Inflammatory bowel disease care in the COVID-19 pandemic era: the Humanitas, Milan experience

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Abstract

The outbreak of the COVID-19 caused by Coronavirus SARS-CoV2, is rapidly spreading worldwide. This is the first pandemic caused by a Coronavirus in history. More than 150,000 confirmed cases worldwide are reported by the SARS-CoV2, with more than 5,000 COVID-19-related deaths on March 14th, 2020.

Fever, chills, cough, shortness of breath, generalized myalgia, malaise, drowsy, diarrhoea, confusion, dyspnoea, and bilateral interstitial pneumonia are the common symptoms. No therapies are available, and the only way to contain the virus spread is to regularly and thoroughly clean oneself hands with an alcohol-based hand rub or wash them with soap and water, to maintain at least 1 metre (3 feet) distance from anyone who is coughing or sneezing, to avoid touching eyes, nose and mouth, and to stay home if one feels unwell.

No data are available on the risk of COVID-19 and outcomes in inflammatory bowel disease (IBD) patients. Outbreak restrictions can impact on the IBD care. We aim to give a viewpoint on how operationally manage IBD patients ensuring quality of care in the current pandemic era.

Keywords: Coronavirus, COVID-19, inflammatory bowel disease, quality of care, pandemic

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The outbreak of the new Coronavirus (SARS-CoV2) officially named SARS-CoV-2, which causes COVID-19, is rapidly spreading worldwide. This is the third serious Coronavirus outbreak in less than 20 years, following SARS in 2002–2003 and MERS in 2012, and the first pandemic caused by a Coronavirus in history. The outbreak was firstly reported in December 2019 in China, but it has rapidly spread to other Asian countries, and, since February 2020, in Italy, Europe, with increasing incidence in all European countries, and, nowadays, in all continents. Currently (as of March 14, 2020), more than 150,000 confirmed cases worldwide are reported by the SARS-CoV2, with more than 5,000 COVID-19-related deaths. Currently, Italy is the most affected country in Europe (more than 20,000 cases), accounting 55% of confirmed cases who required hospitalization for COVID-19, 10% of patients admitted in Intensive Care Units, and 8% mortality.

Compared to MERS-CoV and SARS-CoV, SARS-CoV2 appears to be less fatal, but more contagious. The virus shares 87.1% of its genome with the SARS-CoV, and is able to use all ACE2 proteins, except for mouse ACE2, as an entry receptor to enter ACE2-expressing cells, but not cells that do not express this receptor. The SARS-CoV2 does not use other coronavirus receptors, such as aminopeptidase N (APN) and dipeptidyl peptidase 4 (DPP4). The main route of contamination appears to be by small virus-laden droplets displaced by airflows. However, there is increasing evidence that ACE2 protein, which has been proven to be a cell receptor for SARS-CoV-2, is abundantly expressed in the glandular cells of gastric, duodenal and rectal epithelia, supporting the entry of SARS-CoV-2 into the host cells. The continuous positive detection of the viral RNA from faeces suggests that the infectious virions are secreted from the virus-infected gastrointestinal cells, and therefore, the faecal-oral route should be considered.

Pooled analysis of confirmed COVID-19 cases reported between 4 January 2020 and 24 February 2020 from 50 provinces, regions, and countries outside Wuhan, Hubei province, China estimates that the median incubation period is 5.1 days (95% CI, 4.5 to 5.8 days), and 97.5% develops symptoms within 11.5 days (CI, 8.2 to 15.6 days) of infection. Under conservative assumptions, 101 out of every 10 000 cases (99th percentile, 482) will develop symptoms after 14 days of active monitoring or quarantine.

