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COVID-19 and Gastrointestinal Tract Symptoms: Recognition, Containment, and Learning From the Past.

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COVID-19 and Gastrointestinal Tract Symptoms: Recognition, Containment, and Learning From the Past

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Coronavirus disease 2019 (COVID-19) is the first coronavirus pandemic in the United States, but globally it is the third coronavirus outbreak of the 21st century. Almost no data were available to guide the hospital medicine response to previous coronaviruses; however, for COVID-19, hospitalists can look to more than a decade of research conducted in the wake of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).

Data gathered from these outbreaks taught us that gastrointestinal (GI) tract symptoms were characteristic of both SARS and MERS.[1] The importance of GI tract transmission for these infections was not fully recognized until after a large community outbreak had been precipitated by an index patient with diarrhea, most likely via airborne transmission.[2] Thus, a lesson learned from these previous human coronavirus outbreaks is the importance of early recognition of GI tract signs—sometimes the only presenting symptoms—by clinicians and infection control professionals. Such recognition is critical to avoid delayed diagnosis and unintended transmission events in hospital settings.[3] Therefore, to inform patient care and hospital containment efforts, we summarize current data on the characteristics of GI tract symptoms for these recent coronavirus outbreaks and describe practical measures for preventing transmission due to GI tract viral shedding in hospital settings.

GI TRACT MANIFESTATIONS OF HUMAN CORONAVIRUS INFECTION

Fever and respiratory tract symptoms were highlighted early in the COVID-19 outbreak and are widely considered to be the main symptoms of COVID-19. As the outbreak has evolved, GI tract complaints (notably vomiting, diarrhea, anorexia, and abdominal pain) have emerged as prevalent symptoms, which sometimes occur in the absence of non-GI tract symptoms. Compared with SARS coronavirus (SARS-CoV) 1 or MERS coronavirus, in which GI tract symptoms occurred in approximately one-quarter of infected patients,[1] rates of GI tract symptoms may be lower for SARS-CoV-2, though prevalence data is still evolving and highly variable. Recent analyses describing the pooled prevalence of GI tract symptoms are summarized in Table 1. Combined results of these meta-analyses suggest that the "true" population rate of GI tract symptoms in patients with COVID-19 is likely between 10% and 20%.

Characterizing the time course of GI tract symptom appearance (ie, at presentation, on admission, during hospitalization) is important, although often neglected and poorly documented, for the accurate recognition of COVID-19. One meta-analysis determined that GI tract symptoms were the presenting symptoms in 10% of COVID-19 cases analyzed,[7] but data on this issue remain lacking. In other recent cohorts, between 3% and 16% of patients presented with at least one GI tract symptom (nausea, vomiting, diarrhea, and abdominal pain) without concurrent respiratory tract symptoms.[8,9] Importantly, GI tract symptoms that emerge later in the disease course of COVID-19 could result from viral pneumonia or systemic inflammatory response syndrome (especially anorexia, abdominal pain, and nausea/vomiting) or from antibiotics or other therapeutic agents

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given during treatment (especially nausea/vomiting and diarrhea).

Interestingly, COVID-19 studies from Asia generally report a somewhat lower prevalence of GI tract symptoms. These differences in prevalence rates could be due to a tendency to focus on more immediately threatening respiratory tract symptoms because they are more likely to cause clinical deterioration, lack of awareness of GI tract manifestations earlier in the pandemic, differences in classification of diarrhea, variability in screening protocols for GI tract symptoms, viral strain variability, and varying ethnic susceptibilities to viral GI tract infection.

Patients with COVID-19 also have serologic evidence of liver dysfunction, most commonly a mild increase in alanine aminotransferase, aspartate aminotransferase, and bilirubin levels and low concentrations of albumin, although severe liver injury has been reported.[8,9] A recent review of COVID-19 and liver disease concluded that COVID-19 was frequently associated abnormal liver function test results but that such results were generally mild and transitory.[10] Patients with more severe cases of COVID-19 also had a greater likelihood of liver injury. Relatively little data are currently available concerning COVID-19 in patients with preexisting liver disease, such as cirrhosis and nonalcoholic fatty liver disease. It is not yet known whether the etiology of liver injury is related to viral infection of hepatocytes, COVID-19 treatments, systemic inflammation due to the infection, or other causes. Taken together, however, these findings suggest that evidence of liver injury should be considered a GI tract manifestation of COVID-19.

