Therapeutic Advances in Gastroenterology

Review

The complex relationship between viruses and inflammatory bowel disease – review and practical advices for the daily clinical decision-making during the SARS-CoV-2 pandemic

Ther Adv Gastroenterol

2021, Vol. 14: 1–13

DOI: 10.1177/1756284820988198

Klaudia Farkas*, Daniella Pigniczki*, Mariann Rutka, Kata Judit Szántó, Tamás Resál, Renáta Bor, Anna Fábián, Zoltán Szepes, György Lázár and Tamás Molnár

***Abstract*:** The coronavirus disease 2019 (COVID-19) outbreak emerged in December 2019 in China and rapidly spread worldwide. Inflammatory bowel disease (IBD) patients are likely to be more susceptible to viral infections, and this is significantly influenced by the type of therapy they receive. Thus, issues specifically concerning the medical treatment of IBD patients were shortly addressed at the beginning of the pandemic. However, recently available data on the occurrence and outcome of SARS-CoV-2 infection in IBD patients does not address the concerns raised at the beginning of the pandemic. Growing evidence and the rapid changes happening over the past few weeks have helped elucidate the current situation, contribute to our understanding of the disease, and many previously raised questions could now be answered. We hereby summarise available evidence regarding viral infections and IBD, focusing on SARS-CoV infections, and we provide practical recommendations related to patient management during the COVID-19 pandemic era.

Keywords: COVID-19, inflammatory bowel disease, management, pandemic

Received: 9 June 2020; revised manuscript accepted: 26 December 2020.

Correspondence to:
Tamás Molnár
First Department of Medicine, University of Szeged. 8-10 Korányi Alley, Szeged, H6720, Hungary
molnar.tamas@med.u-szeged.hu

Klaudia Farkas
Mariann Rutka
Kata Judit Szántó
Tamás Resál
Renáta Bor
Anna Fábián
Zoltán Szepes
First Department of Medicine, University of Szeged, Szeged, Hungary

Daniella Pigniczki
György Lázár
Department of Surgery, University of Szeged, Szeged, Hungary

*These authors share first authorship.

Historical synopsis

The first case of respiratory failure proved to be associated with a new coronavirus species was presented in December 2019, diagnosed in Wuhan, Hubei province, China.[1] In the following 3 months, this virus proved able not only to cross the borders of the country but also to spread across the world, becoming a pandemic. By 12 February 2020, the virus was named 'severe acute respiratory syndrome coronavirus 2' (SARS-CoV-2), causing the disease referred to as coronavirus disease 2019 (COVID-19).[2]

A pandemic takes a vast toll on the global economy, on social life and on medical services and supplies. In such a situation, we must recognise the most vulnerable points in medical care and identify the potentially modifiable parts of patient management to avoid unnecessary health damage. New standards for treatment options should be developed that aim towards decreasing susceptibility to the infectious disease. Patients with chronic diseases and those receiving immunosuppressive or biological therapy may be at higher risk of contracting infectious diseases, and the expected consequences and outcomes of a SARS-CoV-2 infection or even a manifest COVID-19 in such patients should be explored. It might prove necessary to implement reasonable therapeutic changes into the daily clinical practice during the current pandemic situation in order to provide the most beneficial outcome.

The present study focuses on the treatment options for inflammatory bowel disease (IBD), considering the above-mentioned issues during the COVID-19 pandemic. We also review the current knowledge on the relationship between viral infections and IBD.

It is well known that genetic, environmental and immunological factors also contribute to the development of IBD. In the case of Crohn's disease (CD), it has been hypothesised that viral infections may trigger an unbalanced immune response.[3]

Viral pandemics with different mortality rates have long been a part of human history (Table 1), but almost no information is available on their association with IBD.[4] Looking at these pandemics through the lens of a gastroenterologist, each can cause gastrointestinal (GI) complaints with predominantly atypical abdominal symptoms.

In the current situation, it is necessary to be aware of the nature and mortality potential of the Coronaviridae. This family features enveloped, single-stranded RNA viruses classified into four genera. SARS-CoV-2 and SARS-CoV-1 are the members of the β genus, which, together with the Middle East respiratory syndrome coronavirus (MERS-CoV), are the human-infecting species causing respiratory and GI symptoms[4,5] (Table 2). An outbreak of MERS-CoV occurred in 2012. The mortality rate was 2.5–7.5%, and GI symptoms were present in approximately 25% of the patients. Abdominal pain and diarrhoea were most commonly observed and, in some patients, GI symptoms developed even prior to respiratory symptoms (e.g. coughing and pneumonia). Furthermore, measurable faecal levels of viral RNA were present in 14.6% of the examined stool samples.

In SARS-CoV-2 infections, stool viral RNA levels have exhibited a progressive increase from the fifth day of the illness, remaining detectable even until the 30th day.[5] Regarding genome sequences, SARS-CoV-2 and SARS-CoV-1 exhibit 82% similarity. Angiotensin-converting enzyme 2 (ACE-2) cell receptors have been confirmed as viral targets; these are widely present not only in the respiratory tract but also in the GI tract. Based on a current meta-analysis, 17.6% of the patients with COVID-19 have experienced GI symptoms, such as anorexia, diarrhoea, nausea, vomiting and abdominal pain. GI symptoms are seen particularly in patients with more severe forms of COVID-19.[6] Patients with GI symptoms, defined as diarrhoea or nausea/vomiting, at the time of testing, were significantly more likely to test positive for SARS-CoV-2 than negative (61% *versus* 39%).[7] SARS-CoV-1 infections had a mortality of about 10%, whereas SARS-CoV-2 has a 2%–10% mortality rate. Therefore, coronavirus infections may have similar pathomechanisms and manifestations; nevertheless, they are associated with different mortality rates. This may, in part, be due to differences in virulence but may also reflect differences in the immune response towards the disease. For SARS-CoV-2, continuous activation of different immune cells may result in a 'cytokine storm'.[8] The emergence of a SARS-like virus from bats targeting ACE-2 receptors in 2013[9] had previously raised the potential for worldwide pandemic. We need to bring up the question: could we have been more cautious?

