

Time to Negative SARS-CoV-2 PCR Should Not Delay Care Among Patients With Inflammatory Bowel Diseases

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INTRODUCTION

The outbreak of SARS-CoV-2 has resulted in a pandemic affecting millions of individuals. The virus causes a clinical presentation varying from no symptoms to multiorgan failure and death.^{1,2} There was initial concern that patients with inflammatory bowel diseases (IBD), including Crohn disease (CD) and ulcerative colitis (UC), would have increased risk for infection and severe outcomes given that treatment often involves immunosuppressants, which increase the risk of various infections.³ Common clinical practice is to hold immunosuppressants after development of a serious infection, and current recommendations are to hold most immunosuppressants if an individual with IBD is diagnosed with SARS-CoV-2 and develops COVID-19.⁴

Although current recommendations from the International Organization for the Study of Inflammatory Bowel Disease advise holding biologics during COVID-19 infection,⁴ there was initial confusion regarding when to restart therapy. Many outpatient centers required 2 negative nasal polymerase chain reaction (PCR) tests to resume therapy even if patients were asymptomatic for >14 days. The reported time to negative PCR varies, with many studies reporting >14 days and 1 study reporting a mean of 24 to 25 days among patients who achieved negative PCR tests.⁵ Xu et al⁶ and Qi et al⁷ reported a median of 17 days from illness onset to negative PCR. Factors associated with prolonged clearance in these studies

included male sex, older age, mechanical ventilation, corticosteroid treatment, higher median body temperature, longer time from symptom onset to admission, and hospital length of stay.^{6,7} The impact of immunosuppressive medications on viral clearance is unknown, and there was concern that unnecessary delay in restarting biologics could increase IBD flares. We therefore aimed to evaluate the time to negative SARS-CoV-2 PCR among patients with IBD.

MATERIALS AND METHODS

Study Population

Patients with IBD and a positive SARS-CoV-2 PCR were identified using 3 methods: (1) the Partners Research Patient Data Repository (Appendix A), (2) surveying gastroenterologists, and (3) reviewing the electronic medical record for positive SARS-CoV-2 PCR tests among patients cared for by IBD specialists. Retrospective chart review was conducted to collect data on IBD characteristics, medications, and follow-up PCR testing.

Statistical Analysis

The χ^2 test was utilized for statistical comparisons of categorical variables. Two-tailed *P* values ≤ 0.05 were considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

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Conflicts of interest: Rachel W. Winter has consulted for AbbVie and Nestle. Ashwin N. Ananthakrishnan has served as a scientific advisory board member for AbbVie, Gilead, and Kyn Therapeutics and received research grants from Pfizer. Jessica R. Allegretti has consulted for Pfizer, Takeda, Janssen, Finch Therapeutics, Pandion, Servatus, Artugen, and Iterative Scopes and received research support from Merck. Kristin E. Burke, Bharati Kochar, and Walter W. Chan have no conflicts of interest to declare.

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Statement of Ethics

This study was approved by the Mass General Brigham Institutional Review Board, protocol #2020P0000983.

RESULTS

Thirty-one patients with IBD (16 CD, 15 UC) who tested positive for SARs-CoV-2 and had a follow-up PCR test once they were asymptomatic were included (Table 1). Three patients were on vedolizumab. Five patients, all with UC, had a negative PCR test within 14 days. At 14 days after initial diagnosis, 10 patients with UC and all 16 patients with CD remained PCR-positive on testing. One patient was still PCR-positive at 61 days after diagnosis but remained asymptomatic (Fig. 1). Nineteen patients had a test completed within 14 days (16 patients on anti-tumor necrosis factor (TNF) drugs and 3 on vedolizumab). Overall, 1/16 patients (6.25%) in the anti-TNF group and 1/3 patients (33.3%) in the vedolizumab group cleared the virus within 14 days. Median time to clearance was 22 days (interquartile ratio, 16-37 days). Neither age, body mass index, nor class of biologic medication affected time to negative PCR, although a higher proportion of patients on vedolizumab had

TABLE 1. Patient Demographics

Characteristic	n (%) (n = 31)
Male	10 (32.3)
Age (y), median	38
Race	
White	28 (90.3)
Non-White	3 (9.7)
Combination therapy	4 (12.9)

a negative PCR within 14 days compared to patients on anti-TNF medications (33.3% vs 6.3%; *P* = 0.16).

DISCUSSION

In our cohort of patients with IBD, the majority were still positive via PCR 14 days after their first test, despite being asymptomatic. There were no identifiable risk factors identified for prolonged PCR positivity.

The SARS-CoV-2 PCR nasopharyngeal swab tests for the presence of the virus but does not specifically test for active virus. All patients retested were asymptomatic and were being tested for clearance to resume biologics. The clinical relevance of persistent positive tests in patients who are asymptomatic remains unclear. Therefore, the requirement of a negative PCR test to resume therapy for IBD is likely unnecessary. The International Organization for the Study of Inflammatory Bowel Disease has recommended that infusions may resume after a negative PCR or 2 weeks after initial diagnosis if patients are asymptomatic for at least 72 hours. As shown, most patients did not have a negative PCR 2 weeks after initial diagnosis. Waiting for a negative test will delay care and could potentially increase the risk of IBD flare.

