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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

21. Piha-Paul SA, Oh D-Y, Ueno M, et al. Efficacy and safety of pembrolizumab for the treatment of advanced biliary cancer: results from the KEYNOTE-158 and KEYNOTE-028 studies. Int J Cancer 2020;147:2190–2198.

Correspondence
Address correspondence to: Amaia Lujambio, PhD, Icahn School of Medicine at Mount Sinai, Oncological Sciences, 1470 Madison Avenue, Hess 6-111, New York, New York 10029. e-mail: amaia.lujambio@mssm.edu.

Conflicts of interest
This author discloses the following: Amaia Lujambio has received research funding from Pfizer and Genentech and consulting fees from AstraZeneca. Anthony Lozano discloses no conflicts.

Most current article

© 2022 by the AGA Institute.
0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2022.05.047

Rear Window—What Can the Gut Tell Us About Long-COVID?

See "Postacute COVID-19 is characterized by gut viral antigen persistence in inflammatory bowel diseases," by Zollner A, Koch R, Jukic A, et al, on page 495; and "Reduced replication efficacy of severe acute respiratory syndrome coronavirus 2 omicron variant in "mini-gut" organoids" by Miyakawa K, Machida M, Kawasaki T, et al, on page 514.

While life-threatening acute coronavirus disease 2019 (COVID-19) is mostly linked to respiratory insufficiency or exacerbation of underlying comorbidity, up to 50% of patients with acute COVID-19 may experience mild to moderate gastrointestinal symptoms,[1] because intestinal cells are also prone to infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) and widely express the viral entry receptor angiotensin-converting enzyme 2 (ACE2).[2] In this issue of *Gastroenterology*, two articles focus on the intestine and pressing issues in dealing with the COVID-19 pandemic.[3,4] The article by Miyakawa et al[3] addresses the direct infection of intestinal cells by SARS-CoV2. Gastrointestinal symptoms, including diarrhea, abdominal cramping, and pain, are frequently observed in patients with COVID-19,[5–8] possibly due to direct infection of the intestinal cells. In fact, stomach cells and epithelial cells of the small and large intestine have been shown to express ACE2 and the coreceptor transmembrane protease, serine 2 (TMPRSS2),[2,9,10] underlining the possibility that these cells are directly targeted by SARS–CoV2.

The possibility that gastrointestinal cells are infected by SARS–CoV2 was previously demonstrated by studies in intestinal organoids. These studies showed that SARS-CoV2 infection may cause direct infection of epithelial cells, followed by production of infectious viral particles.[11] However, the question about potential differences in gastrointestinal infection due to variants of the virus remained to be investigated. In this issue, Miyakawa et al[3] now make use of mini-guts as tools to study cell-type specific replication behavior of novel variants of potential concern. Other studies had previously observed altered cell-type specific viral replication efficacies of B.1.529/ Omicron BA.1 compared with B.1.617.2/Delta in lower airway organoids, while upper airway replication was increased.[12,13]

Extending these findings, Miyakawa et al[3] now show reduced viral replication efficacy of Omicron BA.1 and BA.2 compared with the B.1.617.2/Delta variant. This interesting observation correlated to less cell damage as well as to reduced lactose dehydrogenase and high mobility group box 1 protein (HMGB1) release, induced by BA.1 and BA.2. It will be important to follow epidemiology and gastrointestinal symptomatology of the current Omicron wave to assess whether this translates to clinically observed reductions in gastrointestinal symptoms associated to Omicron infection.

For many patients, COVID-19 has been a transient acute illness. However, persistence of symptoms and newly occurring signs of disease not attributable to other causes have emerged in others and lead to an ongoing need to characterize epidemiology, natural history, pathophysiology, diagnosis, and treatment of the phenomenon of post-COVID-19 syndrome, also called post-COVID conditions, long-COVID, postacute COVID-19, or chronic COVID.[14] In addition, it has been observed that the burden of cardiovascular comorbidities is increased in COVID-19 survivors and remains elevated up to 1 year compared with historical control populations,[15] even in patients not hospitalized during acute disease.