The pathophysiology underlying GI tract symptoms in COVID-19 cases is not completely clear, but active viral replication may take place in the GI tract, with initial viral entry occurring through the angiotensin-converting enzyme 2 receptor. Generally, angiotensin-converting enzyme 2 receptors are highly expressed in the GI system, even more abundantly than in the lungs, and GI mucosa can therefore serve as a viral target site. Viral replication in the GI tract is supported by a report that identified intracellular viral nucleocapsid protein in biopsy results of gastric, duodenal, and rectal epithelial cells, another report finding live SARS-CoV-2 in stool, and yet another reporting high stool viral loads on polymerase chain reaction (PCR) and intestinal cells expressing subgenomic viral messenger RNA in hospitalized patients.[11-13] These data parallel reports from the SARS and MERS literature, which illustrate that these viruses probably infected the GI tract.

Although the prevalence among patients from different geographic regions, racial/ethnic backgrounds, and age groups needs to be clarified, these findings challenge the assumption that the "typical" patient with COVID-19 has exclusively respiratory tract symptoms and fever or that COVID-19 infection is improbable in the absence of respiratory tract symptoms.

GI TRANSMISSION OF COVID-19

Previous outbreaks can possibly shed light on transmission concerns for SARS-CoV-2. Fecal shedding and airborne transmission appear to have been pivotal in a notable superspreading event for SARS that involved an index patient with diarrhea and high viral loads in stool and urine.[2] The aerosolization of SARS-CoV-1 and transmission via the plumbing and ventilation systems have been argued to be the mechanisms that precipitated this event. Because the GI tract presentations of COVID-19 bear similarity to those caused by SARS and MERS, the prevalence of GI tract symptoms in these patients and the shedding of virus in stool should raise parallel concerns. Already, GI tract transmission of COVID-19 has been reported in a hospital spreading event in which one patient who had COVID-19 with abdominal symptoms infected several health care workers and other patients.[14] To prevent such events in hospital environments, the 2 primary considerations related to GI tract symptoms are (1) the mechanisms of GI tract transmission and (2) the time course of GI tract shedding.

Known and Possible Mechanisms of Transmission

As noted for SARS and other enteropathogenic viruses, patients shed virus from

TABLE 1. Pooled Prevalence of GI Tract Symptoms From COVID-19 Meta-analyses

Variable	Parasa et al[4]	Cheung et al[5]	Tariq et al[6]	Mao et al[7]
No. of studies	29	60	78	35
No. of patients	4805	4243	12,797	6686
All GI tract symptoms	NA	18%	NA	15%
Diarrhea	7%	13%	12%	9%
Nausea/vomiting	5%	10% (vomiting)	9%	6%
Abdominal pain	NA	9%	6%	3%
Liver injury	20% AST, 15% ALT	NA	NA	3%
Anorexia	NA	27%	22%	21%
Stool sample positivity	41%	48.1%	NA	54%

ALT = alanine aminotransferase; AST = aspartate aminotransferase; COVID = coronavirus disease 2019; GI = gastrointestinal.

emesis and feces that can lead to surface contamination in patient areas, creating a transmission risk via contact from infected surfaces. Touching these surfaces and then touching the face, nose, or mouth can result in self-inoculation with the virus. Furthermore, it is well established (although not well publicized) that toilet flushing has the potential to generate infectious droplets and aerosols resulting in contamination of the surfaces and air with some enteric pathogens, especially in viruses. Notably, as discussed previously, aerosolization of SARS-CoV-1 probably triggered a SARS superspreading event,[2] highlighting the importance of this transmission mode.

For transmission via GI tract secretions to occur, live virus needs to be secreted in stool or vomit and remain viable on surfaces or air, which is not yet fully understood for SARS-CoV-2. However, virus has been detected by PCR in the stools of patients from numerous cohorts, and live virus was isolated from the stools of patients without diarrhea in one small cohort. More research and validation from larger patient cohorts would be valuable to ascertain the infectiousness of fecal bioaerosols, especially since the viability of SARS-CoV-2 in air has not been fully determined. To our knowledge, thus far there has been only one report of infectious virus being isolated from stool samples.[13] Although reports remain inconclusive, it is prudent for any enclosed air facility with a dense population of COVID-19 cases, especially hospitals, to remember that this mode of transmission was an important factor in previous coronavirus outbreaks.[2,3]

Whether stool samples that test positive by PCR contain infectious virus remains to be determined, as does the sensitivity and specificity of stool PCR relative to clinical disease and infectiousness. As infectiousness is best measured in culture and few studies have cultured stool, there is no consensus on whether stool samples generally contain live or dead virus. Moreover, although the ability of a sample to grow virus in culture should be the ultimate criterion standard for the infectiousness of both respiratory tract and stool samples, this reference is rarely employed because of lag time, inconvenience, and the reluctance of laboratories to culture COVID-19 because of potential infection. Clearly, having a firm distinction between "PCR positive" and "likely to be infectious" would be very clinically useful.

