

Viewpoint

# 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 involving the SARS-CoV2, with more than 5000 COVID-19-related deaths on March 14, 2020. Fever, chills, cough, shortness of breath, generalised myalgia, malaise, drowsiness, 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 one's hands with an alcohol-based hand rub or wash them with soap and water, to maintain at least 1 m [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 to manage IBD patients and ensure quality of care in the current pandemic era.

**Key Words:** Coronavirus; COVID-19; inflammatory bowel disease; quality of care; pandemic

## Introduction

The outbreak of the new coronavirus [SARS-CoV2] officially named SARS-CoV-2, which causes COVID-19, is rapidly spreading worldwide.<sup>1</sup> This is the third serious coronavirus outbreak in less than 20 years, following SARS in 2002–2003 and MERS in 2012,<sup>2</sup> and the first pandemic caused by a coronavirus in history. The outbreak was first reported in December 2019 in China, but it has rapidly spread to other Asian countries and, since February 2020, to Italy and Europe, with increasing incidence in all European countries, and now 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 5000 COVID-19-related deaths.<sup>3</sup> Currently, Italy is the most affected country in Europe [more than 20 000 cases], accounting for 55% of confirmed cases requiring hospitalisation for COVID-19, 10% of patients being admitted to intensive care units, and 8% mortality.<sup>3</sup>

Compared with MERS-CoV and SARS-CoV, SARS-CoV2 appears to be less fatal but more contagious.<sup>4</sup> 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].<sup>5</sup> 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.<sup>6</sup> The continuous positive detection of the viral RNA from faeces suggests that the infectious virions are secreted from the virus-infected gastrointestinal cells,<sup>6</sup> and therefore the faecal-oral route should be considered.<sup>7,8</sup>

Pooled analysis of confirmed COVID-19 cases reported between January 4, 2020 and February 24, 2020 from 50 provinces, regions, and countries outside Wuhan, Hubei province, China, estimates that the median incubation period is 5.1 days (95% confidence interval [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.<sup>9</sup>

The major clinical manifestations in coronavirus infection, are fever, chills, cough, shortness of breath, generalised myalgia, malaise, drowsiness, diarrhoea, confusion, dyspnoea, and bilateral interstitial pneumonia.<sup>4</sup> 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 progress to or co-exist with consolidations within 1–3 weeks.<sup>10</sup> At the moment, infection by SARS-CoV2 is diagnosed by a SARS-CoV2 nucleic acid amplification test from an oropharyngeal swab; however, the combination of amplification test and CT may improve the diagnosis of COVID-19,<sup>10,11</sup> as 19% of patients can have lung involvement with no symptoms,<sup>10</sup> and amplification tests on biological samples might be negative in almost 50% of patients with infection.<sup>11</sup> Moreover, patients may have viral RNA present in faeces and, at smaller rate, in urine for 2–10 days after the oropharyngeal swab returns to negative.<sup>6,12</sup>

A small study<sup>13</sup> 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- $\alpha$ ], 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 a longer time when the virus may be present in stools during the rehabilitation phase.<sup>12</sup>

## IBD patients

### Advice

At the moment, no reports on IBD patients have been published<sup>14</sup> 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 Organization [WHO] to the general population<sup>15</sup> as follows.

- Regularly and thoroughly clean hands with an alcohol-based hand rub or wash them with soap and water.

- Clean surfaces with an alcohol-based sanitiser where infected droplets may lie.
- Maintain at least 1 m [3 feet] distance from anyone who is coughing or sneezing.
- Avoid touching eyes, nose, and mouth [a mask may help in preventing this].
- Stay at 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 into all regions of Italy, with the main focus in Lombardy, has led the Italian Government to lock down 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.