There remains an incomplete understanding of the pathophysiology of post-COVID-19 syndrome. Different hypotheses can be formulated to explain ongoing symptoms in the postacute phase:

1. Tissue damage that occurred during acute COVID-19 as a result of direct viral toxicity, vessel injury, microthrombosis or macrothrombosis, and ongoing or incomplete healing processes might cause persistent symptoms.[16,17]

2. Incomplete viral clearance and persistent low-level viral replication or continued presence of viral antigens in specialized niches of the body might affect recovery.

3. Autoimmune attacks instigated by the immune response to SARS-CoV2 might cause ongoing damage to specific tissues.

4. Increased body awareness and the perceived association of diffuse symptoms to COVID might spike reporting of symptoms that usually would remain unnoted by health care providers.

5. Consequences of aggressive therapy—especially in the setting of postcritical illness—might contribute to prolonged or incomplete recovery.

Fecal shedding of viral RNA has been observed to persist longer than oropharyngeal shedding of SARS-CoV2,[18,19] putting the gastrointestinal tract into the focus of the study of postacute sequelae of COVID-19. In this issue, Zollner et al[4] describe substantial novel scientific arguments to this debate by demonstrating persistence of viral antigens in the colon as long as 257 days after initial virus detection, even in the absence of persistent fecal shedding. They made use of various detection methods, including detection of viral RNA by quantitative polymerase chain reaction (RNA-dependent RNA polymerase, nucleocapsid, spike, and envelope proteins) as well as immunofluorescence of colonic biopsy specimens (nucleocapsid protein). They included 46 patients in Austria with inflammatory bowel disease (IBD) who had also experienced a SARS-CoV2 infection from October 2020 to February 2021.

During scheduled routine colonoscopy for control of IBD activity, the study team took tissue samples, and patients who were experiencing ongoing COVID-related symptoms were compared with those with a complete symptom resolution. Interestingly, the authors found persistence of viral antigens in many intestinal tissue samples. Persistence of viral antigen was strongly associated to ongoing symptoms in this study cohort. Owing to the selection of the study cohort, whether these findings are limited to patients with IBD currently remains unclear.[9] However, Natarajan et al[19] reported the association of persistent viral shedding to persistent gastrointestinal symptoms in a general population.

On the basis of the current evidence, an IBD-related effect thus seems rather unlikely, although one cannot exclude the possibility that effects on viral persistence in patients with IBD are more pronounced due to IBD-related changes of intestinal epithelial cells or accompanying medication (eg, corticosteroid use). Furthermore, whether prolonged persistence of viral components is gut-specific remains unclear. Prolonged detection of viral RNA in feces compared with oropharyngeal swabs does not at all prove an organ-restricted effect. Fecal RNA can be seen as the integral of the entire gastrointestinal tract rather than the direct shedding of the oropharyngeal swab content, and gastrointestinal tissue samples as in the current study are far more easily accessible than lower airway samples.

Taken together, the reported findings by Zollner et al[4] do not directly prove the functional role of persisting viral antigens as causative for persistent symptoms or the specificity of the gut as a reservoir of viral antigens. However, this report makes an important contribution to the field by showing that persistent viral antigens in the intestine are present in patients with long-COVID and may play a key role the pathogenesis of post-COVID symptoms.

Further studies are clearly needed to further define the molecular mechanisms of post-COVID conditions. However, the ease of tissue sampling in the gut could potentially guide further studies of immunologic mechanisms of prolonged persistence in the context of postacute COVID-19. Colonoscopy thus provides an unexpected “rear window" to the mystery of post-COVID syndrome and provides an easily accessible way to detect viral persistence.

