# Should We Be Screening for SARS-CoV-2 in IBD Patients Before Initiation of Biologic Therapy?

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## INTRODUCTION

Before initiation of biologic therapy, current guidelines recommend screening for hepatitis B virus, human immunodeficiency virus, and latent mycobacterium tuberculosis infections.[1,2] It is also recommended to screen for susceptibility to primary varicella zoster virus (VZV) infection, and it is suggested to check for hepatitis C virus infection. With the current coronavirus disease 2019 (COVID-19) pandemic and the high prevalence of asymptomatic infected individuals, the question is raised as to whether or not we need to check for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection before initiation of biological therapy in inflammatory bowel disease (IBD) patients.

SARS-CoV-2 is the viral pathogen that leads to COVID-19. Infected patients may be asymptomatic or may have mild, moderate, or severe symptoms.[3] Although any age group may develop severe COVID-19, risk factors for worse disease severity and worse outcomes include older age and the presence of comorbid conditions such as hypertension, diabetes mellitus, cardiovascular disease, chronic lung disease, cancer, obesity, smoking, and chronic kidney disease.[4]

## HOW TO TEST FOR SARS-COV-2?

The World Health Organization (WHO), Center for Disease Control and Prevention (CDC), and the Infectious Diseases Society of America (IDSA) recommend checking a SARS-CoV-2 nucleic acid amplification test (NAAT) primarily by reverse transcription polymerase chain reaction (RT-PCR) in symptomatic individuals who are suspected to have COVID-19, even when the clinical suspicion for COVID-19 is low.[5–8] A nucleic acid test (NAT) detects a nucleic acid sequence and subsequently identifies a particular virus. The viral genes targeted so far include the N, E, S, and RdRP genes.[5] As the amount of genetic material is small, many NATs need to amplify the genetic material, and these are called NAATs. There are different ways of amplification, and these include RT-PCR, strand displacement amplification, or transcription mediated amplification; the former is what is most commonly used for SARS-CoV-2.

The sensitivity of the SARS-CoV-2 RT-PCR test is highest when obtained from bronchoalveolar lavage specimens (93%), followed by sputum (72%), nasal swabs (63%), and pharyngeal swabs (32%). If a negative result is obtained from a patient with a high index of suspicion for COVID-19 virus infection, particularly when only upper respiratory tract specimens are collected, additional specimens, including from the lower respiratory tract if possible, should be collected and tested.[5,9] The IDSA panel suggests collecting nasopharyngeal, mid-turbinate, or nasal swabs rather than oropharyngeal swabs or saliva alone for SARS-CoV-2 RNA testing in symptomatic individuals with upper respiratory tract infection or influenza-like illness who are suspected of having COVID-19.[7]

The CDC has a serologic ELISA-based antibody test. It is used as part of surveillance efforts to better understand how much of the population has been infected with SARS-CoV-2 and how the virus is spreading through the population over time.[6] Higher viral loads on RT-PCR are detected soon after symptom onset and decrease towards the second week of infection.[10] To increase the sensitivity of diagnosis in the second week of illness, combination of IgM ELISA and/or total antibodies against SARS-CoV-2 in addition to RT-PCR is recommended. This highlights the potential importance of serological diagnostic testing in patients who present later in the course of infection by the time their viral load is very low, below the detection limit of RT-PCR. The role of serologic testing in the acute diagnosis of infection is limited, as the antibodies are detected 6 to 15 days after disease onset.[11,12]

Serologic antigen tests are being developed and hold promise as a quick and convenient mean of testing for current SARS-CoV-2 infection.[13]

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## ARE IBD PATIENTS AT A HIGHER RISK OF SARS-COV-2 INFECTION AND DEVELOPMENT OF COVID-19? ARE IBD PATIENTS MORE LIKELY TO HAVE A WORSE OUTCOME IF THEY DEVELOP COVID-19?

