

COVID-19 and the management of patients with inflammatory bowel disease: a practical decalogue for the post-pandemic phase

Alfredo Papa*, Valerio Papa, Loris Riccardo Lopetuso, Antonio Gasbarrini and Antonio Tursi* 

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Abstract: The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has raised several concerns for patients with chronic immune-mediated diseases, including inflammatory bowel disease (IBD). As the outbreak appears to be in the descending phase, at least in some part of the world, as in most European countries, guidance is urgently needed to provide optimal care for our IBD patients in order to gradually and safely reduce the gap in care that has been accumulated in the months of lockdown and to face all the backlogs. Therefore, we have provided a decalogue of practical recommendations for gastroenterologists to manage patients with IBD in the post-peak phase of the COVID-19 pandemic. They include all the aspects of IBD care, not only pharmacological ones but also endoscopy, surgery, psychological treatment, telemedicine, diagnostics and educational tasks provided by doctors and patient associations.

Keywords: COVID-19, endoscopy, inflammatory bowel disease, medical treatment, surgery

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the largest outbreak involving humanity from about a century ago to today. Globally, on 15 June 2020, 7,553,182 cases have occurred worldwide, with 423,349 deaths.¹ The pandemic started in China and Southeast Asia (439,343 cases with 12,126 deaths), but subsequently spread to Europe and America with a higher number of cases and deaths (3,638,525 with 196,440 deaths in America and 2,378,958 cases with 187,468 deaths in Europe).¹ Although COVID-19 mainly causes respiratory symptoms, it is now well known that it is also characterized by less common symptoms such as: diarrhea, nausea, vomiting and abdominal discomfort.^{2,3} Since SARS-CoV-2 may colonize the gastrointestinal tract,⁴ among gastroenterologists there is concern that patients with inflammatory

bowel diseases (IBDs), including Crohn's disease (CD) and ulcerative colitis (UC), may be at increased risk of SARS-CoV-2 infection or poorer COVID-19 course, due to the chronic nature of the disease and the medications used for their treatment.⁵ In fact, the therapeutic armamentarium for the management of IBD includes both steroids and immunosuppressants, which may predispose not only to opportunistic infections, but also to viral infections.⁶ In the last few months, several reassuring data have been accumulating on the prevalence rate of COVID-19 and its outcomes in patients with IBD.⁷ Interestingly, the impact of the different IBD-related therapies on the clinical course of COVID-19 is also better understood.⁷

As expected, during the pandemic, most of the elective clinical activities were suspended and the medical services really provided have reduced

Correspondence to:

Antonio Tursi
Territorial
Gastroenterology Service,
ASL BAT, Via Torino, 49,
Andria (BT), 76123, Italy
antotursi@tiscali.it

Alfredo Papa
Antonio Gasbarrini
Department of Medical and
Surgical Sciences, Division
of Internal Medicine
and Gastroenterology,
Policlinico Universitario
"A. Gemelli" IRCCS
Foundation, Rome, Italy
Catholic University, Rome,
Italy

Valerio Papa
Catholic University, Rome,
Italy

Department of Digestive
Surgery, Policlinico
Universitario "A. Gemelli"
IRCCS Foundation, Rome,
Italy

Loris Riccardo Lopetuso
Department of Medical and
Surgical Sciences, Division
of Internal Medicine
and Gastroenterology,
Policlinico Universitario
"A. Gemelli" IRCCS
Foundation, Rome, Italy
Department of Medicine
and Ageing Sciences, "G.
d'Annunzio" University
of Chieti-Pescara, Chieti,
Italy

Center for Advanced
Studies and Technology
(CAST), "G. d'Annunzio"
University of Chieti-
Pescara, Chieti, Italy

*AP and AT contributed
equally to the manuscript.



