

# Management of Crohn's disease in an immunosuppressed COVID-19-positive patient: safety-driven prioritisation of nutritional therapy as a bridge to restarting immunosuppression

Clare Harris, Richard James Harris, Louise Downey, Markus Gwiggner

Department of Gastroenterology, University Hospital Southampton NHS Foundation Trust, Southampton, UK

**Correspondence to**  
Dr Clare Harris;  
clare\_wij@doctors.net.uk

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## SUMMARY

Active inflammatory bowel disease (IBD), combined immunosuppression and corticosteroid therapy have all been identified as risk factors for a poor outcome in COVID-19 infection. The management of patients with both COVID-19 infection and active IBD is therefore complex. We present the case of a 31-year-old patient with Crohn's disease, on dual immunosuppression with infliximab and mercaptopurine presenting with inflammatory small bowel obstruction and COVID-19 infection. The case highlights the use of nutritional therapy, which remains underused in the management of adults with IBD, to manage his flare acutely. Following negative SARS-CoV-2 PCR testing and SARS-CoV-2 IgG testing confirming an antibody response, ustekinumab (anti-interleukin 12/23) was prescribed for long-term maintenance.

## BACKGROUND

SARS-CoV-2 has been identified as the causative pathogen in the ongoing global coronavirus (COVID-19) pandemic which started in Wuhan, China in December 2019.<sup>1 2</sup> There is currently a lack of robust data on the impact of COVID-19 infection on patients with inflammatory bowel disease (IBD) and in particular those who are immunosuppressed. However, ongoing studies, including the SECURE-IBD (Surveillance Epidemiology of Coronavirus Under Research Exclusion) and Physician REsponse to disease flares and Patient Adaptation in Response to Events in Inflammatory Bowel Disease during the COVID-19 pandemic databases, may help to address this gap in the evidence.<sup>3 4</sup> The data published to date from SECURE-IBD show that compared with monotherapy, dual immunosuppression with immunomodulators and tumour necrosis factor (TNF) alpha antagonists is positively associated with the adverse outcomes of COVID-19-related hospitalisation or death compared with monotherapy. Oral and parenteral corticosteroids appear to have the highest risk of therapy-associated adverse outcomes.<sup>5</sup>

The British Society of Gastroenterology has published guidance on the management of IBD in the context of COVID-19.<sup>6</sup> However, there is a lack of high-quality evidence on which to base management decisions. IBD physicians are relying on expert opinion and limited global experience rather than published peer-reviewed data. This case

report describes the individualised corticosteroid free management of an immunosuppressed patient with IBD with asymptomatic COVID-19 infection who presented with worsening abdominal pain and had radiological evidence of small bowel obstruction secondary to a severe flare of Crohn's disease. As described in this case, we suggest it is essential for COVID-19-infected patients with IBD to have tailored, carefully considered management plans and avoid the 'knee-jerk' prescribing of long courses of high-dose corticosteroids.

## CASE PRESENTATION

A 31-year-old man with complex stricturing and penetrating ileocolonic Crohn's disease presented to the emergency department in May 2020, during the coronavirus pandemic, with a 24-hour history of progressive abdominal pain and vomiting with preceding increased stool frequency. Following previously low infliximab (IFX) drug levels with low-level antibodies, he was on escalated treatment with mercaptopurine 100 mg daily and IFX 5 mg/kg every 4 weeks (trough level 10.4 mg/L, negative anti-drug antibodies).

This patient had no significant medical history or comorbidities of note and had never previously been hospitalised due to his Crohn's disease.

On examination, he was afebrile and haemodynamically stable. His abdomen was soft but generally tender with 'tinkling' bowel sounds. Respiratory examination was normal and he had no classical symptoms of COVID-19 at presentation.

## INVESTIGATIONS

Admission blood tests showed a white cell count of  $17.1 \times 10^9/L$ , neutrophil count  $13.1 \times 10^9/L$  and C reactive protein (CRP) 18 mg/L which increased to 51 mg/L the next day. Stool PCR excluded enteric infection, including *Clostridioides difficile*. Faecal calprotectin was raised at 707  $\mu g/L$ . An abdominal CT showed complex fistulising Crohn's involving the sigmoid colon and terminal ileum with evidence of subacute small bowel obstruction (see figure 1).