It is known that immunosuppression reduces humoral immunity and neutrophil activity, leading to an increased risk of viral infections and an increased severity of the infection.[14] Among IBD patients, an increased risk of viral infections has been described, particularly in the setting of immunomodulator and biologic use.[15,16] A recent study by Wisniewski et al showed that IBD patients are 3-times more at risk for the development of serious systemic viral infections including cytomegalovirus, Epstein-Barr virus, VZV, and herpes simplex virus compared with the general population, mainly due to clinically active IBD at onset of viral infection and exposure to thiopurines.[17] In a meta-analysis by Ford et al, antitumor necrosis factor (anti-TNF) therapy in IBD patients was shown to double the risk of opportunistic infections.[16]

To date, available data do not show that IBD patients are at an increased risk for infection with SARS-CoV-2 or the development of COVID-19.[18–21] Additionally, there are no data to suggest that immunosuppression increases susceptibility to SARS-CoV-2 or that it impacts disease course.[22] The International Organization for the Study of IBD (IOIBD) reported that it remains uncertain whether the use of IBD medications such as azathioprine, methotrexate, anti-TNF, and tofacitinib increase the risk for SARS-CoV-2 infection and subsequent COVID-19.[18] For that reason, it is recommended that IBD patients who are in remission continue their maintenance medications in order to maintain remission and avoid relapse of their disease and need for therapy escalation or hospitalization.[20]

Recently published data from the Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD) international registry show that systemic corticosteroids (adjusted odds ratio [aOR] 6.9; 95% CI, 2.3–20.5) but not anti-TNF biological agents (aOR 0.9; 95% CI, 0.4–2.2), along with older age (aOR 1.04; 95% CI, 1.01–1.02) and presence of 2 or more comorbid conditions (aOR 2.9; 95% CI, 1.1–7.8) are associated with severe COVID-19 and worse outcomes.[23] In this interim report looking at 525 IBD patients with COVID-19, 7% had severe COVID-19, and 3% (16 patients) died. Age-standardized mortality ratios for IBD patients were 1.7 (95% CI, 0.9–2.5) relative to data from the United States. This important study shows that IBD patients have the same risk factors as the general population for the development of severe COVID-19. It also highlights the importance of stopping steroids due to their negative impact on severity of COVID-19. Anti-TNF agents did not increase the risk for COVID-19 infection and were not a risk factor for more severe COVID-19.

## WHAT SHOULD IBD PATIENTS DO IF THEY ARE INFECTED WITH SARS-COV-2?

In the event that an IBD patients is found to have SARS-CoV-2 but has not developed COVID-19, it is recommended to make some adjustments to their medication regimen: (1) decrease prednisone to <20 mg daily or switch to budesonide, (2) hold thiopurines, methotrexate, and tofacitinib, and (3) delay dosing of all monoclonal antibody biological therapies by 2 weeks.[20,24] If the patient does not develop COVID-19 during these 2 weeks, then it is suggested to resume the medications after the 2 weeks.[20]

In IBD patients who develop COVID-19, management will depend on the status of the individual's IBD and severity of COVID-19. Inflammatory bowel disease patients with COVID-19 should stop thiopurines, methotrexate, and tofacitinib and resume only when the patient has recovered.[20] For COVID-19 patients due for a dose of ustekinumab, anti-TNFs, or vedolizumab, these injections or infusions should be delayed.[20,24] For IBD patients requiring systemic corticosteroids for severe exacerbation of disease or hospitalization, the recommendation is to limit high doses and limit the duration of use if possible.[20] Hospitalized ulcerative colitis patients should limit intravenous corticosteroids to no more than 3 days and transition to alternative therapies such as infliximab or a calcineurin-inhibitor.[20]

Regarding resuming IBD therapy in those patients who develop COVID-19, the American Gastroenterological Association guidance suggests that IBD treatment can be resumed after complete resolution of the COVID-19 symptoms or if the patient undergoes testing confirming clearance of the infection.[20] The IOIBD expert panel recommends following a "symptom-based" strategy to decide about recommencement of IBD medications, rather than relying on a "test-based" strategy, taking into consideration the patient's IBD and COVID-19 severity.[18] In asymptomatic patients with SARS-CoV-2 infection, immunosuppressive medications may be resumed after 10 days from the first positive test. Inflammatory bowel disease patients with COVID-19 may resume immunosuppressive medications at least 72 hours after resolution of fever and respiratory symptoms. Inflammatory bowel disease patients with severe COVID-19 should delay the resumption of immunosuppressive therapy until complete recovery, and each case should be individualize based on the severity of IBD.[18]

