Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

American Journal of Infection Control 49 (2021) 385–386

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Brief Report

Direct COVID-19 infection of enterocytes: The role of hypochlorhydria

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Key Words:
Proton pump inhibitors
Fecal-oral transmission
Asymptomatic transmission

COVD-19 disease is characteristically respiratory in nature; however, some patients have gastrointestinal symptoms. These include changes in taste, nausea/vomiting, abdominal pain, and diarrhea. A report has been published of a young patient who repeatedly tested positive in stool samples while nasopharyngeal tests remained negative. This raises doubts about our understanding of the dynamics of COVID-19 disease. The current report describes a need for selective stool testing to explore fecal shedding of viral RNA and presents a hypothesis for direct infection of enterocytes in cases of hypochlorhydria.

INTRODUCTION

Diarrhea and changes in taste are among the most prevalent gastrointestinal (GI) symptoms of COVID-19 disease and can occur in nearly 50% of patients.[1,2] Clinical and virological aspects of enteric COVID-19 disease have been reviewed, with authors suggesting the need for study of possible fecal-oral transmission.[1,3] Such studies are justified by observed GI symptoms and detection of positive stool samples. In children, initial GI symptoms may be mild and transient,[4] but a case has been reported of positive fecal tests occurring in the absence of positive nasopharyngeal tests or respiratory symptoms.[5] The purposes of this brief report are to emphasize the importance of testing stool samples under certain conditions and to suggest a novel route of direct enterocyte infection by COVID-19 in cases of developmental or acquired hypochlorhydria.

HYPOCHLORHYDRIA AND ORAL INFECTION

Many defenses exist in the upper parts of the GI system to protect against infection by ingested pathogens. The low pH (1.5-3.0) of gastric acid is a particularly important one. In cases of hypochlorhydria (low stomach acid), the gastric environmental pH is raised to pH 3-5. For this reason, hypochlorhydria is associated with an increased risk for enteric infection.[6,7] A large proportion of the human population suffers from hypochlorhydria. For example, gastric acid secretion is often depressed in the elderly,[6] a high-risk population for contracting COVID-19 disease. Acquired *Helicobacter pylori* infection and the use of proton pump inhibitors (PPI) are also associated with low stomach acid,[7] as is stress.[8]

COVID-19 virus may not survive normal gastric acid pH levels of 1.5-3, but there is evidence that it can survive a pH level of 3 or above.[9] If COVID-19 virus can resist the pH levels of 3-5 typical of hypochlorhydria, it would have a route from mouth to intestine, where the virus could directly infect ACE2-bearing enterocytes there.[1]

Although there is observational evidence that long-term or high-level use of PPI is associated with an increased risk of testing positive for COVID-19,[10] certain histamine-2 receptor antagonists (H2RA) and a PPI have been observed to improve disease outcome in patients already infected with COVID-19 virus.[11] This improvement in disease outcome is reportedly due to negative effects of the drugs on viral replication or on viral enzyme activity.[11] Thus, roles of both PPI and H2RA in COVID-19 disease merit further study.

To date, COVID-19 transmission through ingestion of contaminated food is not considered a concern. However, the route of virus delivery that results in GI symptoms and fecal shedding might still be oral. The fact that changes in taste can be an early symptom of COVID-19 infection[2] suggests that the virus does enter and infect the mouth. During exercise, occupational exertion, eating, drinking, or vocalizing, the mouth could be the recipient of infected droplets or aerosols. Thus, oral delivery of virus may occur, particularly in those not wearing masks at the time of exposure.

In fecal-oral transmission, the organism initially enters the body through the mouth. For COVID-19, evidence that the gut is infected directly, and not secondarily to respiratory infection, is provided by negative nasopharyngeal tests in the presence of positive fecal

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E-mail address: juliedibner@sbcglobal.net (J.J. Dibner).
Funding: There is no funding.
Conflicts of interest: There are no conflicts of interest.
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https://doi.org/10.1016/j.ajic.2020.08.002

samples collected simultaneously.[5] Escape through the compromised gastric acid defense system of hypochlorhydria could give COVID-19 virus access to intestinal enterocytes. Hypothetically, the initial infection of an individual could occur there.

SIGNIFICANCE OF COVID-19 DETECTION IN STOOL

COVID-19 viral RNA has been detected in stool samples,[1,3-5] as has intact virus.[12] Infectivity of a fecal isolate in Vero E cell culture has been described.[13] Actual transmission of COVID-19 disease to another person through the fecal-oral route has not been reported. SARS-CoV-1, a coronavirus with 80% genomic nucleotide identity to COVID-19 virus,[1] was also detected in patient stool samples.[1,3,14] In the case of SARS-CoV-1, fecal virus was shown to remain viable for 4 days as demonstrated by infection of Vero E cells in culture.[14] Certainly, being infectious in cell culture is no indication that fecal virus is a contagion threat to people, but it does suggest that all of the viral RNA detected in stool was and is not simply excreted nucleic acid remnants. Definitive proof that fecal COVID-19 RNA represents infective virus must await basic research. A recent review of our current understanding of COVID-19 viral transmission[15] is recommended to interested readers.