dramatically.⁸ Outpatient visits, colonoscopies and non-urgent surgery have been postponed, as recommended by the most qualified international societies and organizations with an interest in IBD, with the aim of avoiding patient contact with the hospital environment and allowing patients with IBD to maintain rigorous isolation and reduce the risk of contagion.⁸⁻¹¹

As we gradually return to normal, at least in Europe but also in other parts of the world where the numbers of the pandemic decrease significantly, we must face new challenges related to both uncertainty for the future, given the risk of possible new outbreaks, and the ability to reorganize clinical activities for our IBD patients to address the backlogs and reduce the possible “collateral damage” of COVID-19.¹² However, for many IBD patients, the lack of face-to-face contact with the treating physicians, added to the uncertainty and fear about the future and the course of their disease, also exacerbated psychological symptoms.¹³

In this paper we provide a “decatalogue” of practical advice for the management of patients with IBD in the post-pandemic phase based on the best available evidences and expert opinions.

The decatalogue

Educate patients to continue to comply with the general rules for the prevention of COVID-19 according to the indication of the World Health Organization

The transmission routes of the SARS-CoV-2 include two main forms of transmission. The first is a direct person-to-person transmission route, including cough, sneeze, droplet inhalation; the second is a contact transmission, including contact with oral, nasal and eye mucous membranes and transmission by saliva or gastrointestinal secretions.¹⁴ Since the beginning of the pandemic, the World Health Organization has provided general recommendations for the prevention of COVID-19.¹⁵ They include: to wash hands frequently and properly with soap or alcohol-based sanitizer, to maintain social distancing (at least 1 m of distance), to avoid touching eyes, nose and mouth, to cover mouth and nose when coughing or sneezing, to seek medical care early when fever, cough or difficulty in breathing are recorded, to wear personal protective equipment (PPE), in

particular the facial mask when social distancing is not possible to maintain or in closed places, to stay informed and follow any advice provided by own healthcare providers.¹⁵ All individuals, and among these particularly IBD patients due to their own frailty, must continue to adhere to these behaviors to prevent the spread of the infection.⁹⁻¹¹ In fact, although the pandemic is in the waning phase, at least in some parts of the globe, the virus is still circulating, and the level of attention must not be lowered in order to avoid new epidemic waves. Thus, gastroenterologists, in every circumstance and by all available means (outpatient visits, by telemedicine, social media, etc.) should always remind their patients to follow these recommendations to reduce the risk of spreading SARS-CoV-2. This educational task is fundamental since prevention is still the best way to reduce the risk of contamination.

Do not discontinue current biological therapy or delay new prescriptions

The impact of the IBD treatments on COVID-19 risk and outcome is still under debate. However, since the beginning of the pandemic, data have been accumulating and demonstrating that biological therapy, anti-tumor necrosis factor (TNF)- α in particular, has not increased the risk of COVID-19 as feared. A retrospective study from the United States including a large cohort of IBD patients reported that the incidence rate of COVID-19 per 1000 IBD patients was of 0.61 in patients treated with anti-TNF- α and 1 in those not in treatment with anti-TNF- α ($p=0.618$).¹⁶ Interestingly, a recent case report¹⁷ and larger studies^{18,19} hypothesized that anti-TNF- α antibodies could guarantee a milder course of COVID-19. In fact, in the SECURE-IBD database (>1500 patients enrolled), as of 16 June 2020, 16% of patients treated with anti-TNF- α agents required hospitalization, and only 2% experienced unfavorable outcomes, defined as intensive care unit admission, ventilator use, or death.¹⁸ One possible explanation for this beneficial effect is that anti-TNF α antibodies could achieve effective control of the so-called “cytokine storm” that occurs in severe COVID-19-related pneumonia, thereby mitigating the course of the disease. Further support for the recommendation not to suspend ongoing anti-TNF- α treatment comes from a recent survey carried out on a cohort of Chinese patients.²⁰ Indeed Chen *et al.* reported that 27.7% (107/386) of the contacted

