



CLINICAL PRACTICE GUIDELINES

COVID-19 and inflammatory bowel disease: Questions arising from patient care and follow-up during the initial phase of the pandemic (February–April 2020)[☆]



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KEYWORDS

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Abstract COVID-19 is a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was described in China in late 2019. There are currently more than three million diagnosed cases, constituting a pandemic which has caused a worldwide crisis. The devastating effects of this infection are due to its highly contagious nature and although mild forms predominate, in absolute values, the rates for severe forms and mortality are very high. The information on the characteristics of the infection in inflammatory bowel disease is of special interest, as these patients have higher attendance at health centres, which may increase their risk of infection. Furthermore, the treatments used to control the inflammatory activity may modify the disease course of COVID-19. The Spanish Working Group on Crohn's Disease and Ulcerative Colitis and the Spanish Nurses Working Group on Inflammatory Bowel Disease have prepared this document as a practical response to some common questions about the treatment of these patients.

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COVID-19 y enfermedad inflamatoria intestinal: preguntas surgidas de la atención y seguimiento de los pacientes durante la fase inicial de la pandemia (febrero-abril 2020)

Resumen La COVID-19 es un síndrome respiratorio agudo grave producido por el coronavirus SARS-CoV-2 que se describió en China a finales de 2019. Actualmente hay más de tres millones de casos diagnosticados, constituyendo una situación de pandemia que ha ocasionado una crisis a nivel mundial. El efecto devastador de esta infección se debe a su alta contagiosidad y, aunque predominan las formas leves, los casos graves y la mortalidad en valores absolutos son muy elevados. La información sobre las características de la infección en la enfermedad inflamatoria intestinal tiene especial interés, y esto es debido a que estos pacientes tienen una mayor frecuentación de centros sanitarios, lo que puede incrementar el riesgo de contagio. Además, los tratamientos que se administran para el control de la actividad inflamatoria podrían modificar la evolución de la COVID-19. El Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa, en colaboración con el Grupo Enfermero de Trabajo en EII, ha elaborado este documento que tiene como objetivo responder de forma práctica algunas dudas frecuentes en el tratamiento de estos pacientes.

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Introduction

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first detected in China in December 2019.^{1,2} Since then, there has been a rapid spread of the infection caused by this microorganism (COVID-19) all over the world, with 257,454 associated deaths reported to date (Center for Systems Science and Engineering, Johns Hopkins University, updated 06/05/2020).

In Spain, the first case of COVID-19 was detected on 31 January 2020. Since then, a total of 220,325 cases have been diagnosed and the number of deaths from the infection is 25,857 (Ministry of Health and Consumer Affairs, updated 05/05/2020). The international SECURE-IBD registry aims to monitor cases detected in patients with inflammatory bowel disease (IBD), and has so far included 959 patients, 37 of whom have died (<https://covidibd.org>, updated 05/05/2020). Despite the fact that the infection usually causes a mild illness, its highly infectious nature, added to its potential complications, have caused an unprecedented effect on our society. It is estimated that the incidence of COVID-19 in patients with IBD is similar to that of the general population,^{3,4} although we still have very little data on its impact on this group. The Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa (GETECCU) [Spanish Working Group on Crohn's Disease and Ulcerative Colitis] has carried out a large number of initiatives in this field, including publishing its recommendations on the management of these patients.⁵ The aim of this document is to continue with the recommendations established by GETECCU and, in collaboration with the Grupo Enfermero de Trabajo en EII (GETEII) [Nursing Working Group on IBD], answer some of the most common practical questions on the care of people with IBD which have been raised in our clinics over the first months (February–April 2020) of the SARS-CoV-2 pandemic.

Is it justified for a patient undergoing treatment with biologicals and immunosuppressants to request preventive sick leave given the pandemic situation? Are there occupations at particular risk?

The risk of infection related to different occupations can be influenced by multiple factors. We currently know that the highly infectious nature of this infection requires social distancing to be maintained and hygiene measures ensured. Therefore, patients whose work means a minimum distance between people cannot be maintained or who are at risk of contact with secretions should seek to adapt their activity, preferably to teleworking. If that is not possible, then sick leave should be considered. This could be especially relevant for healthcare personnel or when work involves direct and close contact with the public. These measures are particularly important in the case of active disease, comorbidity or receiving treatment with prednisolone above 20 mg/day or equivalent, thiopurines, methotrexate, calcineurin inhibitors, Janus kinase inhibitors or biological drugs.^{6,7}

What should an IBD patient living with a confirmed or possible COVID-19 patient do?