IBD and viral infections – including SARS-CoV-2 virus

There is no evidence that patients with IBD have been at higher risk for infection and worse disease course during each previous coronavirus epidemic. However, such patients do seem to have an increased susceptibility to viral infections, independently of their medical therapy. Furthermore, a recently published study found that IBD patients have three times higher risk of developing a viral disease with subsequent hospitalisation than the control population.[10] Disease activity and azathioprine therapy were also found to be risk factors for these conditions. Regarding the pathogens, cytomegalovirus (CMV) infection was the main cause of hospitalisation.[10]

Meanwhile, patients receiving immunosuppressive and biological therapy are at greater risk of opportunistic infections (OIs), especially those with persistent chronic diseases. Generally, patients receiving combination therapy are at high risk of developing OIs: for pneumonia, the risk is twice as high, whereas patients receiving combination therapy have a 13-fold higher risk of a viral infection than those receiving non-combination therapy. Regarding monotherapies, anti-TNF drugs may predispose to pneumonia, whereas azathioprine is mostly associated with viral infections.[11] Corticosteroid treatment facilitates the development of serious infections.[12]

Table 1. Deadliest epidemics ever recorded.[4]

Name of the virus	Family	Main symptoms	GI symptoms	Any data with IBD	Mortality
Marburg	Filoviridae	Haemorrhagic fever	Loss of appetite, vomiting, diarrhoea, hepatitis	No	> 80%
Ebola	Filoviridae	Haemorrhagic fever	Diarrhoea, vomiting, abdominal pain	No	>70%
Rabies	Rhabdoviridae	Encephalitis, meningitis	Abdominal pain, dysphagia	No	≈100%
HIV	Retroviridae	Immunodeficiency, opportunistic infections	Colitis-like symptoms can occur	HIV infection can alter the course of IBD. Many of the opportunistic infections in HIV can mimic IBD[1]	50%
Smallpox	Poxyviridae	Skin bumps, blindness	Vomiting rarely	Live vaccine, contraindicated in immunosuppressed patients	30%
Hantavirus	Bunyaviridae	Pneumoniae, haemorrhagic fever	Haemorrhagic gastropathy	No	12–36%
Influenza	Orthomyxoviridae	Fever, myalgia	Vomiting, diarrhoea, abdominal pain	Low vaccination rate and high rate of vaccine hesitancy in IBD	<1%
Dengue	Flaviviridae	(Haemorrhagic) fever	Vomiting, diarrhoea	Combination therapy with anti-TNF and sunitinib showed effectiveness in animal model	2.5%
Rotavirus	Reoviridae	Childhood diarrhoea	Diarrhoea, vomiting	6-thioguanine inhibits rotavirus replication through suppression of Rac1 GDP/GTP cycling	<1%
SARS-CoV	Coronaviridae	Fever, pneumonia, ARDS	Diarrhoea, vomiting	No	10%
MERS-CoV	Coronaviridae	Fever, pneumonia, ARDS	Diarrhoea, vomiting	No	35%
SARS-CoV-2	Coronaviridae	Fever, pneumonia, ARDS	Anorexia, diarrhoea, vomiting	No	5%?

ARDS, acute respiratory distress syndrome; GI, gastrointestinal; IBD, inflammatory bowel disease; GI, gastrointestinal; MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV, severe acute respiratory syndrome coronavirus.

With these relationships in mind, IBD patients should be regarded as a high-risk group in the COVID-19 pandemic. However, growing evidence suggests that IBD *per se* does not increase the risk of coronavirus infection – exemplified by responses coming from different questionnaire surveys,[13–15] though the first two publications on IBD patients during the pandemic did not report any patients with SARS-CoV-2 infection, neither from China nor from Italy.[16,17] On the basis of the most recent data (Spain, Italy and SECURE-IBD Registry), we may infer that diarrhoea occurs more frequently amongst SARS-CoV-2-infected IBD patients (21%) than in the general population.[18,19] The predictors of COVID-19 pneumonia and mortality, however, remain the same as in the general population (i.e. age >65 years, comorbidity), although the risk is further increased by

Table 2. Human infecting species of Coronaviridae.[4]

Name of the virus	Family	First identification	Main symptoms	Range of symptoms	GI symptoms	Any data with IBD	Mortality	Incubation period	Animal vector	Area of pandemic	Vaccine
SARS-CoV	Coronaviridae	2002, China	Fever, pneumonia, ARDS	Fever, malaise, myalgia, headache, diarrhoea, shivering, cough, dyspnoea, diarrhoea	Diarrhoea, vomiting	No	10%	2–7 days	Bat, civet	Worldwide	None
MERS-CoV	Coronaviridae	2012, Saudi Arabia	Fever, pneumonia, ARDS	Fever, cough, shortness of breath, diarrhoea	Diarrhoea, vomiting	No	35%	~5 days	Bat, camel	Middle East	None
SARS-CoV-2	Coronaviridae	2019, China	Fever, pneumonia, ARDS	Fever, dry cough, fatigue, sore throat, diarrhoea, conjunctivitis, headache, loss of taste or smell, shortness of breath, chest pain, loss of speech or movement, rash on skin	Anorexia, diarrhoea, vomiting	No	5%	~5–6 days up to 14 days	Bat?	Worldwide	None

ARDS, acute respiratory distress syndrome; GI, gastrointestinal; IBD, inflammatory bowel disease; MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV, severe acute respiratory syndrome coronavirus.

active IBD and corticosteroid therapy.[20,21] However, the role of corticosteroid therapy is controversial in the COVID-19 pandemic. In the Surveillance Epidemiology of Coronavirus Under Research Exclusion-IBD database, evidence of greater prevalence of milder COVID-19 cases was reported in patients treated with anti-TNF-α than in patients undergoing steroid treatments. As of 15 May 2020, 19% of patients treated with anti-TNF-α agents required hospitalisation and only a minority (3%) experienced unfavourable outcomes, defined as intensive care unit admission, ventilator use, or death. Conversely, 66% of patients taking oral or parenteral steroids needed hospitalisation, with 26% experiencing unfavourable outcomes.[22] Further support to this theory comes from the results of the Italian Group for the Study of Inflammatory Bowel Disease study, which reported 60% reduction in mortality among patients receiving anti-TNF-α antibodies (although not statistically significant); however, corticosteroid use was associated with a trend toward statistical significance, with COVID-19-related pneumonia ($p=0.05$) and death ($p=0.064$).[23] On the other hand, steroid use should be avoided, if possible, or rapid steroid tapering should be considered owing to the risk of respiratory or opportunistic infection that could complicate the course of COVID-19. Glucocorticoids presumably have various effects in the different phases of the cytokine storm; therefore, they can be recommended as an ultimate last resource if needed. However, in the early phase of the infection, steroids may aggravate the outcome of the disease – as seen in case of many other infections.