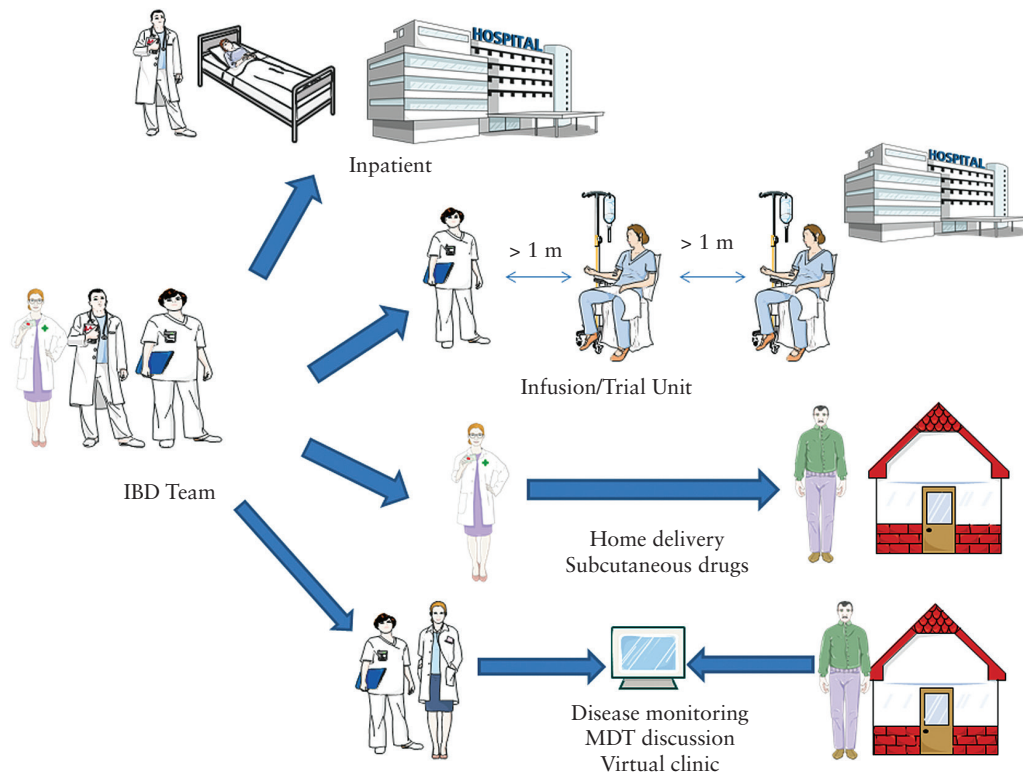
## 2.2. The IBD Unit in Milan: how to deal with IBD and pandemic

Our IBD unit follows more than 5000 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 hospitalisations and the distraction of doctors and nurses to this emergency situation, together with the limitations in travel 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,<sup>16</sup> our unit has adopted several strategies [Figure 1].

### 2.2.1. 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 and two physicians to the remote monitoring. Since the multidisciplinary team [MDT] meetings can increase the risk of contacts among people, these 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 posted 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 to a safe distance from each other. The access to our unit has been restricted to only patients needing infusions or clinical trial procedures, and no caregivers are allowed to stay in



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

the area. The entire team wears PPE and strictly follows the WHO recommendations to prevent any contamination.<sup>15</sup>

**2.2.2. 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 has arranged home delivery and adequate drug supplies [at least 4 months] to all patients receiving 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 at home and to complete a questionnaire about IBD symptoms and quality of life, together with their routine laboratory tests, 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], C-reactive protein [CRP], and faecal calprotectin levels in asymptomatic patients.

**2.3. 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 that IBD flares are difficult to manage in this situation, we advise all patients to continue their therapies, especially if in remission. Specific web pages are available to give patients updated information on COVID-19 for IBD patients.<sup>17</sup> The use of steroids during COVID-19 is controversial,<sup>18</sup> but it seems that low-dose and short-term steroids are not associated with worse prognosis even in patients with critical COVID-19 pneumonia,<sup>19</sup> 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 with these agents, who strictly follow the preventive recommendations. Since there are no data in for or against monoclonal antibodies [although antiIL-6 agents appear to be promising for COVID-19 pneumonia<sup>20</sup>], patients continue their treatment; but we are postponing the start of new therapies if the patients has no symptoms [i.e., prevention of postoperative recurrence in patients with low-moderate risk of recurrence].

**2.4. Patient 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 is given by email and telephone, case by case. Our hospital sends newsletters by email every day to all patients recorded in our general database.

**2.5. Final considerations**

This COVID-19 is heavily impacting on everybody’s daily life, including health care 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 leaving home especially because, beside the common risk of contracting SARS-CoV2 from air droplets, the additional risk of infection in public toilets cannot be excluded. Data on the incidence and prognosis of COVID-19 in IBD patients are strongly needed.

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## Conflict of Interest

GF received consultancy fees from Ferring, MSD, AbbVie, Takeda, Janssen, Amgen, Sandoz, Samsung Bioepis, Celltrion; SD has served as a speaker, consultant, and advisory board member for Schering-Plough, Abbott [AbbVie] Laboratories, Merck and Co., UCB Pharma, Ferring, Cellnex, Millenium Takeda, Nycomed, Pharmacosmos, Actelion, Alfa Wasserman, Genentech, Grunenthal, Pfizer, Astra Zeneca, Novo Nordisk, Cosmo Pharmaceuticals, Vifor, and Johnson and Johnson; the other authors have no conflict to disclose.

## Author Contributions

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

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