It should be noted that widespread fecal testing of all COVID-19 patients with diarrhea is neither warranted nor prudent. There are many potential causes of diarrhea in hospitalized COVID-19 patients. Among them are the alterations in intestinal microflora associated with antiviral or antibiotic drug treatments, with nonenteric nutrition, or with pre-existing GI illness.[16] Evidence of direct cytopathic effects on enterocytes should be explored before testing for COVID-19 viral markers.[16] The indiscriminate use of fecal testing would be a waste of resources needed elsewhere and false positive results could lead to inappropriate conclusions or nonproductive recommendations. Potential other causes of diarrhea in patients should be explored before stool testing for COVID-19 viral markers is initiated.

CONCLUSIONS

The significance of COVID-19 viral RNA detected in stool samples remains to be determined, but the observation raises the question of fecal-oral transmission. If such transmission occurs, a negative test result for virus of respiratory origin might not mean that recovering patients are no longer contagious. Patients with no evidence of respiratory shedding could still be contagious by fecal shedding and oral transmission. If individuals with hypochlorhydria are susceptible to infection by oral exposure, the prevalence of low stomach acid in the population could lead to further transmission. Fecal-oral transmission would be in addition to the airborne transmission already identified. Thus, hypochlorhydria may lead to less efficient, but equally dangerous, transmission of COVID-19 disease.

References

1. Kopel J, Perisetti A, Gajendran M, et al. Clinical insights into the gastrointestinal manifestations of COVID-19. *Dig Dis Sci*. 2020;65:1932–1939.
2. Aziz M, Perisetti A, Lee-Smith W, et al. Taste changes (dysgeusia) in COVID-19: a systematic review and meta-analysis. *Gastroenterology*. 2020;159:1132–1133.
3. Ding S, Liang T. Is SARS-CoV-2 also an enteric pathogen with potential fecal-oral transmission? A COVID-19 virological and clinical review. *Gastroenterology*.. 2020; 159:53–61.
4. Wong S, Lui R, Sung J. COVID-19 and the digestive system. *J Gastroenterol Hepatol*. 2020;35:744–748.
5. Jiang X, Luo M, Zou Z, et al. Asymptomatic SARS-CoV-2 infected case with viral detection positive in stool but negative in nasopharyngeal samples lasts for 42 days. *J Med Virol*. 2020;92:1807-1809.
6. Majumdar A, Basson M. Effect of aging on the gastrointestinal tract. editor in chief. In: Johnson L, ed. *Physiology of the Gastrointestinal Tract*. 4th ed Cambridge: Academic Press; 2006.
7. Parsons B, Ijaz U, D'Amore R, et al. Comparison of the human gastric microbiota in hypochlorhydric states arising as a result of Helicobacter pylori-induced atrophic gastritis, autoimmune atrophic gastritis and proton pump inhibitor use. *PLoS Pathog*. 2017;13:e1006653.
8. Esplugues J, Barrachina MD , Beltran B. et al. Inhibition of gastric acid secretion by stress: a protective reflex mediated by cerebral nitric oxide. *PNAS*. 1996;93:14839–14844.
9. Chin A, Chu A, Perera M, et al. Stability of SARS-CoV-2 in different environmental conditions. *Lancet Microbe*. 2020;1:e10.
10. Almario C, Chey W, Spiegel B. Increased risk of COVID-19 among users of proton pump inhibitors. *Am J Gastroenterol*. 2020;115:1707–1715.
11. Aguila E, Cua I. Repurposed GI drugs in the treatment of COVID-19. *Dig Dis Sci*. 2020;65:2452–2453.
12. Zhang Y, Chen C, Zhu S, et al. Isolation of 2019-nCoV from a stool specimen of a laboratory-confirmed case of the coronavirus disease 2019 (COVID-19). *China CDC Weekly*. 2020;2:123–124.
13. Xiao F, Sun J, Yonghao X, et al. Infectious SARS-CoV-2 in feces of patient with severe COVID-19. *Emerg Infect Dis*.. 2020;26:1920–1922.
14. World Health Organization. First data on stability and resistance of SARS coronavirus compiled by members of WHO laboratory network. 2003. Available at: https://www.who.int./csr/sars/survival_2003_05_04/en. Accessed May 29, 2020.
15. Ong S, Coleman K, Chia P, et al. Transmission modes of severe acute respiratory syndrome coronavirus 2 and implications on infection control: a review [e-pub ahead of print]. *Singapore Med J*. https://doi.org/10.11622/smedj.2020114. Accessed November 19, 2020.
16. Perisetti A, Gajendran M, Goyal H. Putative mechanisms of diarrhea in COVID-19. *Clin Gastroenterol Hepatol*. 2020;18:3054–3055.