As mentioned above, Brenner *et al.* developed an IBD registry to monitor SARS-CoV-2 infection.[22,24] The SECURE Registry aimed to define the impact of COVID-19 on patients with IBD and to evaluate how certain factors might impact on COVID outcomes. However, the registry has some limitations. For instance, some cases with mild symptoms may be lost because of restricted COVID testing, and some cases of IBD-related hospitalisation would incorrectly be associated with COVID-19 if the patient incidentally tested positive for the virus. By the time that this article was written, 701 IBD patients were registered with positive test results, 414 patients with CD and 287 patients with ulcerative colitis (UC). Hospitalisation was required for 28% of CD and

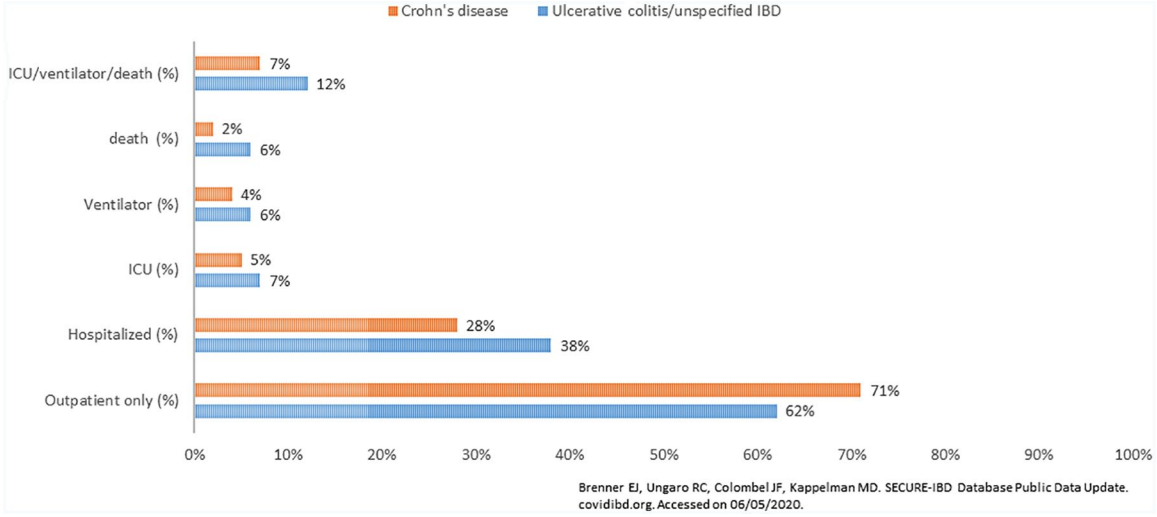

Figure 1. Outcome of SARS-CoV-2 infection in patients with IBD.[24]
IBD, inflammatory bowel disease; ICU, intensive care unit.

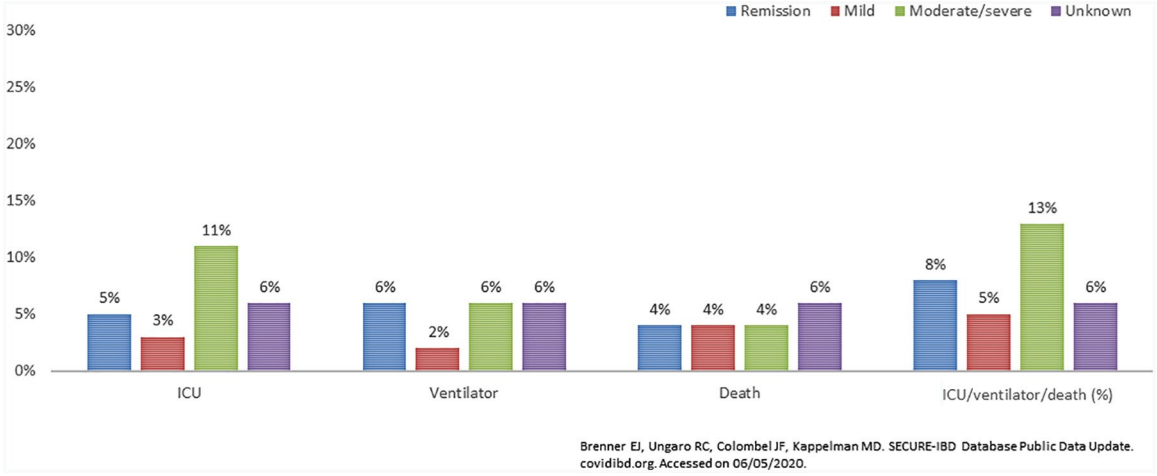

Figure 2. Disease activity and outcome of COVID-19 in patients with inflammatory bowel disease.[24]
ICU, intensive care unit.

38% of UC patients, whereas 4% and 6% were admitted to intensive care units; the mortality turned out to be 2% and 6%, respectively (Figure 1). Severe complications appeared to be associated with disease activity, and there was a clear correlation with older age (Figures 2 and 3). Death was most common amongst patients receiving steroid therapy (13%) (Figures 4 and 5). The surprisingly high death rate in patients administered mesalazine (8%) could be explained at least in part by the age of these patients [79 years (data coming from 9 April)]. However, the safety of mesalazine use is still a controversial issue without any exact (statistical bias?) reason. From another viewpoint, since the registry collects data from all over the world, the high proportion of patients receiving 5-aminosalicylic acid (5-ASA) may reflect countries with poor access to advanced treatments, such as biological therapy; hence, the use of 5-ASAs should be much higher even in CD as well.

What are the factors potentially explaining this unexpected favourable scenario?