Two aspects need to be taken into account in this situation. First, strict general isolation measures should be established in the home, which means avoiding contact with the infected patient at all levels, i.e. constant separation of the individuals, with their own room and separate bathrooms, if possible. When this is not possible, strict hygienic measures should be used after using bathrooms (washing surfaces with bleach, soap and alcohol). It may also be necessary to wear a mask in common areas of the house, wash clothes daily

and ensure adequate ventilation. Second, the IBD patient should carefully self-monitor for possible signs of COVID-19, especially fever, respiratory symptoms or diarrhoea.⁵ The risk of complications in patients with IBD will depend on the degree of activity of the disease, with it being higher in active patients.⁸ Immunosuppressive medication could also affect how COVID-19 develops. In any case, such patients should keep in close contact with their usual IBD unit so that personalised measures can be taken in the event of symptoms.

Are patients with IBD more susceptible to COVID-19?

Patients with IBD are known to have a greater risk of severe and opportunistic infections.⁹ Therefore, hypothetically, they could be at higher risk of SARS-CoV-2 infection compared to the general population. With the data currently available, which is very limited and probably skewed, IBD patients do not seem to be at increased risk of contracting this particular infection.³ This could be due to the fact that IBD patients, specifically those with pharmacological immunosuppression, are aware of their increased risk of infection, and they have probably applied better, earlier and stricter measures of protection, social distancing and hygiene.

Should we test for active or prior coronavirus infection before starting immunosuppressive or biological therapy in patients with IBD? Which test or tests (PCR, rapid serological tests, regulated IgM + IgG serology, etc.) would be indicated?

Ruling out the presence of SARS-CoV-2 infection is recommended before starting immunosuppressive therapy for IBD. The method of choice during the epidemic should be PCR determination in nasopharyngeal exudate. In positive patients, delaying the start of immunosuppression is recommended, as long as the IBD activity allows.¹⁰⁻¹² However, there are patients with severe activity in whom the immunosuppressive therapy cannot be delayed. The decision to start immunosuppressants in patients with active IBD and COVID-19 will depend on the severity of the IBD inflammatory activity and the severity of the infection. It should be noted that the SARS-CoV-2 PCR can be positive in asymptomatic or minimally symptomatic patients. Moreover, anti-TNF drugs can have a beneficial effect on the progression of both IBD activity and COVID-19,¹³ so patients with severe IBD should not have their therapy stopped purely because of a positive PCR.¹⁴

Having the PCR result means quick and precise decisions can be taken early to prevent complications from COVID-19 in positive PCR cases. In the future, if a large proportion of the general population acquires immunity, the inclusion of COVID-19 serology in the infection screening before starting immunosuppression in patients with IBD should be assessed. In any event, application of these techniques will probably depend on local policies, taking available resources into account.

Is COVID-19 more severe in patients with IBD than in the general population?

COVID-19 does not appear to be more severe in patients with IBD compared to the general population,^{3,15} even when including patients on immunosuppressive therapy. In the SECURE-IBD multicentre registry, 959 patients have been reported (168 of them in Spain): 33% required hospitalisation, 6% were admitted to the ICU, 5% required assisted breathing and the mortality rate was 4% (SECURE-IBD Database: <http://covidibd.org/current-data>. Updated 05/05/2020). Similar data have been reported for a series of cases in Spain.¹⁴ An Italian series has shown that patients with active IBD are more likely to require hospitalisation and assisted breathing than patients with quiescent IBD,⁸ so it seems that IBD-related inflammatory activity not controlled by medication could be a poor prognostic factor. We also need to keep in mind that IBD patients tend to be younger and have less associated comorbidity than the general population.¹⁶ Older age and the presence of comorbidities are in themselves the most significant risk factors for a poor outcome from COVID-19.¹⁷ Confirming this, being over 65, Charlson index >1 and active IBD were recently reported to be independently associated with mortality from COVID-19 in patients with IBD. In contrast, no relationship has been detected between mortality and immunosuppressive therapy.⁸

Are patients with IBD on immunosuppressive and biological therapy more susceptible to COVID-19?