## SHOULD WE SCREEN FOR SARS-COV-2 IN ASYMPTOMATIC PATIENTS BEFORE INITIATION OF BIOLOGICAL THERAPY?

The true incidence and prevalence of SARS-CoV-2 in the general population is not known. Rates will vary geographically, and estimates vary between 18%–25% for SARS-CoV-2 infection in asymptomatic people.[25] Whether to screen for SARS-CoV-2 in asymptomatic IBD patients before initiation of biologic therapies remains controversial, with some

suggesting screening in all such patients.[26,27] The rationale is that SARS-CoV-2 patients who receive immunosuppressive medications will have a delay in viral clearance, may become symptomatic, and possibly worsen COVID-19 course.[26, 28, 29] Additionally, the IDSA recommends SARS-CoV-2 RNA testing in asymptomatic individuals before immunosuppressive treatment regardless of a known exposure to COVID-19, with a strong recommendation despite very low evidence.[7] This recommendation defines immunosuppressive procedures as cytotoxic chemotherapy, solid organ or stem cell transplantation, long acting biologic therapy, cellular immunotherapy, or high-dose corticosteroids.[7] Testing should ideally be performed as close to the planned treatment/procedure as possible (eg, within 48–72 hours).[7] Similarly, the European Society for Blood and Marrow Transplantation issued a statement that all patients should have a negative SARS-CoV-2 test result, regardless of presence of upper respiratory symptoms, before the start of treatment.[30]

Whether chemotherapeutic immunosuppression is equivalent to IBD immunosuppression with biologic therapy is not clear. Inflammatory bowel disease patients requiring the initiation of biologic monoclonal antibody therapies usually have active gastrointestinal inflammation or fistula and are symptomatic from their Crohn's disease or ulcerative colitis. It is our opinion that SARS-CoV-2 testing before initiation of biological therapy for IBD is not required and should be considered distinct from chemotherapeutic immunosuppression or bone marrow transplant patients. Our rationale for this recommendation is the lack of data to suggest increased complications of COVID-19 in IBD patients on biologics. Similarly, there is a practical consideration for testing all patients receiving a biologic therapy and whether the current testing availability would be able to support this practice worldwide. Finally, if testing is performed before the first dose of biologic, the primary question will be, what will be the strategy for each subsequent dose, especially for some as frequent as every 1 to 2 weeks?

Data supporting our recommendation to not test asymptomatic IBD patients initiating biologics for SARS-CoV-2 are reliant on studies of patients on biologics who develop COVID-19. In the recently published SECURE-IBD article, IBD patients receiving anti-TNF agents or anti-IL-12/23 did not increase COVID-19 complications or duration of disease.[23] It was noted that patients receiving vedolizumab had a higher rate of severe COVID-19; however with the small sample size, it is difficult to conclude that this is meaningful, and more data are needed.[23] In our opinion, we still consider vedolizumab similar to other monocloncal antibodies. Feldmann et al suggested that anti-TNF agents may actually have a protective effect on lung inflammation during COVID-19, although the data are limited.[31] Similarly, reports from liver transplant recipients suggest that immunosuppression does not increase COVID-19 complications, although it may prolong viral shedding.[14, 32–34] If patients have upper respiratory tract symptoms or a fever or any suspicion for COVID-19, then we do recommend testing for SARS-CoV-2.