1. *Age*. The average age of the IBD population is lower than the age of the background population. Therefore, only a small proportion

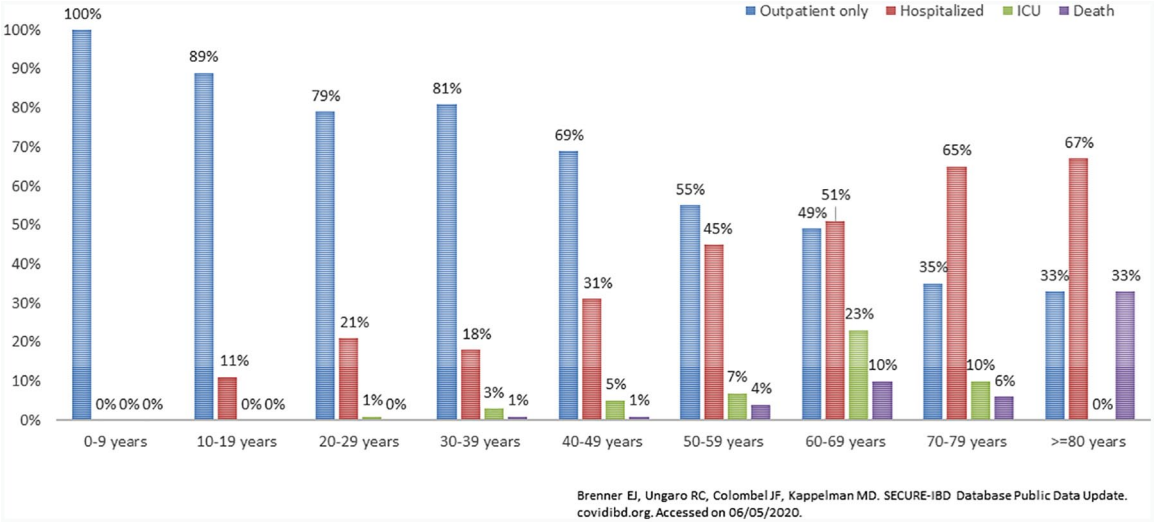

Figure 3. Outcome of COVID-19 by age in patients with inflammatory bowel disease.[24]
ICU, intensive care unit.

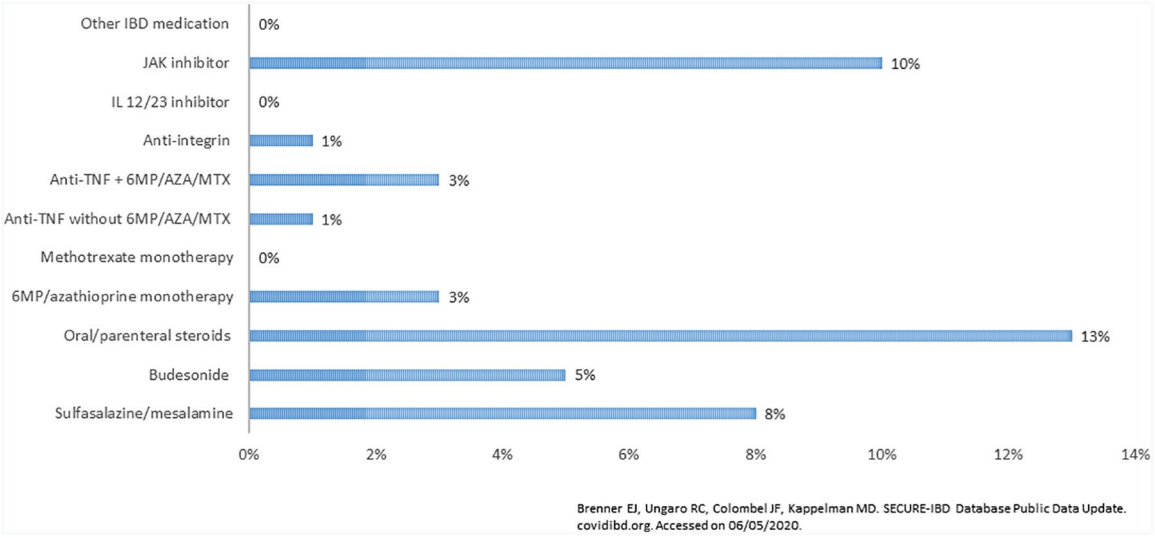

Figure 4. Proportion of COVID-19 cases associated with death, by therapy.[24]
Anti-TNF, anti-tumour necrosis factor; AZA, azathioprine; IBD, inflammatory bowel disease; MTX, methotrexate.

of IBD patients are supposed to be in the most vulnerable range (>65 years).[25]

2. *Gender*. Although 60% of the patients affected by the COVID-19 pandemic are males, IBD has a moderate female predominancy.[25]
3. *Therapy*. Baseline therapy comprises mesalazine and budesonide, which are not known to increase the risk of infection. Most patients can be managed optimally with these safe, basic medications.
4. *Serological screening for viral infections and tuberculosis*. The disease itself and the specific treatments aimed at reducing immune system activity (immunosuppressive or biological therapy) may expose the patients to specific risks, for example, novel bacterial and viral infections or reactivation of latent infections such as tuberculosis, hepatitis B or C, varicella, cytomegalovirus and Ebstein-Bar virus. Serological screening for infections conducted at the time of IBD diagnosis