The major clinical manifestations in coronavirus infection, are fever, chills, cough, shortness of breath, generalized myalgia, malaise, drowsy, diarrhoea, confusion, dyspnoea, and bilateral interstitial pneumonia. COVID-19 pneumonia manifests with chest CT imaging abnormalities, even in asymptomatic patients, with rapid evolution from focal unilateral to diffuse bilateral ground-glass opacities that progressed to or co-existed with consolidations within 1-3 weeks. At the moment, infection by SARS-CoV2 is diagnosed by SARS-CoV2 nucleic acid amplification test from oropharyngeal swab, however the combination of amplification test and CT scan may improve the diagnosis of COVID-19, as 19% of patients can have lung involvement with no symptoms, and amplification tests on biological samples might be negative in almost 50% of patients with infection. Moreover, patients may have viral RNA present in faeces and, at smaller rate, in urines for 2-10 days after the oropharyngeal swab returns to negative.

A small study on 29 patients with different grades of severity of COVID-19 pneumonia showed clinical characteristics of common viral pneumonias. In this study, there were statistically significant differences in the expression levels of interleukin-2 receptor (IL-2R) and IL-6 in the serum of the three groups (P<0.05), among which the critical group was higher than the severe group and the severe group was higher than the mild group.
No statistically significant differences in serum levels of tumour necrosis factor-alpha (TNF-α), IL-1, IL-8, IL-10, hs-CRP, lymphocyte count and LDH were found among the three groups (P>0.05). Low CD4+ T cells in blood are associated with longer virus clearance time and more severe course of the disease, resulting in longer time when the virus may be present in stools during the rehabilitation phase\textsuperscript{12}.

**Advices for IBD patients**

At the moment, no reports on IBD patients have been published\textsuperscript{14}, and no specific recommendation can be given to IBD patients based on direct evidence. Because the SARS-CoV2 infection is not an opportunistic infection and is extremely contagious, patients with IBD should follow the same recommendations given by the World Health Organisation (WHO) to the general population\textsuperscript{15}:

- Regularly and thoroughly clean oneself hands with an alcohol-based hand rub or wash them with soap and water.
- Clean surfaces with an alcohol-based sanitizer where infected droplets may lay
- Maintain at least 1 metre (3 feet) distance from anyone who is coughing or sneezing.
- Avoid touching eyes, nose and mouth (a mask may help in preventing from this)
- Stay home if one feels unwell.
- Wear a mask to avoid infecting other people even in case of mild symptoms, and, in any case, when the safety distance cannot be kept.
- Wear gloves when going shopping, using the gasoline pump, and all other outside activities at risk of hand contamination
- Avoid using public toilets as much as possible (toilet bowl, sink, and door handle can be contaminated)

Recently, the rapid increase of new cases and the diffusion of the positive cases in all regions of Italy, with the main focus in Lombardy, has led the Italian Government to lockdown the area, strongly limiting all public activities, especially where people can gather together, and to recommend staying home to all people, unless for urgent and necessary matters, like going to hospital or pharmacies. These necessary decisions have forced IBD units and IBD patients to dramatically change and restructure the way to manage IBD patients.

**The IBD Unit in Milan: how to deal with IBD and pandemic**

Our IBD unit follows more than 5,000 patients coming from all regions of Italy (almost 75% of patients come from other regions), and it is part of one of the largest university hospitals in Lombardy. Since the outbreak has started, our hospital has been massively involved in the management of COVID-19 patients, requiring many clinicians to be reassigned to dedicated COVID-19 infected inpatients. The overload of hospitalizations and the distraction of doctors and nurses on this emergency situation, together with the limitations in travels, even within the same area, has led to the need of a rapid change in the management of IBD patients at any level. IBD patients are severely worried about the impact of their disease and medications on the risk and the prognosis of COVID-19, and many of them are forced to come to hospital because of active disease, complications, and drug administration. In order to maintain the quality standard of care\textsuperscript{16}, our unit has adopted several strategies (Figure 1).