In conclusion, many patients with SARS-CoV-2 remain asymptomatic and do not develop COVID-19. Inflammatory bowel disease is not a risk factor for SARS-CoV-2 infection or COVID-19. It is unclear if immunosuppression increases susceptibility to SARS-CoV-2 or if it impacts disease course. Preliminary data from the SECURE-IBD registry show that anti-TNF and anti-IL-12/23 agents do not worsen disease course, whereas corticosteroids do. In IBD patients who develop severe disease and who have no symptoms concerning COVID-19, we do not advise screening for SARS-CoV-2. Routine testing in its current form would likely delay the initiation of biological therapy, which could lead to complications of IBD, including the need for corticosteroids and hospitalization. Until rapid testing for SARS-CoV-2 is available for everyone at a low cost, with high sensitivity and specificity, and can be done repeatedly as point of care monitoring, we do not recommend routing testing for COVID-19 before initiation of IBD biologics.

## REFERENCES


1. Rahier JF, Magro F, Abreu C, et al.; European Crohn's and Colitis Organisation (ECCO). Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis.* 2014;8:443–468.
2. Hashash JG, Abu Fadel C, Hosni M, et al. Approach to latent tuberculosis infection screening before biologic therapy in IBD patients: PPD or IGRA? *Inflamm Bowel Dis.* 2020. doi:10.1093/ibd/izaa139
3. Liu K, Fang YY, Deng Y, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. *Chin Med J (Engl).* 2020;133:1025–1031.
4. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med.* 2020; e200994. doi:10.1016/S2468-1253(20)30116-3
5. World Health Organization. *Laboratory Testing for 2019 Novel Coronavirus (2019-nCoV) in Suspected Human Cases.* https://www.who.int/publications-detail/laboratory-testing-for-2019-novel-coronavirus-in-suspected-human-cases-20200117. Accessed May 27, 2020.
6. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/lab/virus-requests.html. How to Get CDC's COVID-19 Diagnostic Test and Supplies. Accessed May 27, 2020.
7. Hanson KE, Caliendo AM, Arias CA, et al. Infectious Diseases Society of America. Infectious Diseases Society of America Guidelines on the Diagnosis of COVID-19. https://www.idsociety.org/practice-guideline/covid-19-guideline-diagnostics. Accessed May 27, 2020.
8. Yu F, Yan L, Wang N, et al. Quantitative detection and viral load analysis of SARS-CoV-2 in infected patients. *Clin Infect Dis.* 2020. doi:10.1093/cid/ciaa345
9. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA.* 2020;323:1843–1844. doi:10.1001/jama.2020.3786
10. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. *N Engl J Med.* 2020;382:1177–1179.
11. Venter M, Richter K. Towards effective diagnostic assays for COVID-19: a review. *J Clin Pathol.* 2020;73:370–377. doi:10.1136/jclinpath-2020-206685
12. To KK, Tsang OT, Leung WS, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. *Lancet Infect Dis.* 2020;20:565–574. doi:10.1016/S1473-3099(20)30196-1
13. Food and Drug Administration Office of the Commissioner. *Coronavirus (COVID-19) Update: FDA Authorizes First Antigen Test to Help in the Rapid Detection of the Virus that Causes COVID-19 in Patients*. Published May 12, 2020. https://www.fda.gov/news-events/pressannouncements/coronavirus-covid-19-update-fda-authorizes-first-antigen-test-help-rapiddetection-virus-causes. Accessed May 31, 2020.
14. D'Antiga L. Coronaviruses and immunosuppressed patients: the facts during the third epidemic. *Liver Transplant.* 2020;26:832–834. doi:10.1002/lt.25756