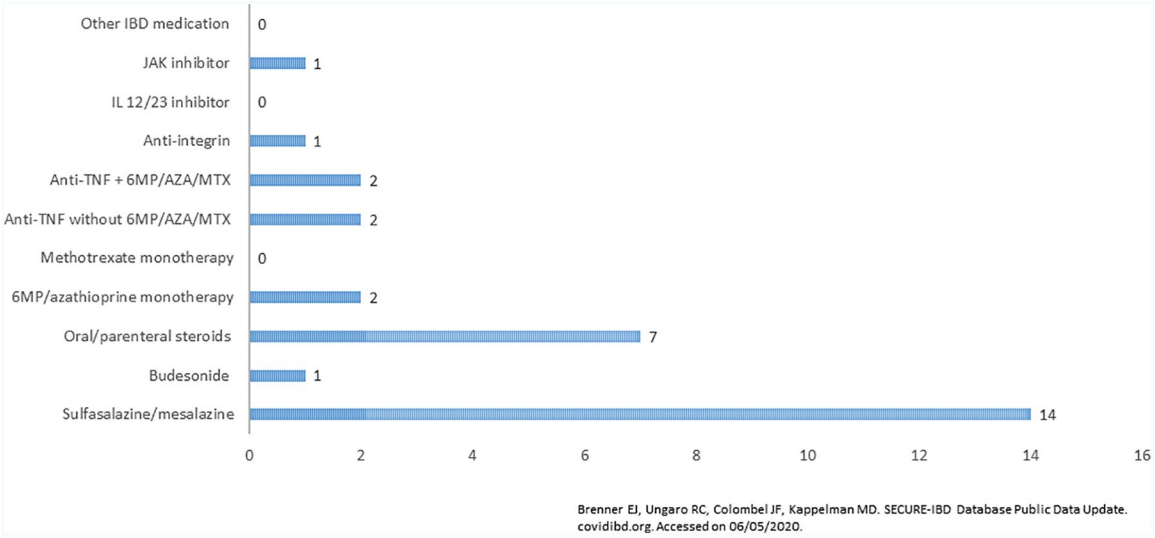

Figure 5. Number of COVID-19 cases associated with death by different therapy.[24]
JAK, janus kinase; Anti-TNF, anti-tumour necrosis factor; AZA, azathioprine; IBD, inflammatory bowel disease; MTX, methotrexate.

is necessary since with screening of infections we evaluate the patients' vaccination and their immune status as well. In the case of inappropriate immunisation, proper intervention is necessary to be implemented, in order to proceed with appropriate vaccination if protection is missing.

5. *Comorbidities*. There is a significantly lower incidence of hypertension and diabetes amongst IBD patients. Both conditions can aggravate the course of COVID-19.[26]
6. *Non-steroidal anti-inflammatory drugs (NSAIDs)*. Although it has been suggested to increase the risk of developing COVID-19, NSAIDs are less commonly administered to IBD patients than to the control population.[27] However, recent studies have questioned the link between NSAID exposure and adverse outcomes of COVID-19.[28–30]

Patient management during the COVID-19 pandemic

Although several recommendations for managing patients with IBD have been published, none of them could provide a complete solution for all the situations related to the pandemic. Referring to these previous guidelines, we would like to develop a more practical approach to handling the challenges. First of all, we should emphasise that IBD relapses are associated with an increased risk of a more severe course of COVID-19, with the need for corticosteroid use, possible multiple hospital visits or admissions potentially involving colonoscopic examinations. Previous data confirmed that the clinical and demographic variables associated with unfavourable COVID-19 outcomes, such as old age, presence of comorbidities and male gender, were comparable between patients with IBD and the general population. As shown in the study of the Italian Group for the Study of Inflammatory Bowel Disease, those age 65 years and older, comorbidities and active IBD were associated with worse COVID-19 outcomes. Thus, IBD activity at the time of COVID-19 diagnosis is a risk factor for a worse clinical outcome.[20,23] Moreover, from the viewpoint of pathomechanism, immunohistochemical analyses revealed higher ACE-2 protein expression in inflamed IBD samples as compared with controls. Furthermore, ACE-2 activity in the colon was elevated in non-inflamed colon in IBD patients as compared with controls and active IBD. The average expression of soluble ACE2 was increased in patients with IBD (mainly in CD) and a higher ACE-2:ACE ratio in plasma was noted in patients with IBD as compared with controls without IBD. Cytokines expressed in IBD, such as IFN-gamma, can potentially induce ACE-2 expression, which is consistent with the idea that mucosal inflammation may increase the expression of ACE-2. A study showed higher levels of ACE2 in inflamed intestinal areas in CD

Table 3. Risk assessment of SARS-CoV-2 infection in patients with IBD.

	Risk assessment		
	High	**Medium**	**Low**
Patient-dependent risk factors	Age >65 years	Male sex	Patients without any high or medium risk factors
	Comorbidity(ies)	Smoking	
	Severe malnutrition	Moderate IBD activity	IBD in remission
	Short bowel syndrome		
	Abdominal surgery within 30 days		
	Lymphopenia		
	Severe IBD activity		
Pandemic-dependent risk factors	SARS-CoV-2 positive contact person	Frequent personal contacts in workplace	Strict following of local pandemic rules
	Decline of local pandemic rules	Frequent travelling with public transport	Working in home-office
		Metropolitan resident	
		Partial follow of local pandemic rules	
Therapy-dependent risk factors	Prednisone >20 mg	Prednisone <20 mg	Mesalazine
		Immunosuppressive monotherapy	Budesonide
	Azathioprine + anti-TNF		Topical therapy
		Biological monotherapy	Others (antibiotics, probiotics, nutritions)

anti-TNF, anti-tumour necrosis factor; IBD, inflammatory bowel disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

patients as compared with patients with UC. Finally, the fusion of SARS-CoV-2 with the host cell membrane is critical for uptake in cells and is modulated by the S protein. Activation of the S protein *via* proteolytic cleavage is controlled by host trypsin-like proteases, whose activity is upregulated in IBD, and this effect might facilitate infection in patients with IBD. Overall, these findings suggest the possibility that patients with IBD might be particularly more susceptible to COVID-19.[31] The aim above all is to avoid flare-ups with a continuous and effective medical treatment. Another particularly important factor is detailed risk management. Therapeutic changes should be employed only if the patient is at advanced risk (age older than 65 years, presence of comorbidities, male gender, active IBD, non-adherence to pandemic regulations) of developing COVID-19 (even if not yet infected) or if the patient has a positive test of SARS-CoV-2 or even has manifest COVID-19.