This study has a number of limitations. The study includes a small number of patients who tested positive and had follow-up testing. Our infusion center stopped requiring confirmation of a negative test and now relies on symptom resolution, limiting the patients who were available for analysis. In addition, the long-term consequences of a prolonged positive PCR are not currently known, including whether patients with prolonged positive PCR remain able to transmit SARS-CoV-2 to others or whether there are long-term effects of the virus on those infected. Our infusion centers have not reported increases in infection among staff or patients despite eliminating the requirement of a negative test, but it would be very difficult to contact-trace and track transmission from these patients.

CONCLUSIONS

This study shows that the majority of patients with IBD, and particularly those with CD, continue to have a positive SARS-CoV-2 PCR test 14 days after an initial positive test. Thus, waiting for negative PCR may result in further delay of care and/or increased risk of IBD flare. Additional studies are needed to identify the factors affecting delayed clearance in this vulnerable patient population.

APPENDIX A

METHODS

Study approval was obtained from the institutional review board of Partners HealthCare, which includes 12 community and academic teaching hospitals in Massachusetts and New Hampshire and is the largest health care

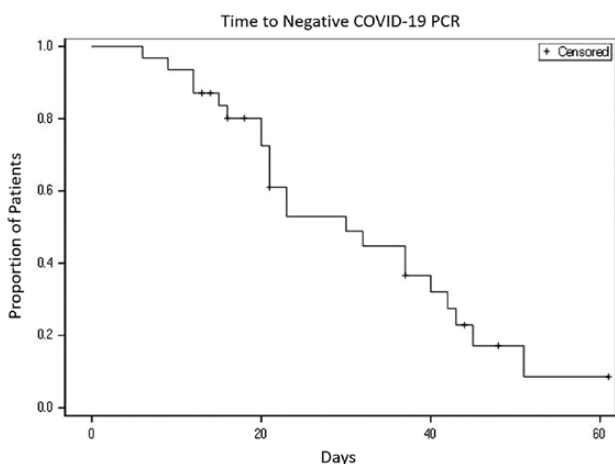


FIGURE 1. Kaplan-Meier curve of time to negative SARS-CoV-2 PCR.

provider in Massachusetts. Brigham and Women's Hospital and Massachusetts General Hospital are 2 tertiary referring hospitals within Partners that have IBD centers that collectively care for more than 5000 patients with Crohn's disease and ulcerative colitis. Prior publications have described the use of the Partners Research Patient Data Repository, an up-to-date data repository containing information on all patient encounters, laboratory results, radiology tests, and procedures that occur within any of the institutions within the Partners HealthCare system.⁸ Inclusion criteria for the Partners Research Patient Data Repository search were male and female patients aged ≥ 18 years with at least one International Classification of Diseases, 10th edition (ICD-10) code for Crohn disease (K50.x) or ulcerative colitis (K51.x) between January 1, 2019, and April 25, 2020, and a prescription for at least 1 of the following medications: (1) oral aminosalicylates (mesalamine, balsalazide, sulfasalazine); (2) immunomodulators (azathioprine, mercaptopurine, methotrexate); (3) biologics, including tumor necrosis factor- α antagonists, anti-integrins (vedolizumab), or anti-interleukin-12/23 agents (ustekinumab); or (4) Janus kinase

inhibitors (tofacitinib). This method of identifying a study population by medication prescription and diagnosis was used to increase the accuracy of selecting a study population with IBD.

REFERENCES

1. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382:1708–1720.
2. Richardson S, Hirsch JS, Narasimhan M, et al.; the Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA*. 2020;323:2052–2059.
3. Long MD, Martin C, Sandler RS, et al. Increased risk of pneumonia among patients with inflammatory bowel disease. *Am J Gastroenterol*. 2013;108:240–248.
4. International Organization for the Study of Inflammatory Bowel Disease. COVID 19 and IBD webinars and guidelines. <https://ioibd.org/covid-19-and-ibd-webinars-and-guidelines/>. Published May 14, 2020. Accessed January 19, 2021.
5. Carmo A, Pereira-Vaz J, Mota V, et al. Clearance and persistence of SARS-CoV-2 RNA in COVID-19 patients. *J Med Virol*. 2020;92:2227–2231.
6. Xu K, Chen Y, Yuan J, et al. Factors associated with prolonged viral RNA shedding in patients with COVID-19. *Clin Infect Dis*. 2020;71:799–806.
7. Qi L, Yang Y, Jiang D, et al. Factors associated with the duration of viral shedding in adults with COVID-19 outside of Wuhan, China: a retrospective cohort study. *Int J Infect Dis*. 2020;96:531–537.
8. Gupta V, Rodrigues R, Nguyen D, et al. Adjuvant use of antibiotics with corticosteroids in inflammatory bowel disease exacerbations requiring hospitalisation: a retrospective cohort study and meta-analysis. *Aliment Pharmacol Ther*. 2016;43:52–60.