IBD patients discontinued their medication during the pandemic and among these more than half (50.5%) were in treatment with biological agents.²⁰ The impact of medication discontinuation was devastating as 22.7% and 29.3% of patients with UC and CD, respectively, had an exacerbation of the disease with the need for hospitalization and surgical intervention in a not negligible percentage of cases.²⁰ Reassuring data also seem to be reported for tofacitinib, although on a limited number of patients.²¹ In conclusion, the data thus far suggest that anti-TNF α agents (and also the other biologics or tofacitinib) should not be discontinued since the available evidence shows that the benefits prevail in the risk/benefit ratio between the control of IBD disease activity and the potential risks of favoring SARS-CoV-2 infection. In addition, we also want to recommend not delaying the use of biologic therapies. Indeed, the most important goal to obtain for IBD patients is to induce or maintain steroid-free clinical remission, particularly during the COVID-19 pandemic. Any delays in the access to biologic therapies could have a significant negative impact on disease outcomes, including a higher rate of hospitalizations, surgeries and emergency department visits related to IBD.^{22–24}

Prescribe steroids only if they are strictly needed and consider a rapid tapering of their dosage

After the first description of the dramatic effect of steroids administration on the outcome of a patient with UC and COVID-19,²⁵ also larger studies analyzed the impact of steroids on the prognosis of IBD patients affected by COVID-19. The SECURE-IBD database found that COVID-19 cases in IBD patients treated with steroids had a worse prognosis.¹⁸ As of 16 June 2020, 57% of IBD patients taking oral or parenteral steroids needed hospitalization, with 19% experiencing unfavorable outcomes defined as intensive care unit admission, ventilator use, or death.¹⁹ These findings were further supported by the results of the IG-IBD study, which reported a significant association between use of steroids and COVID-19-related pneumonia ($p=0.05$) and a trend towards increased mortality ($p=0.064$).¹³ However, we cannot rule out that some confounding factors may have influenced these data. In fact, a co-existent severe exacerbation of IBD with need for steroid therapy could be the underlying factor associated with the

worst prognosis of COVID-19. In conclusion, since there are no definitive data on whether the use of steroids increases the risk of severe COVID-19, it seems prudent to minimize their use and to think of therapeutic alternatives, such as biologics (e.g. anti-TNF- α) even as rescue therapy for acute severe UC or “first line” treatment for moderate–severe flare of CD or UC. However, this recommendation is based on clinical observations and expert advice and not on data from controlled studies.²⁶ In addition, in patients already on steroid therapy it is advisable to progressively taper to the lowest possible dosage without any delay.

Keep your patients in follow-up by preferring remote methods: telemedicine, internet, social media

IBDs are generally managed by a traditional model, the classical outpatient face-to-face consultations. The majority of IBD centers offer the same type of routine follow-up visits for both CD and UC irrespective of demographics, disease history, geographic location and distance to the clinic. The only significant variation in the visits is the frequency of appointments, dependent on the characteristics of the disease (phenotype, activity and current treatment). As previously reported, the COVID-19 pandemic has resulted in a dramatic shift in providing medical care. Social distancing and lockdown led to a global suspension of traditional face-to-face outpatient visits, and IBD patients, as well as any patient suffering chronic disease, have suffered from this suspension. However, several digital technologies that can be applied to tackle major clinical problems and diseases are now available. These digital technologies include: the Internet of Things, with next-generation telecommunication networks;^{27,28} big-data analytics;²⁹ artificial intelligence that uses deep learning;^{30,31} blockchain technology.³² Of course, these technologies may work synergistically, enhancing the chance to manage health by using modified algorithms to ensure secured but traceable data.³² All these methodologies have been tested in IBD management during the COVID-19 pandemic. In detail, during the pandemic phase, Chinese clinicians communicated with IBD patients by extensively using social media (WeChat) as an educational and instructional tool, with excellent results.³³ A recent survey conducted on 56 different countries across North and South America, Europe, Australia,