Despite no respiratory symptoms, he was screened and tested positive for SARS-CoV-2 with a rapid PCR test (QIAstat-Dx Respiratory) on admission.<sup>7</sup> Chest radiograph and CT chest were both unremarkable. There is evidence that certain blood biomarkers change with increasing severity of COVID-19. They can be used to monitor and evaluate the severity of



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**Figure 1** CT image showing proximal small bowel dilatation (short arrow) above complex distal ileal disease (long arrow).

the illness and are associated with a poorer prognosis.<sup>8 9</sup> In our patient, these included ferritin 247 µg/L, D-dimer 303 µg/L, lactate dehydrogenase 556 U/L and a lymphocyte count of  $1.7 \times 10^9/L$ . However, these biomarkers are not entirely specific to COVID-19 infection and are also indicators of other inflammatory processes including active IBD.<sup>10</sup> This offers an alternative explanation for his abnormal results. Nonetheless, these markers can also be altered in less severe cases of COVID-19 infection and thus remained of concern.<sup>11 12</sup> His alanine aminotransferase rose to 202 U/L during admission. A non-invasive liver screen was unremarkable and an ultrasound scan showed mild fatty liver disease only with previously normal liver function tests.

## TREATMENT

Given the available SECURE-IBD data showing worse outcomes in patients on corticosteroids, the conventional approach to IBD management with high-dose intravenous hydrocortisone was avoided. This patient's case was discussed carefully with all members of the IBD multidisciplinary team (including specialist IBD surgeons, gastroenterologists, radiologists, nurses and dietitians) at the tertiary centre where he was being treated. Surgery was not considered a first-line treatment due to both the complexity of his disease and the recognised poor outcomes of surgery in COVID-19 infection,<sup>13</sup> nor was this felt necessary as there was no evidence of complete bowel obstruction. Following these discussions and with the consent of the patient, the option of exclusive enteral nutrition (EEN) was pursued as the best option. Under close dietetic supervision, he was prescribed Modulen IBD 20% 500 mL four times per day. This was based on a weight of 98 kg and a height of 1.7 m giving him a body mass index of 33.9 kg/m<sup>2</sup> with the aim of providing 2000 kCal and 78 g protein per day. Modulen is a nutritionally complete powdered formulation manufactured by Nestlé and may be used as a sole source of nutrition. In view of his recent IFX drug monitoring levels suggesting secondary loss of response, and to reduce the perceived risk of COVID-19 complications, both his mercaptopurine and IFX were stopped. He was also started on broad-spectrum intravenous antibiotics for 48 hours on admission.

## OUTCOME AND FOLLOW-UP

This patient had an excellent clinical and biochemical response to EEN. He was discharged after 6 days following rapid improvement in his abdominal symptoms and normalisation of his inflammatory

markers (CRP of 5 mg/L at discharge). It must be noted that this marked reduction in inflammatory markers may be attributed to an additional infective component for which he had received a short course of antibiotics. To inform decisions regarding future immunosuppression, SARS-CoV-2 PCR swab testing was repeated at discharge which returned negative. Two weeks later, antibody testing was performed which confirmed a SARS-CoV-2 IgG response. Following this evidence of viral clearance and immunological response, immunosuppression was restarted for long-term treatment of his Crohn's disease. Due to loss of response to IFX, he was switched out of class from a TNF antagonist to ustekinumab, a monoclonal antibody to the p40 subunit of interleukin 12 and interleukin 23.

## DISCUSSION

At the time of writing this article, there were >100 million global cases of COVID-19 infection with >2.5 million deaths (>100 000 of those deaths in the UK).<sup>14</sup> The exact risk of COVID-19 to patients with IBD is still unknown. The current consensus is that patients with IBD are not at greater risk of contracting COVID-19.