15. Pauly MP, Tucker LY, Szpakowski JL, et al. Incidence of hepatitis B virus reactivation and hepatotoxicity in patients receiving long-term treatment with tumor necrosis factor antagonists. *Clin Gastroenterol Hepatol.* 2018;16:1964–1973.e1.
16. Ford AC, Peyrin-Biroulet L. Opportunistic infections with anti-tumor necrosis factor-α therapy in inflammatory bowel disease: meta-analysis of randomized controlled trials. *Am J Gastroenterol.* 2013;108:1268–1276.
17. Wisniewski A, Kirchgesner J, Seksik P, et al.; Saint-Antoine IBD Network. Increased incidence of systemic serious viral infections in patients with inflammatory bowel disease associates with active disease and use of thiopurines. *United Eur Gastroenterol J.* 2019; 2050640619889763.
18. *IOIBD Update on COVID19 for Patients with Crohn's Disease and Ulcerative Colitis | IOIBD*. https://www.ioibd.org/ioibd-update-on-covid19-for-patients-with-crohns-disease-andulcerative-colitis/. Accessed May 25, 2020.
19. Gutin LS, Lam AY, Velayos FS, et al. Going viral: management of IBD in the era of the COVID-19 pandemic. *Dig Dis Sci.* 2020;65:1571–1575.
20. Rubin DT, Feuerstein JD, Wang AY, et al. AGA clinical practice update on management of inflammatory bowel disease during the COVID-19 pandemic: expert commentary. *Gastroenterology.* 2020;S0016-5085(20)30445-5. doi:10.1053/j.gastro.2020.03.062
21. Norsa L, Indriolo A, Sansotta N, et al. Uneventful course in IBD patients during SARS-CoV-2 outbreak in northern Italy. *Gastroenterology.* 2020; [Online ahead of print].
22. Ungaro RC, Sullivan T, Colombel JF, et al. What should gastroenterologists and patients know about COVID-19? *Clin Gastroenterol Hepatol.* 2020;18:1409–1411.
23. Brenner EJ, Ungaro R, Gearry RB, et al. Corticosteroids, but not TNF antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel diseases: results from an international registry. *Gastroenterology.* 2020. https://doi.org/10.1053/j.gastro.2020.05.032.
24. Rubin DT, Abreu MT, Rai V, et al. Management of patients with Crohn's disease and ulcerative colitis during the COVID-19 pandemic: results of an international meeting. *Gastroenterology.* 2020;S0016-5085(20)30465-0. doi:10.1053/j.gastro.2020.04.002
25. Kenji M, Katsushi K, Alexander Z, et al. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. *Euro Surveill.* 2020;25:pii=2000180. https://doi.org/10.2807/1560-7917.
26. Zingone F, Savarino EV. Viral screening before initiation of biologics in patients with inflammatory bowel disease during the COVID-19 outbreak. *Lancet Gastroenterol Hepatol.* 2020;5:525.
27. NMB News. https://www.nbcnews.com/health/health-news/how-many-people-have-had-coronavirus-no-symptoms-n1187681. How many people have had coronavirus with no symptoms? Accessed May 27, 2020.
28. Zingone F, Buda A, Savarino EV. Screening for active COVID-19 infection and immunization status before biologic therapy in IBD patients at the time of the pandemic outbreak. *Dig Liver Dis.* 2020;52:604–605.
29. Ritchie AI, Singanayagam A. Immunosuppression for hyperinflammation in COVID-19: a double-edged sword? *Lancet.* 2020;395:1111.
30. Ljungman P, Mikulska M, de la Camara R, et al. The challenge of COVID-19 and hematopoietic cell transplantation; EBMT recommendations for management of hematopoietic cell transplant recipients, their donors, and patients undergoing CAR T-cell therapy. *Bone Marrow Transplant.* 2020. https://doi.org/10.1038/s41409-020-0919-0.
31. Feldmann M, Maini RN, Woody JN, et al. Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. *Lancet.* 2020;395:1407–1409.
32. *Clinical Best Practice Advice For Hepatology and Liver Transplant Providers During the COVID-19 Pandemic: AASLD Expert Panel Consensus Statement*. www.aasld.org/sites/default/files/2020-05/AASLD-COVID19-ClinicalInsights-May142020-FINAL-v2.pdf. Accessed June 3, 2020.
33. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 Novel Coronavirus in Wuhan, China. *Lancet.* 2020;395:497–506.
34. Bhoori S, Rossi RE, Citterio D, et al. COVID-19 in long-term liver transplant patients: preliminary experience from an Italian transplant centre in Lombardy. *Lancet Gastroenterol Hepatol.* 2020. doi:10.1016/S2468-1253(20)30116-3.