Asia and Africa found that an almost complete suspension of face-to-face visits during COVID-19 was reported by >75% of the interviewed, and that telemedicine currently accounted for over half of all IBD consultations.³⁴ Most of them were performed by phone because 53.3% of respondents did not have access to a video consultation setup, but many other non-integrated solutions such as GoToMeeting, Google, Microsoft Teams, WeChat and WhatsApp were widely used. Finally, face-to-face provision remained the most popular format for IBD outpatient visits, even if it was significantly lower than at pre-pandemic times.³⁴ The current question is: how has the pandemic changed the landscape of the management of IBD patients? The answer is that the COVID-19 outbreak can be an opportunity to transform current systems of IBD care, increasing a not face-to-face management for selected indications. In the near future, until the desirable disappearance of the pandemic, a significant proportion of IBD outpatient visits should be performed through telemedicine, preferably by video consultation, in order to maintain social distancing and to avoid contact with healthcare professionals at the same time addressing backlogs.

Prefer non-invasive methods to monitor disease activity

We are convinced that even in the immediate post-pandemic phase, the use of non-invasive monitoring of disease activity in patients with IBD, combined with the use of telemedicine, should be a priority pursued by gastroenterologists.³⁵ Therefore, we suggest for assessing clinical activity the use of patient-reported outcomes (PROs) and non-invasive tests/exams such as blood tests [C-reactive protein (CRP)], fecal biomarkers (calprotectin) and intestinal ultrasound. In fact, the use of non-invasive alternatives to endoscopy, at least for the monitoring of the effectiveness of therapy and to adhere to the “tight control” of disease activity, was a topic discussed even before COVID-19.^{36,37} In detail, the symptoms to be evaluated in the PROs are the number of bowel movements and abdominal pain for CD and the number of bowel movements and rectal bleeding for UC.³⁸ Therefore, asymptomatic patients or patients with mild symptoms and normal values of biomarkers (CRP and calprotectin) need no outpatient visit, if restrictions on normal activities still persist. As regards the monitoring of patients under biologics or immunosuppressants,

telemedicine consultation should be the preferred modality of follow-up, reserving the outpatient visits for patients with abnormal laboratory exams or unsatisfactory PROs. However, in addition to the inflammatory biomarkers it is advisable to consider also intestinal ultrasound, particularly for postoperative follow-up of CD patients.³⁹

It should also be emphasized that the symptoms of IBD exacerbation, especially if fever is present, may be difficult to distinguish from those of SARS-CoV-2 infection.⁴⁰ Furthermore, SARS-CoV-2 has been reported to cause colitis.⁴¹ Therefore, especially if the patient needs an outpatient visit or hospitalization, it is advisable to perform a nasopharyngeal swab for the molecular research of SARS-CoV-2 as a part of the IBD flare workup.⁴²

Advise patients to seek psychological support if necessary

Mental health disorders are a current problem since a considerable number of subjects will develop severe psychological problems such as mood disorders, anxiety disorders, or posttraumatic stress disorders.⁴³ In this context, IBD patients require greater attention to avoid adverse disease-related outcomes. Indeed, a cross-sectional survey explored the emotional state, perception and concerns of Saudi patients with IBD during the COVID-19 crisis. Many patients expressed symptoms of anxiety, although not depression. Female patients, patients educated up to a high school diploma and those with indeterminate colitis were more likely to develop anxiety.⁴⁴ Another considerable issue is linked to pediatric disease and therapeutic compliance. A recent report detected preliminary consequences related to COVID-19 lockdown in IBD children.⁴⁵ It found a considerable percentage of patients underreporting IBD symptoms and an increased risk of reduced compliance to immunoregulatory therapies. It did not identify any new incident IBD cases, suggesting a potential diagnostic delay. Of note, it did not register specific health-related quality of life red flags, with overall scores not differing from previous cohorts.⁴⁵ These results may be partially explained by decreased stressful events, such as school, or by an increased parental closeness. In this scenario, a mindfulness-based approach could represent a powerful tool to manage IBD outcomes.⁴⁶ Mindfulness-based interventions, understood as