On the basis of the recommendations of the British Society of Gastroenterology, we present a modified approach regarding the risk factors of IBD patients. Three main aspects should be considered: patient-dependent factors, therapy-based factors and other (mainly pandemic-related) factors (Table 3). Moreover, we present our recommendations based on a comprehensive analysis of the recommendations of the International Organisation for the Study of Inflammatory

Table 4. Therapeutic recommendation according to the pandemic situation and SARS-CoV-2 risk for IBD patients in remission or with mild disease activity.[32,33]

Situation	5-ASA	BUD	PRED <20 mg	PRED >20 mg	AZA	MTX	Anti-TNF	Anti-TNF plus AZA	VEDO	UST	TOFA
Remission or mild IBD activity											
SARS-CoV-2 negative patient, low–medium risk	+	+	+	?	+	+	+	+	+	+	+
SARS-CoV-2 negative patient, high risk	+	+	?	–	+	+	+	?	+	+	?
SARS-CoV-2 positive patient without COVID-19	+	+	?	–	–	–	?	–	?	?	–
COVID-19 disease	+	?	–	–	–	–	–	–	?	–	–

+= continue therapy; – = stop therapy; ? = dose reduction, change or postpone therapy.
5-ASA, mesalazine; Anti-TNF, anti-tumour necrosis factor (infliximab or adalimumab); AZA, azathioprine; BUD, oral budesonide; IBD, inflammatory bowel disease; MTX, methotrexate; PRED, prednisone; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; TOFA, tofacitinib; UST, ustekinumab; VEDO, vedolizumab.

Table 5. Therapeutic recommendation according to the pandemic situation and SARS-CoV-2 risk for IBD patients with moderate or severe disease activity.[32,33]

Situation	5-ASA	BUD	PRED <20 mg	PRED >20 mg	AZA	MTX	Anti-TNF	Anti-TNF plus AZA	VEDO	UST	TOFA
Moderate or severe IBD activity											
SARS-CoV-2 negative patient, low–medium risk	+	+	+	+	–	–	+	–	+	+	+
SARS-CoV-2 negative patient, high risk	+	+	>	>	–	–	+	–	+	+	?
SARS-CoV-2 positive patient without COVID-19	+	+	–	>	–	–	+	–	+	+	–
COVID-19 disease	+	+	–	>	–	–	+	–	+	?	–

+= start therapy; – = do not start therapy; ? = not enough evidence; > = shorter time than usual (decrease the time of intravenous administration of corticosteroids to 3 days and taper the oral steroid dose below 20 mg prednisone as quickly as possible).
5-ASA, mesalazine; Anti-TNF, anti-tumour necrosis factor (infliximab or adalimumab); AZA, azathioprine; BUD, oral budesonide; IBD, inflammatory bowel disease; MTX, methotrexate; PRED, prednisone; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; TOFA, tofacitinib; UST, ustekinumab; VEDO, vedolizumab.

Bowel Disease and the guidelines of the American Gastroenterological Association regarding patient management (Tables 4, 5).[32,33]

Patient not infected with SARS-CoV-2–IBD in remission

- Personalised risk evaluation and therapy modification if necessary (considering age, comorbidities, lymphocytopenia, steroid requirement and combination therapy). Lymphopenia (lymphocyte count $<1.0 \times 10^9$/L) is an independent risk factor of COVID-19-related mortality.[34]
- Maintenance of remission with unmodified treatment in low- and medium-risk patients.
- Taper the dose of corticosteroids, even when using oral budesonide MMX. Evidently, the use of prednisone should be decreased to a dose of at least below 20 mg.[32]
- Consider the risk/benefit of combination therapy, stop azathioprine and continue

biological monotherapy in the case of patients with a high risk of infection. Drug-induced risk of viral infections is exemplified by azathioprine and anti-TNF combination therapy. Although azathioprine is supposed to require a few weeks for total elimination, no exact information is available on the elimination time of the drug (half-life of azathioprine is 5 h), and the pandemic may continue for many more months. Azathioprine monotherapy does not confer any such increased risk; therefore, it can be continued.[35] Moreover, risk of relapse is higher if azathioprine monotherapy is ceased when compared with the cessation of azathioprine as a part of combination therapy.

- Prioritise the prevention of infection by adequate patient education.
- Omit unnecessary appointments with the patients (use electronic prescription, adalimumab receiving points, mobile or online appointments).
- Protective equipment and other safety considerations in the biological therapy wards.
- Prescribe the maximum possible amount of medications.

Patient not infected with SARS-CoV-2–IBD in relapse

- Be aware of the patient's compliance.
- UC:
  - Dosage escalation of mesalazine;
  - Local treatment, mesalazine and oral budesonide;
  - Try budesonide MMX instead of corticosteroid;
  - In severe flare-ups: use a short course (3 days) of intravenously administered steroid. If the patient does not respond to steroid therapy, infliximab or cyclosporine is recommended. If the patient responds to steroid therapy, any of the anti-TNF agents, vedolizumab or ustekinumab is suggested to use.[36]
- CD:
  - Ileal location: oral budesonide;
  - Colonic location: mesalazine, sulfasalazine;
  - In severe flare-ups: short course (3 days) of intravenously administered steroid and adalimumab as an anti-TNF drug (possible use of vedolizumab or ustekinumab if local/national regulation permits). Adalimumab is recommended because of its subcutaneous administration; however, if there is no adequate response to steroids, infliximab or cyclosporine should be introduced.[37]

- Do not start azathioprine due to its slow onset of action and increased risk of infection. Azathioprine causes lymphopenia in 10% of the patients, and every fifth patient receiving azathioprine exhibits a decrease below 0.5×10^9/L.[38] The study by Wisniewski *et al.* confirmed that increased risk of serious viral infections was associated with exposure to thiopurines, and clinically active IBD at onset of infection.[10]
- Less frequently, a moderate decrease is also observable during methotrexate and tofacitinib therapy.[39] Therefore, we would advise being aware of azathioprine-induced lymphopenia in SARS-COV-2 high-transmission areas.
- Biological therapy should preferably be administered subcutaneously with proper patient education, and the maximal amount should be prescribed.
- GI-selective vedolizumab or ustekinumab may be a good choice in patients with advanced age or comorbidities.