Time Course of Virus Shedding

Infected persons may shed virus in all phases of illness and, notably, continue to shed virus in stool during recovery phases, even after respiratory tract samples test negative for the virus. Consequently, individuals who have negative results on respiratory tract swab tests, thus appearing noninfectious, could still shed virus in stool. Infectivity is highly heterogeneous among patients and between different viral strains, and until more data are available to understand infectivity in all phases, it is important for hospitals to consider the potential for

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TABLE 2. Key Considerations for Prevention of Gastrointestinal Tract Transmission of Human Coronaviruses in Hospitals

Recommendation	Key points
1. Elevate awareness about GI symptoms of COVID-19 and potential for fecal-oral transmission	• Around one-fifth of COVID-19 patients have GI symptoms • Index patient in a previous large SARS outbreak had diarrhea • Teach staff to recognize COVID-19 cases without respiratory symptoms • Post signs alerting patients and staff to all symptoms of COVID-19 (fever, respiratory, GI) • Ask screening questions about GI symptoms even if patients do not have fever or respiratory symptoms
2. Consider scaling up isolation precautions	• Isolate patients with n/v, diarrhea, and other GI tract symptoms under the appropriate airborne and contact protocols • Two possible modes of transmission: ○ Contaminated surfaces (fomites) ○ Bioaerosols from flushing uncovered toilets • Diarrhea possibly indicates higher viral RNA positivity and viral load in stool
3. Improve environmental controls	• Consider that toilet flushing could be an aerosol-generating procedure • Closing the toilet lid before flushing provides a 12-fold reduction in bioaerosol spread • Ensure adequate ventilation and plumbing systems

COVID-19 = novel coronavirus disease 2019; GI = gastrointestinal; n/v = nausea and vomiting.

transmission from viral shedding[3] during all illness phases, including asymptomatic and convalescent phases of illness.

CONSIDERATIONS FOR HOSPITAL INFECTION CONTROL

Hospital infection control responses to COVID-19 can directly extrapolate from lessons learned during the SARS and MERS outbreaks. We suggest essential considerations for hospital containment strategies for human coronaviruses (Table 2).

Elevate Awareness About GI Tract Symptoms of COVID-19

It is important for patients and health care staff to receive education on how to recognize all possible initial presentations of patients with COVID-19, including those who do not present with the typical fever and respiratory tract symptoms.[3] Currently, messages alert patients to notify staff of respiratory tract symptoms and fever on entry to most health care facilities; however, these messages should be expanded to include GI tract symptoms. This elevated awareness would allow for immediate and rapid isolation on presentation and timely testing for COVID-19, which was found to likely prevent transmission in SARS.[3] Protocols for screening patients for COVID-19 symptoms should include questions about GI tract as well as respiratory tract symptoms.

Consider Scaling Up Isolation Precautions With Consideration for GI Tract—Mediated Transmission

Patients who have any symptoms of COVID-19 (including GI tract symptoms) should be immediately placed in isolation precautions until the disease is appropriately ruled out. Isolation measures should take into account the potential for fecal-oral transmission. Future planning should encompass adequate facility measures to permit isolation for future infectious outbreaks in order to prevent nosocomial superspreading events.[3]

Improve Environmental Controls

Aggressive environmental cleaning with disinfectants is critical.[3] Additionally, prevention of airborne spread from toilets and plumbing should be considered.[3] All staff should know that toilet flushing generates bioaerosols that can either enter the air or land on surfaces. Staff should also be aware that covering flushed toilets is the simplest way to block these aerosols (closing the toilet lid before flushing provides a 12-fold reduction in bioaerosol spread). Where this is not possible, health care workers should be advised to close lavatory doors during flushing. Environmental services staff should also receive education on the role of toilets as fomites and the need for aggressive cleaning in patient rooms and clinical work areas. Adequate ventilation should be utilized in patient toileting areas. Finally, as data continue to emerge either supporting or refuting the possibility of airborne spread of SARS-CoV-2,[15] air sanitation via ultraviolet light irradiation of circulating air should be considered for enclosed environments such as hospitals.[16]

CONCLUSION

If recent coronavirus outbreaks are any indication, COVID-19 will probably not be the last coronavirus to move from animals to humans and pose a clinical and containment concern for clinicians and hospitals. Clinicians should be aware of GI tract symptoms that are prevalent with COVID-19, and indeed, other notable human coronavirus infections to date. Clinicians should also be aware that these symptoms can occur early in the disease and in the absence of respiratory tract symptoms. Infection control knowledge from previous outbreaks should guide the response to COVID-19 and any future coronaviruses.[3] In particular, lack of awareness of GI tract transmission and potential bioaerosolization of the virus was an infection control gap with previous coronavirus outbreaks.[2] These lessons will help hospitals and other health care facilities to avoid transmission events seen in previous outbreaks.

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