an awareness of the experience of the present moment and emphasizing the attention paid to one's thoughts, bodily sensations and emotions, have shown to be effective among patients with IBD.⁴⁷ They often combine meditation with contemporary cognitive-behavioral approaches, and several mechanisms behind their effectiveness have been identified.⁴⁸ In fact, their positive effects on various mental health conditions have been reported in diverse clinical and non-clinical populations. Overall, mindfulness-based therapy administered as part of standard clinical practice has been shown to effectively improve inflammatory biomarkers in patients diagnosed with IBD.⁴⁸

Schedule (or re-schedule) endoscopic examinations if you recognize a non-deferrable indication, giving priority to the most urgent cases

During the lockdown until to the flattening of the pandemic curve, endoscopic examinations have been drastically reduced and limited only to the not deferrable cases.^{49,50} Currently, with the containment of the pandemic, the previously not performed endoscopies should be rescheduled. This scenario inevitably implies a very delicate and demanding task consisting in the shift from an open access endoscopy to a filtered access.^{50,51} Endoscopic exams will be rescheduled according to an order of priority decided on a case-by-case basis. In addition to emergencies, other indications are added at this stage for patients with IBD that can no longer be postponed, as they could lead to medium- and long-term negative consequences that can become irreversible.⁵⁰ A list of the main indications, although not exhaustive, is as follows: (a) to confirm a suspected new diagnosis of IBD with moderate-to-severe symptoms; (b) to change therapy (also considering enrollment in clinical trials) or to postpone indication to surgery in patients with known IBD refractory to ongoing medical treatment; (c) to assess a CD postoperative recurrence in symptomatic patients; (d) to screen for dysplasia in high-risk patients [with co-existent primary sclerosing cholangitis (PCS), persistently active disease, previous detection of dysplasia]; (e) patients with colonic stenosis documented by imaging techniques; (f) severe pouchitis. Obviously, the resumption of endoscopic activity must be carried out by observing the most scrupulous recommendations for the reduction of the risk of contagion for patients and healthcare professionals.^{12,50,52} In particular,

before access to the endoscopy room, the pretest probability of COVID-19 should be established based on a standard questionnaire including epidemiologic and clinical risk factors, such as the appearance of suggestive symptoms in the last 14 days (fever, cough, sore throat, loss of smell or taste, shortness of breath).⁵⁰ Furthermore, before accessing endoscopy, body temperature control is recommended. Subsequently, in asymptomatic subjects, the addition of a point of care (POC) test, ready in about 15 min, measuring IgG and IgM anti SARS-CoV-2, could lead to a higher level of safety.⁵³ In patients resulted positive at POC test (both IgM and/or IgG) non-urgent endoscopy should be deferred until the execution of a nasopharyngeal swab with molecular test for SARS-CoV-2. Similarly, in patients with symptoms compatible with COVID-19 or with epidemiological risk factors for SARS-CoV-2 infection, non-urgent endoscopy will be postponed until the execution of a molecular test to obtain a definitive diagnosis. Obviously, urgent endoscopic examinations in patients with symptoms suggestive for COVID-19 or at high epidemiological risk must be performed with the maximum of precautions (in a negative-pressure room or, if not available, in a dedicated room with adequate ventilation, full PPE and high-filter respiratory masks). At the end of the procedure the patient should be reviewed by an infectious diseases team and tested for SARS-CoV-2.⁵³