Patient with SARS-CoV-2 infection without clinical symptoms–IBD in remission or with mild activity

- Decrease corticosteroid dose (<16 mg prednisone).
- Use oral budesonide instead of other steroid drugs.
- Termination of azathioprine, methotrexate and tofacitinib therapy.
- If possible, postpone all type of biological treatment for about 14 days or until seroconversion

Patient with symptomatic COVID-19–IBD in remission or with mild activity

- IBD treatment depends on COVID-19 severity.
- Termination of all types of medication, except for mesalazine, oral budesonide and local treatment (and enteral nutrition).
- Be aware that some treatments for COVID-19 may interact with IBD drugs: hydroxychloroquine and anti-TNF can cause nerve

damage; lopinavir/ritonavir can block the metabolism of steroids, tacrolimus and tofacitinib; tocilizumab can cause abscess formation in patients with CD.[31,40]

Patients with symptomatic COVID-19–IBD with severe activity

- IBD treatment depends on the severity of the COVID-19 course.
- Differentiation between GI symptoms possibly caused by SARS-CoV-2 and CMV is important, involving faecal calprotectin analysis and CMV polymerase chain reaction.
- A short-term, 3-day intravenous steroid therapy is recommended.
- Introduction of infliximab or cyclosporine therapy after intravenous steroid administration.
- The recommendation regarding the use of subcutaneous *versus* intravenous biological therapy relies primarily on avoiding visits to clinics and hospitals, and travel to the hospital using public transport should be avoided, which might be at least just as important as the mode of therapy.
- Endoscopy: only in the case of fulminant IBD, if surgical intervention or CMV colitis should be evaluated.
- If surgery is needed: it might be advisable to opt for an open surgical technique instead of laparoscopic intervention (to avoid aerosol formation).[41]

Other pandemic factors comprise environmental factors, such as home and living environment, workplace, commute and travelling mode and other factors, such as compliance of wearing protective equipment and the relevance and frequency of medical attendance and assistance.

Conclusively, it is clear that the COVID-19 pandemic has produced a novel and rather unprecedented challenge in the field of medical care, which is not easy to adapt to. Our responsibility is to attempt to guide our IBD patients through this period safely and to minimise their risk of infection, and COVID-19-related exacerbation of their disease. Meanwhile, it is critical that the patients receive treatment of sufficient quality. This requires extensive clinical experience and a thorough understanding of our patients' compliance, social background and medical history. Clinicians should be continuously updated and have extensive insight into the current pandemic situation. With this article, we aim to summarise some of the main points of the optimal patient management during the COVID-19 pandemic, and to assist the clinicians in processes of decision-making.

Acknowledgements

We would like to acknowledge the work of Mark Marcus Philip MD in linguistic revision of the manuscript.

Author contributions

Study concept and design: Klaudia Farkas, Daniella Pigniczki, Tamás Molnár. Data acquisition and interpretation: Klaudia Farkas, Daniella Pigniczki, Mariann Rutka, Kata Judit Szántó, Tamás Resál, Renáta Bor, Anna Fábián, Zoltán Szepes, György Lázár, Tamás Molnár. Drafting and revision of the manuscript: Klaudia Farkas, Daniella Pigniczki, Anna Fábián, Tamás Molnár. All authors approved the final version of the submitted manuscript.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Disclaimers

The manuscript, including related data, tables and figures, has not been previously published, and the manuscript is not under consideration elsewhere.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the research grants of the National Research, Development and Innovation Office (Grant ID: 125377,129266 and 134863), by the EFOP–3.6.2-16-2017-00006, Faculty of Medicine, University of Szeged, by the National Excellence Programme (20391-3/2018/FEKUSTRAT to FK), by the New National Excellence Program of the Ministry of Human Capacities (UNKP-19-4-SZTE-44, UNKP-20-5-SZTE-161 to FK), Janos Bolyai Research Grant (BO/00598/19/5) and the Géza Hetényi Research Grant (to FK, MR and BA) by the Faculty of Medicine, University of Szeged, University of Szeged Open Access Fund (4775).

ORCID iDs

Renáta Bor https://orcid.org/0000-0001-9393-5240

Tamás Molnár https://orcid.org/0000-0002-4913-7599

References

1. Meo SA, Alhowikan AM, Al-Khlaiwi T, *et al.* Novel coronavirus 2019-nCoV: prevalence, biological and clinical characteristics comparison with SARS-CoV and MERS-CoV. European *Eur Rev Med Pharmacol Sci* 2020; 24: 2012–2019.
2. World Health Organization. Novel coronavirus (COVID-19) situation. *Secondary novel coronavirus (COVID-19) situation*, https://experience. arcgis. com/experience/ 685d 0ace 5216 48f8 a5be eeee 1b9125cd (2020, accessed 5 October 2020).
3. Yang L, Tang S, Baker SS, *et al.* Difference in pathomechanism between Crohn's disease and ulcerative colitis revealed by colon transcriptome. *Inflamm Bowel Dis* 2019; 25: e154.
4. World Health Organization. https://www.who.int/ (accessed 5 September 2020).
5. Yeo C, Kaushal S and Yeo D. Enteric involvement of coronaviruses: is faecal–oral transmission of SARS-CoV-2 possible? *Lancet* 2020; 335–337.
6. Cheung KS. Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from the Hong Kong cohort and systematic review and meta-analysis. *Meta-Analysis; Gastroenterology* 2020; 159: 81–95.
7. Nobel YR, Phipps M, Zucker J, *et al.* Gastrointestinal symptoms and COVID-19: case-control study from the United States. *Gastroenterology* 2020; 159: 373–375.e2.
8. Ragab D, Eldin HS, Taeimah M, *et al.* The COVID-19 cytokine storm; what we know so far. *Front Immunol* 2020; 11: 1446.
9. Ge X, Li J, Yang X, *et al.* Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. *Nature* 2013; 503: 535–538.
10. Wisniewski A, Kirchgesner J, Seksik P, *et al.* Increased incidence of systemic serious viral infections in patients with inflammatory bowel disease associates with active disease and use of thiopurines. *United European Gastroenterol J* 2020; 8: 303–313.
11. Kirchgesner J. Risk of serious and opportunistic infections associated with treatment of inflammatory bowel diseases. *Gastroenterology* 2018; 155: 337–346.
12. Toruner M, Loftus EV, Harmsen WS, *et al.* Risk factors for opportunistic infections in patients with inflammatory bowel disease. *Gastroenterology* 2008; 134: 929–936.
13. D'Amico F, Peyrin-Biroulet L, Danese S, *et al.* Inflammatory bowel disease management during the COVID-19 outbreak: a survey from the European Crohn's and Colitis Organization (ECCO). *Gastroenterology* 2020; 159: 14–19.e3.
14. Turner D. COVID-19 and paediatric inflammatory bowel diseases: global experience and provisional guidance (March 2020) from the paediatric IBD Porto group of ESPGHAN. *J Pediatr Gastroenterol Nutr* 2020; 70: 727–733.
15. Haberman R, Axelrad J, Chen A, *et al.* Covid-19 in immune-mediated inflammatory diseases - case series from New York. *N Engl J Med* 2020; 383: 85–88.
16. Mao R, Liang J, Shen J, *et al.* Implications of COVID-19 for patients with pre-existing digestive diseases. *Lancet Gastroenterol Hepatol* 2020; 5: 426–428.
17. Norsa L, Indriolo A, Sansotta N, *et al.* Uneventful course in IBD patients during SARS-CoV-2 outbreak in Northern Italy. *Gastroenterology* 2020; 159: 371–372.
18. Rodríguez-Lago I, Ramírez de la Piscina P, Elorza A, *et al.* Characteristics and prognosis of patients with inflammatory bowel disease during the SARS-CoV-2 pandemic in the Basque Country (Spain). *Gastroenterology* 2020; 159: 781–783.
19. Axelrad JE, Malter L, Hong S, *et al.* From the American epicenter: coronavirus disease 2019 in patients with inflammatory bowel disease in the New York city metropolitan area. *Inflamm Bowel Dis* 2020; izaa162.
20. Bezzio C, Saibeni S, Variola A, *et al.* Outcomes of COVID-19 in 79 patients with IBD in Italy: an IG-IBD study. *Gut* 2020; 69: 1213–1217.
21. Lukin DJ, Kumar A, Hajifathalian K, *et al.*; JRC Study Group; WCM-GI Study Group. Baseline disease activity and steroid therapy stratify risk of COVID-19 in patients with inflammatory bowel disease. *Gastroenterology* 2020; 159: 1541–1544.e2.
22. Brenner EJ, Ungaro RC, 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; 159: 481–491.