However, there is a higher risk of subsequent complications especially for those with active inflammatory disease and for those on specific immunosuppression at time of infection, particularly systemic corticosteroids.<sup>6 15 16</sup> The available data on the SECURE-IBD Database suggest that the use of systemic corticosteroids is a strong risk factor for adverse outcomes following subsequent COVID-19 infection. Furthermore, a subgroup analysis showed a higher risk of hospitalisation and/or death with combined immunomodulator and anti-TNF therapy.<sup>5</sup>

The risks of corticosteroid use in active IBD with concurrent COVID-19 infection are in contrast to the Randomised Evaluation of COVid-thERapY trial results. This study showed a favourable outcome in patients with severe COVID-19 infection treated with dexamethasone with an 8%–26% lower mortality compared with those treated with standard care.<sup>17 18</sup> However, corticosteroid treatment was not beneficial in patients with asymptomatic or mild disease who were on no respiratory support at the time of randomisation and showed possible harmful effects in this group.<sup>18</sup> In addition, the evidence for the use of intravenous hydrocortisone, which is the corticosteroid commonly used for the treatment of active IBD in hospitalised patients, does not seem to offer the same benefit to patients with severe COVID-19 infection.<sup>19 20</sup> The decision to therefore avoid conventional IBD treatment with hydrocortisone was made based on the available information at the time. On balance, we opted for the safest treatment of active IBD with EEN to minimise the potential risk of poor outcomes in an asymptomatic patient with COVID-19 with active IBD.

COVID-19 infection has a mean incubation period of 6 days but there have been reports of incubation periods up to 24 days.<sup>21 22</sup> Therefore, patients may present with a secondary condition before later developing COVID-19 symptoms. Rapid and routine COVID-19 testing of all patients prior to treatment is therefore crucial to their care. The QIAstat-Dx Respiratory SARS-CoV-2 test is a rapid multiplex PCR assay and has been shown to provide highly sensitive, robust and accurate detection of SARS-CoV-2.<sup>23</sup> The test has a rapid turnaround time of approximately 60 min which has significant benefits for patient management as it enables fully informed and appropriate decisions to be made quickly.<sup>24 25</sup>

One of the main complexities of this case was the uncertainty of the exact timepoint of this patient's infection and where in the disease course he was. There was no known direct contact and thus we were unable to predict whether he was early within the incubation period, and currently pre-symptomatic, or later on

in his infection and likely to be classed as an asymptomatic case of COVID-19. The decision to avoid systemic immunosuppression was in part based on this uncertainty. The presence of a SARS-CoV-2 IgG response confirmed the initial PCR result (QIAstat-Dx Respiratory SARS-CoV-2 test has 99.4% sensitivity and 98.6% specificity) making a false positive result highly unlikely.<sup>7 26 27</sup> There is currently no consensus on whether the presence of antibodies offers protection against reinfection and if so, how long that effect may last. However, the presence of IgG antibodies gave some reassurance in this case prior to the initiation of further immunosuppression.

Nutrition is an important aspect of IBD assessment and management. EEN is most commonly used in the paediatric population with Crohn's disease as a first line, steroid-sparing treatment. The evidence for its use in adults with Crohn's disease is weaker but this has been attributed to poor tolerability and compliance. There is however evidence that it can be used to induce remission in adults successfully.<sup>28 29</sup>

Our case is a fairly typical scenario for patients with complex fistulising Crohn's disease. However, the difficulty lies in managing this case during the coronavirus pandemic in a safe and effective way. The evidence for IBD management in the face of COVID-19 is evolving although the optimal strategy is yet to be determined. EEN is a good and safe option to treat specific and suitable individuals with active small bowel Crohn's disease and concomitant COVID-19 infection in an attempt to minimise the risk of adverse outcomes associated with other IBD treatments such as corticosteroids, immunomodulators and biological medicines. We accept that there is not enough evidence in this specific situation to draw any definite conclusions about the use of EEN to manage active IBD in the face of COVID-19 infection and that further evidence is required to make recommendations. What is clear is that restricting the use of long courses of high-dose corticosteroids by using steroid-sparing agents is the preferred way forward. It is paramount that individualised management plans are made by experts taking into account current global experience.

### Learning points

- ▶ There is limited high-quality evidence on the impact of COVID-19 on patients with inflammatory bowel disease although this is evolving with time.
- ▶ Rapid COVID-19 point-of-care testing is crucial in all immunosuppressed patients to guide management and reduce the risk of serious complications.
- ▶ Complex cases such as these require careful and considered expert management, using existing experience from international registers, to determine an optimal individualised management plan.

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