**IBD structure**
In our unit, two physicians have been assigned to the inpatient care. Three physicians have been assigned to the infusion/clinical trial unit and endoscopy, 2 physicians to the remote monitoring. Since the multi-disciplinary team (MDT) meetings can increase the risk of contacts among people, they have been converted to virtual clinics. Any elective surgery has been postponed, and only urgent cases are admitted and managed, both in the Gastroenterology and the surgical units.

One checkpoint to investigate suspected symptoms and signs of COVID-19, to test body temperature, and to provide personal protective equipment (PPE) has been posed at every public entrance of the hospital. All workers and patients must be checked before entering the hospital. Nurses have rescheduled all patients coming for infusions in order to avoid crowding in the waiting area, and have moved infusion seats at safety distance each other. The access to our unit has been restricted only to patients needing infusions or clinical trial procedures, and no caregivers are allowed to stay in the area. The entire team wears PPE and strictly follows the WHO recommendations to prevent any contamination.

Assessment and treatment

Our daily activity in the infusion unit has been limited to intravenous drugs for patients coming from the surrounding area. Our hospital pharmacy arranged home delivery and adequate drug supply (at least 4 months) to all patients under subcutaneous drugs. Patients living in other regions who need infusions are referred to the closest IBD unit temporarily, within the Italian IBD network, and this also happens in case of mild-to-moderate IBD flares. Patients scheduled for a follow-up visit are required to stay home and to send a questionnaire about IBD symptoms and quality of life, together with their routine lab exams, to the nurse and the dedicated doctor, who give recommendations and information about therapy and follow-up procedures. In order to limit the access to the hospital for invasive procedures, decisions are taken based on patients reported outcomes (PRO), CRP and faecal calprotectin levels in asymptomatic patients.

COVID-19 infection and IBD treatments

Based on the assumption that the risk of Coronavirus infection is not different between the general population and IBD patients, but IBD flares are difficult to manage in this situation, we advise all patients to continue their therapies, especially if in remission. Specific webpages are available to give patients updated information on COVID-19 for IBD patients. The use of steroids during COVID-19 is controversial, but it seems that low-dose and short-term steroids are not associated to worse prognosis even in patients critical COVID-19 pneumonia, therefore they can be used to treat IBD flares in case of need. Thiopurines and JAK-inhibitors can decrease the number of activated T-cells, however we are not advising to stop these treatments in patients in remission with these agents who strictly follow the preventive recommendations. Since there are no data in favour or against monoclonal antibodies (although anti-IL-6 agents appear to be promising for COVID-19 pneumonia), patients continue their treatment, but we are postponing the start of new therapies if the patients has no symptoms (i.e. prevention of post-operative recurrence in patients with low-moderate risk of recurrence).

Patients’ education
Patients strongly need to be reassured in this situation. Our nurses advise patients to strictly follow the WHO and the Italian Ministry of Health recommendations. Patients are invited to find any general information on the National IBD society (IG-IBD), and on the Patients’ Association (AMICI) websites. Additional information are given by email and telephone case by case. Our hospital sends newsletters by email every day to all patients recorded in our general database.

Final considerations

This COVID-19 is heavily impacting on everybody’s daily life, including healthcare professionals (HCPs) and patients. IBD teams need to support political decision-making to rapidly adapt priorities, and they should also adapt current IBD strategies to guarantee a minimum standard level of quality of care. Collaboration and communication between HCPs and patients is fundamental. The role of Patients’ Associations together with IBD scientific societies is also crucial. Therapies should not be stopped, but alternative and safer ways of administration, and remote monitoring should be considered. Patients should avoid moving from home, especially because, beside the common risk of contracting SARS-CoV2 from air droplets, the additional risk to be infected in public toilets cannot be excluded. Data are needed on the incidence and prognosis of COVID-19 in IBD patients are strongly needed.

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Authors’ contribution

GF and SD drafted the manuscript; MA, FF, DG, AZ, SR, AS reviewed the manuscript; all the Authors approved the final version of the manuscript.
References


Figure 1. Structure and processes of the IBD unit at Humanitas, Milan, during the COVID-19 pandemic.