23. Papa A, Gasbarrini A and Tursi A. Epidemiology and the impact of therapies on the outcome of COVID-19 in patients with inflammatory bowel disease. *Am J Gastroenterol* 2020; 115: 1722–1724.
24. Brenner EJ, Ungaro RC, Colombel JF, *et al.* SECURE-IBD database public data update, https://covidibd.org/ (accessed 6 May 2020).
25. Betteridge JD, Armbruster SP, Maydonovitch C, *et al.* Inflammatory bowel disease prevalence by age, gender, race, and geographic location in the U.S. military health care population. *Inflamm Bowel Dis* 2013; 19: 1421–1427.
26. Yarur AJ, Deshpande AR, Pechman DM, *et al.* Inflammatory bowel disease is associated with an increased incidence of cardiovascular events. *Am J Gastroenterol* 2011; 106: 741–747.
27. British Society of Gastroenterology (BSG) advice for management of inflammatory bowel diseases during the COVID-19 pandemic, https://www.bsg.org.uk/covid-19-advice/bsg-advice-for-management-of-inflammatory-bowel-diseases-during-the-covid-19-pandemic/ (accessed 5 December 2020).
28. Gianfrancesco M, Hyrich KL, Al-Adely S, *et al.* Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis* 2020; 79: 859–866.
29. Mancia G, Rea F, Ludergnani M, *et al.* Renin-angiotensin-aldosterone system blockers and the risk of Covid-19. *N Engl J Med* 2020; 382: 2431–2440.
30. Castro VM, Ross RA, McBride SM, *et al.* Identifying common pharmacotherapies associated with reduced COVID-19 morbidity using electronic health records. *medRxiv*. Epub ahead of print 5 September 2020. DOI: 10.1101/2020.04.11.20061994.
31. Neurath MF. COVID-19 and immunomodulation in IBD. *Gut* 2020; 69: 1335–1342.
32. The International Organization for the Study of Inflammatory Bowel Diseases (IOIBD). Update on COVID19 for patients with Crohn's disease and ulcerative colitis, https://www.ioibd.org/ioibd-update-on-covid19-for-patients-with-crohns-disease-and-ulcerative-colitis/ (accessed 5 September 2020).
33. 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; 159: 350–357.
34. Ji D, Zhang D, Xu J, *et al.* Prediction for progression risk in patients with COVID-19 pneumonia: the CALL score. *Clin Infect Dis* 2020; 71: 1393–1399.
35. Khan N, Patel D, Xie D, *et al.* Impact of anti-TNF and thiopurines medications on the development of COVID-19 in patients with inflammatory bowel disease: a nationwide VA cohort study. *Gastroenterology* 2020; 159: 1545–1546.e1.
36. Feuerstein JD, Isaacs KL, Schenider Y, *et al.* AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. *Gastroenterology* 2020, 158: 1450–1461.
37. Chela H, Pasha SB, Wan XF, *et al.* A review on medical management of inflammatory bowel disease during the coronavirus disease 2019 pandemic. *J Gastroenterol Hepatol*. Epub ahead of print 2 September 2020. DOI: 10.1111/jgh.15241.
38. Vögelin M, Biedermann L, Frei P, *et al.* The impact of azathioprine-associated lymphopenia on the onset of opportunistic infections in patients with inflammatory bowel disease. *PLoS One* 2016; 11: e0155218.
39. Schulze-Koops H, Strand V, Nduaka C, *et al.* Analysis of haematological changes in tofacitinib-treated patients with rheumatoid arthritis across phase 3 and long-term extension studies. *Rheumatology* 2017; 56: 46–57.
40. Al-Ani A, Prentice R, Rentsch C, *et al.* Review article: prevention, diagnosis and management of COVID-19 in the inflammatory bowel disease patient. *Aliment Pharmacol Ther* 2020; 52: 54–72.
41. SAGES and EAES recommendations regarding surgical response to COVID-19 crisis, https://www.sages.org/recommendations-surgical-response-covid-19/ (accessed 5 September 2020).