The patients with IBD and a higher risk of complications from SARS-CoV-2 are those aged 70 or over who, in addition to IBD, have respiratory or cardiac comorbidities, hypertension, diabetes or malnutrition and/or are on immunosuppressive therapy.⁶ Immunosuppressive therapy includes biological therapy (anti-TNF, ustekinumab, vedolizumab), immunosuppressants (thiopurines, methotrexate, tacrolimus, ciclosporin, tofacitinib), prednisolone >20 mg/day or equivalent, either in monotherapy or combination therapy. The British Society of Gastroenterology also considers that patients with IBD are at particular risk if, regardless of their age or comorbidity, they meet at least one of the following criteria: steroid use at doses of 20 mg/day or more of prednisolone or equivalent; recent initiation of combination therapy (biological with immunosuppressant, maximum six weeks before); moderate or severe disease not controlled with medication; short bowel syndrome with nutritional support or parenteral nutrition requirement.⁶

Does COVID-19 have specific manifestations in patients with IBD? Is there an increased risk of diarrhoea?

In the general population, up to 61% of patients with COVID-19 may report gastrointestinal symptoms, with anorexia (35%), diarrhoea (34%) and nausea (26%) being the most common.¹⁸ It is important to highlight that in up to 20%

of cases gastrointestinal symptoms can be the main symptoms and, in 14%, the first to appear. The predominant symptoms in patients with IBD are similar to the general population, with fever and cough in most cases (77–90% and 66% respectively).^{8,14} In fact, 15–21% of patients with IBD report diarrhoea,^{8,14} a slightly lower proportion than the general population, while the presence of other gastrointestinal symptoms has not been reported. In view of the above finding, during the SARS-CoV-2 pandemic, in IBD patients who develop new gastrointestinal symptoms, especially if in the form of diarrhoea, COVID-19 should be considered within the differential diagnosis.

Are there drug interactions between the treatments for COVID-19 and IBD?

Medical treatment for COVID-19 has involved the use of multiple active substances previously approved for other indications. This point, together with the limited experience with their use in patients with COVID-19, can make it difficult to detect some drug interactions. There are various platforms providing very useful resources which can help with early detection, such as the one set up at www.covid19-druginteractions.org. Important among the interactions described is the possible increased risk of neurological toxicity when using hydroxychloroquine with infliximab or adalimumab. Also listed is the fact that dexamethasone can lower lopinavir/ritonavir levels, while budesonide may increase them. Nevertheless, these treatments are generally considered to be safe in this context.

Do the treatments for COVID-19 have any specific gastrointestinal toxicity? How should it be managed?

Gastrointestinal toxicity has been associated with the specific treatment for COVID-19. It tends to be mild-to-moderate (lopinavir/ritonavir: diarrhoea, nausea, vomiting, abdominal pain, pancreatitis; hydroxychloroquine: anorexia, nausea, vomiting, diarrhoea, abdominal pain) and can be managed with symptomatic treatment (antidiarrhoeals, prokinetics or antispasmodics). *Clostridioides difficile* infection also has to be ruled out, as the treatment for COVID-19 often includes antibiotics (azithromycin, amoxicillin-clavulanic acid, ceftriaxone), which can increase the risk of superinfection, with this bacterium being one of the most common causative agents of nosocomial infections.

When can biological or immunosuppressive therapy be restarted after COVID-19 infection (probable or confirmed)?

In some patients with severe infection, immunosuppressive therapy will have to be withdrawn either temporarily or permanently. In these cases, the timing of reinstating immunosuppressive therapy should primarily take into account the severity of the infection (development of pneumonia, systemic inflammatory response syndrome or cytokine release syndrome), the type of maintenance ther-

apy and the clinical activity of the IBD. In cases in which SARS-CoV-2 has been detected where the patient has stable IBD, the recommendation is to delay the administration of biological drugs and the restart of immunosuppressants for at least two weeks.^{5,19,20} In patients who develop symptoms secondary to the infection, the immunosuppressive therapy should not be reinstated until the symptoms have completely resolved. A PCR test on nasopharyngeal exudate or serology could be indicated prior to restarting therapy and in patients who need to go to the day hospital, but in most cases this is not currently applicable.

During the pandemic, should parenteral vitamin B12 be delayed or stopped in a patient with IBD? Could it be replaced with oral vitamin B12?

The nature of IBD often involves certain nutritional deficiencies, in some cases chronic, particularly in patients with Crohn's disease. Although we cannot make a general recommendation, it seems reasonable to try to prolong the administration interval for parenteral vitamin B12 wherever possible. Oral cyanocobalamin supplementation is an effective alternative in a large percentage of patients. In the current situation, oral supplementation will reduce the number of visits to health centres, so it should be considered in all patients. In practical terms, a weekly dose of two 1 mg ampoules of cyanocobalamin taken orally (total of 2 mg/week) can be effective in achieving or maintaining adequate levels of vitamin B12 in patients with Crohn's disease.²¹

How long can a patient wait for laboratory tests?