Infusion clinic: consider testing all patients for SARS-CoV-2

As reported in point 2 of this article, no infusion therapy should be discontinued. The same precautionary rules adopted in the pandemic peak phase must be adopted in the so-called descending phase of the epidemic curve. Before access to the infusion clinic all patients should have body temperature measured and they should complete a history questionnaire (symptoms compatible with COVID-19? Contact with individuals with SARS-CoV-2 infection?). In addition, we retain that it is advisable, even in the absence of symptoms or previous contact with COVID-19 patients, to propose to all patients at their first access to an infusion clinic after the pandemic to undergo serological testing for SARS-CoV-2. For patients that will not interrupt infusion treatment it is advisable to collect serology for SARS-CoV-2 as soon as the test is available in the clinic. Obviously, to ensure adequate social distancing,

we recommend dividing the patients who should be given the infusion of biological therapy into 1-h blocks. The infusion seats should be spaced at least 2m apart and both the medical staff and the patients should wear face masks and wash their hands before the infusion. Similarly to what happened during the lockdown period, accompanying persons should not be allowed access to the infusion clinic and the number of staff (doctor and nurse) should be limited to the minimum necessary.⁸

Schedule (or re-schedule) surgical interventions, giving priority to the most urgent cases

Surgery is an irreplaceable resource in the therapeutic armamentarium for the management of patients with IBD. With the progressive reactivation of previously suspended surgical services one of the most important issues is to implement strategies to restore surgical activity safely.⁵⁴ During the pandemic, patients with IBD on the waiting list for a planned intervention were forced, due to its cancellation, to manage with extreme difficulty the symptoms that would have been resolvable only with surgery. Just to mention the most frequent clinical situations which need to prioritize surgery we remember: (a) perianal active disease with the presence of abscesses and/or perianal fistulas with local septic complications; (b) patients with CD with recurrent subocclusive episodes not responsive to medical therapy; (c) patients with UC refractory to medical therapy or with evidence of high-grade dysplasia (pending colectomy or subsequent interventions in the case of proctocolectomy with ileoanal pouch construction in two or three surgical times); (d) stenosing or penetrating CD not responsive to medical therapy. Obviously, this is a non-exhaustive list of possible indications for surgery that had accumulated during the pandemic and that will be progressively disposed of based on the priority assessed case-by-case, preferably after a multidisciplinary evaluation. In the current phase, with SARS-Cov-2 still circulating, it is necessary to implement all prescribed precautions to avoid infection for both patients and surgical staff. The main recommendations, in addition to the correct indication to surgery, are: reduce the surgical staff to the bare minimum, use the prescribed PPE (surgeons should be equipped with masks with a microparticle filter as FFP2 or FFP3), test the patient for SARS-CoV-2 before the hospital

admission with nose-pharyngeal swab (in addition to collecting the history of COVID-19 symptoms and/or contact with infected subjects) and perform the surgery (if programmed) only after obtaining the result of the test.⁵⁵

In order to optimize the protection of caregivers from contagious pathogens in the operating room (OR), a negative-pressure OR has been recommended for patients who are positive for COVID-19 or suspected of having the infection.⁵⁶ The use of an active smoke evacuator connected to a proper filter has been recommended for laparoscopic or robotic procedures during the COVID-19 pandemic to reduce the spread of viral particles. While some authors have suggested that it is potentially safer to perform a closed procedure than to have an open abdomen with fluids and smoke able to spread widely, others have stated that it is safer to avoid laparoscopy because of the risk of viral spread in the pneumoperitoneum.⁵⁷ We believe that if the surgeon cannot access the recommended precautionary tools, such as airtight ports and filters, it may be safer to offer laparotomy using full PPE. However, even during laparotomy, great care must be taken to ensure complete immediate evacuation of all diathermy/electrocautery smoke plumes. Thus, the negative-pressure OR again shows its value in helping achieve this safety goal.

Continue educational initiatives by involving patient associations

In this context, patient associations are a key link between physicians and patients and should be increasingly involved in patient education. Close interaction could allow greater patient compliance with the recommendations of healthcare providers and could also help to establish long-lasting, trusting relationships.¹³ Patient associations generally use all available modalities such as internet, video chat, WhatsApp, *et cetera* to obtain the maximum diffusion of information for educational purposes. We believe that this approach is most appreciated by patients in order to be kept up to date on any changes in the treatment modalities in their IBD treatment centers and about the pandemic more generally. Therefore, we strongly recommend, if ever there was a need, that patient associations increase information and educational tasks with the support of their medical consultants at this particular time.