MORITZ LEPPKES
MARKUS F. NEURATH
Department of Medicine 1
University Clinic Erlangen
Friedrich-Alexander University Erlangen-Nürnberg
Erlangen, Germany, *and*
Deutsches Zentrum Immuntherapie (DZI)
Erlangen, Germany

References

1. Lin L, Jiang X, Zhang Z, et al. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. Gut 2020; 69:997–1001.
2. Xiao F, Tang M, Zheng X, et al. Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology 2020;158:1831–1833.e3.
3. Miyakawa K, Machida M, Kawasaki T, et al. Reduced replication efficacy of severe acute respiratory syndrome coronavirus 2 omicron variant in “mini-gut” organoids. Gastroenterology 2022;163:514–516.
4. Zollner A, Koch R, Jukic A, et al. Post-acute COVID-19 is characterized by gut viral antigen persistence in inflammatory bowel diseases. Gastroenterology 2022;163:495–506.
5. Redd WD, Zhou JC, Hathorn KE, et al. Prevalence and characteristics of gastrointestinal symptoms in patients with severe acute respiratory syndrome coronavirus 2 infection in the United States: a multicenter cohort study. Gastroenterology 2020;159: 765–767.e2.
6. Pan L, Mu M, Yang P, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study. Am J Gastroenterol 2020;115:766–773.
7. Dong ZY, Xiang BJ, Jiang M, et al. The prevalence of gastrointestinal symptoms, abnormal liver function, digestive system disease and liver disease in COVID-19 infection: a systematic review and meta-analysis. J Clin Gastroenterol 2021;55:67–76.
8. Neurath MF. COVID-19 and immunomodulation in IBD. Gut 2020;69:1335–1342.
9. Patankar JV, Chiriac MT, Lehmann M, et al. Severe acute respiratory syndrome coronavirus 2 attachment receptor angiotensin-converting enzyme 2 is decreased in Crohn’s disease and regulated by microbial and inflammatory signaling. Gastroenterology 2021;160: 925–928.e4.
10. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:271–280.
11. Lamers MM, Beumer J, van der Vaart J, et al. SARS-CoV-2 productively infects human gut enterocytes. Science 2020;369:50–54.

12. Hui KPY, Ho JCW, Cheung MC, et al. SARS-CoV-2 Omicron variant replication in human bronchus and lung ex vivo. Nature 2022;603:715–720.
13. Meng B, Abdullahi A, Ferreira I, et al. Altered TMPRSS2 usage by SARS-CoV-2 Omicron impacts infectivity and fusogenicity. Nature 2022;603:706–714.
14. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. Nat Med 2021;27:601–615.
15. Xie Y, Xu E, Bowe B, et al. Long-term cardiovascular outcomes of COVID-19. Nat Med 2022;28:583–590.
16. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med 2020;383:120–128.
17. Leppkes M, Knopf J, Naschberger E, et al. Vascular occlusion by neutrophil extracellular traps in COVID-19. EBioMedicine 2020;58:102925.
18. Du W, Yu J, Liu X, et al. Persistence of SARS-CoV-2 virus RNA in feces: a case series of children. J Infect Public Health 2020;13:926–931.
19. Natarajan A, Zlitni S, Brooks EF, et al. Gastrointestinal symptoms and fecal shedding of SARS-CoV-2 RNA suggest prolonged gastrointestinal infection. Med (N Y) 2022;3:371–387.e9.

Correspondence
Address correspondence to: Moritz Leppkes, MD, Department of Medicine 1, University Clinic, Friedrich-Alexander-University Erlangen-Nuremberg, Ulmenweg 18, 91054 Erlangen, Germany. e-mail: moritz.leppkes@uk-erlangen.dee-mail.

Conflicts of interest
The authors disclose no conflicts.

Funding
This work was supported by the Deutsche Forschungsgemeinschaft (TRR241 [B04, C04], SFB1181, FOR2438) and the Bayerisches Staatsministerium für Wissenschaft und Kunst.

Most current article

© 2022 by the AGA Institute.
0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2022.05.044