19 cases in a geographic area.

In this issue of *Mayo Clinic Proceedings*, McDermott et al<sup>6</sup> present insights from past coronavirus outbreaks and the current COVID-19 pandemic pertaining to the recognition of gastrointestinal symptoms. The authors thoughtfully point out that while, until recently, there has been a relative lack of research on treatment and outcomes from SARS-CoV-2, there is a large amount of literature derived from research conducted over the years after the severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) outbreaks. Gastrointestinal symptoms were commonly seen in both SARS and MERS, and the incidence of these symptoms appears to be more frequent in the SARS and MERS outbreaks. An instance of SARS community outbreak in 2004 was linked to airborne spread, and viral concentrations in respiratory secretions were lower than the concentrations in urine and stool.<sup>7</sup> These observations from the past reinforce the notion that feco-oral spread may be an important one in transmitting the disease. The presence of gastrointestinal symptoms should suggest testing for SARS-CoV-2 so as to aid in timely diagnosis and avoid inadvertent transmission. McDermott et al<sup>6</sup> also suggest that it is important to distinguish between the presence of gastrointestinal symptoms when the patient is first seen and those that develop during the course of the illness. Gastrointestinal symptoms commonly develop during hospitalization, and symptoms that develop after diagnosis should be interpreted in context of the usage of medications being trialed for treatment of COVID-19. McDermott et al<sup>6</sup> also hypothesize novel models of disease transmission for COVID-19. It is unclear if the viral particles detected from feces and emesis are infectious and can transmit the disease. In the absence of data, and owing to the detection of viral particles by nucleic acid amplification tests, the risk of transmission via surface

contamination cannot be ruled out. Studies have shown persistence of viral particles on inorganic surfaces for prolonged periods of time.<sup>8</sup> A recent report from China suggested that fecal aerosol transmission in a high-rise building may have led to a community outbreak of COVID-19.<sup>9</sup> These data have implications for community-spread for highly contagious viruses, especially in high-rise buildings with connected air-conditioning and sewage systems.

With data being inconclusive, there is a need for frequent air exchanges and consideration of installation of negative pressure systems while taking care of patients with COVID-19, especially while performing aerosol generating procedures. Another implication of these emerging data is the risk of transmission of SARS-CoV-2 for a commonly done procedure for recurrent *Clostridioides difficile* infection, namely, fecal microbiota transplantation (FMT). *Clostridioides difficile* infection is the most common bacterial infection in hospitals with high morbidity and mortality. Recurrent *C. difficile* is extremely common with the risk being over 60% after 3 or more infections. Fecal microbiota transplantation reduces the risk of recurrent *C. difficile* to less than 15%, owing to restoration of a disrupted microbiome. In 2020, microbiota-based therapies such as FMT are dependent on procurement of donor stool from well-screened donors ruling out microbiome-associated diseases and infections. With the potential transmission of SARS-CoV-2 from stool and the presence of asymptomatic carriage, donors need to be reliably tested for the presence of SARS-CoV-2.<sup>10</sup>

In summary, current understanding of COVID-19 is steadily improving, with new data emerging day by day. Physicians should systematically collect, report, and publicly disseminate data on systemic involvement from COVID-19. Health care policy makers, patients, and the general population should stay abreast of these developments in a rapidly changing field.

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**Potential Competing Interests:** Dr Khanna reports research grants from Rebiotix, Inc (a Ferring company), consulting fees from Shire Plc, Premier, Inc, Facile Therapeutics, ProbioTech, Inc, and Jetson, all outside the submitted work.

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