The use of virtually all hospital and primary care centre healthcare resources for COVID-19 in the initial months of the pandemic made it necessary to reduce as far as possible the number of non-urgent complementary tests for patients with IBD. This mainly affected patients in remission, whose scheduled appointments have been successfully resolved electronically. The quality indicators for the IBD units applied by GETECCU establish the intervals for carrying out monitoring tests for patients on immunosuppressants and biologicals. In a stable situation, these tests (blood count, clinical biochemistry) are performed every three to six months in all GETECCU-accredited IBD units. There are other determinations which are carried out on demand in patients with IBD depending on their clinical status, such as levels of drugs or anti-drug antibodies, faecal calprotectin and microbiological studies of blood or stool specimens. The epidemic situation has made it necessary to review the frequency of these tests and to assess whether or not they could be postponed on an individual basis. In patients with a stable analytical parameter profile over the previous months or years, managing without one of their routine monitoring appointments seems safe and reasonable.

Should IBD patients receiving immunosuppressive or biological therapy have a longer isolation time than the general population?

The Spanish Ministry of Health recommendations for the pandemic directed at patient groups with chronic diseases, including immunosuppressed patients,²² do not make any mention of measures for patients with IBD. In the present phases for the easing of lockdown it states that phase 3 will allow social contact for people who are “not vulnerable or have previous illnesses”.²³ The specific recommendations for patients with IBD should be made on an individual basis, as mentioned above, according to age (>60–70), comorbidities and IBD activity. It is the at-risk patients who should avoid social contact, and who must use barrier prevention measures (mask and gloves) and adhere to strict hygiene at all times. As there is no clear evidence of immunosuppression having a negative impact on the course of COVID-19 in clinically inactive and stable patients, the recommendations in this case should be the same as in the general population, but with scrupulous following of the recommended measures (teleworking if possible, social distancing, masks, etc.).

Is urgent endoscopy necessary during the COVID-19 outbreak? In which cases?

Urgent endoscopy remains essential in certain patients (with or without IBD) during the COVID-19 pandemic. At the most dramatic points of the epidemic peak (2–3 weeks in March, depending on the geographic area), endoscopy was limited to cases with high suspicion of IBD, severe signs and symptoms and suggestive laboratory data, and patients with ulcerative colitis and severe flare-up to obtain biopsies to rule out reactivation of CMV infection.⁵ Now that the situation has improved somewhat, the indications for endoscopic investigations have been expanded and include situations with a high risk of recurrence, recent high-grade dysplasia, or a poor response to certain treatments and involving a significant change in management.

Can isolation anxiety and fear worsen the course of IBD or lead to a flare-up?

Among patients with IBD, 29–35% generally have symptoms of anxiety or depression during remission periods and the figure is 60–80% during flare-ups.²⁴ Negatively perceived stress (distress) has been described as a risk factor for the onset of IBD flare-ups.²⁵ Moreover, the lockdown the general population has been subjected to in many countries during the COVID-19 pandemic has been the cause of a very significant negative psychological impact, increasing the rates of generalised anxiety disorder, stress and sleep problems.²⁶ Therefore it seems reasonable to expect that this influence of the lockdown (including patients’ relatives or friends being affected by SARS-CoV-2) on psychological aspects of patients with IBD has increased their predisposition to suffering from flare-ups of their condition over this period. We will have to wait for the results of future studies on how

patients with IBD were affected during this pandemic and which analyse the psychological impact of this.

Conclusions

The COVID-19 pandemic is posing a formidable health, economic and social challenge of dimensions which are still difficult to quantify for the world population as a whole. At the moment, despite rapid advances in the study of COVID-19, there is still more we do not know than we do know about the disease caused by SARS-CoV-2.

Throughout the months of February, March and April 2020, doctors and nurses who regularly treat patients with IBD were receiving a multitude of questions and queries from these patients, even before the state of emergency had been declared by the Spanish health authorities. In this article we have collected the most frequently asked or relevant questions, and we have tried to answer them with the best evidence available at the time of publishing. Evidently, given the speed at which our knowledge of SARS-CoV-2 infection and its effects on many very different disorders, including IBD, has been acquired, the answers we provide here may change significantly in the coming weeks or months. Even so, we believe that this article may be of help at the present time for colleagues who have to provide care and answers to their patients, with the best available evidence, even if that is somewhat limited. Let us hope that soon we will not only have better answers to our patients’ questions, but also effective vaccines or treatments which enable us to prevent or at least mitigate the damage caused by the virus.

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Conflicts of interest

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