Table 1. The “decalogue”: 10 practical recommendations for the management of patients with IBD in the post-pandemic time.

Recommendation	Practical accomplishment
Educate patients to continue to comply with the general rules for the prevention of COVID-19 according to the indication of the WHO.	Remind patients at all times (outpatient visits, phone calls, chat, email, etc.) to comply with the recommendations for pandemic control provided by the WHO.
Do not discontinue undergoing biological therapy or delay new prescriptions.	Continue prescribing subcutaneous biological therapy and outpatient infusions. Start biological therapy, if indicated, without any delay.
Prescribe steroids only if they are strictly needed and consider a rapid tapering of their dosage.	Use steroid therapy judiciously.
Keep your patients in follow-up by preferring remote methods: telemedicine, internet, social media.	Use telemedicine with its different applications for the follow-up of patients in stable remission and therapy.
Prefer non-invasive methods to monitor disease activity.	Use calprotectin, patients' reported outcomes and intestinal ultrasound as non-invasive tools for treat-to-target strategy.
Advise patients to seek psychological support if necessary.	Offer patients psychological support and the possibility of using mindfulness techniques even remotely. In more severe cases, ask for a consultation with the psychiatrist.
Schedule (or re-schedule) endoscopic examinations if you recognize a non-deferrable indication, giving priority to the most urgent cases.	Gradually resume normal endoscopic procedures for patients with IBD using a prioritization criterion assessed on a case-by-case basis. Use the appropriate PPE to protect patients and healthcare professionals from the risk of contagion.
Infusion clinic: consider testing for SARS-CoV-2 all patients.	Resume (or continue) the activity of the infusion clinic, ensuring the safety of healthcare professionals and patients. Recommended PPE, spacing and subjecting patients to serological tests for SARS-CoV-2 on first access or return to the clinic after lockdown.
Schedule (or re-schedule) surgical interventions, giving priority to the most urgent cases.	Promote urgent surgery postponed for the lockdown, if possible, test the patient with naso-pharyngeal swab for SARS-CoV-2 before hospitalization; gradually insert all the scheduled interventions in the list.
Continue educational initiatives (not necessarily related to COVID-19) by involving patient associations.	Patient associations should offer webinars, videos, chats and other informative material to inform patients about the recommendations to be followed in “real time” to safely continue their treatments and diagnostic controls.

IBD, inflammatory bowel disease; PPE, personal protective equipment; WHO, World Health Organization.

Conclusion

Pending the discovery of a vaccine or effective therapy against SARS-CoV-2, we cannot rule out future re-ignitions of COVID-19 outbreaks. However, in countries where the trend of the pandemic is waning, albeit with still circulating virus, the priority is to resume clinical activity, approaching as much as possible pre-COVID-19 standards. Therefore, as regards patients with IBD, it is necessary to provide practical guidance to gastroenterologists in order to obtain an optimal standard of care, while ensuring the safety of patients and healthcare professionals. This may require further changes in the planning of healthcare activities, both by using different prioritization

criteria for outpatient visits, diagnostic tests and surgical interventions and by continuing to use treatment strategies that have worked well during the pandemic such as telemedicine, psychological support to patients and the educational function of patient associations (Table 1).

Author contributions

AP, VP, LRL, AG and AT: Made a substantial contribution to the concept or design of the work; or acquisition, analysis or interpretation of data;

AP, VP, LRL, AG and AT: Drafted the article or revised it critically for important intellectual content, and approved the version to be published.

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The authors declare that there is no conflict of interest.

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ORCID iD

Antonio Tursi  <https://orcid.org/0000-0001-5767-5541>

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