

The Thrilling Journey of SARS-CoV-2 into the Intestine: From Pathogenesis to Future Clinical Implications

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has a direct impact on the gastrointestinal system, as up to 50% of fecal samples from coronavirus disease 2019 (COVID-19) patients contain detectable viral RNA despite a negative rhino-pharyngeal swab. This finding, together with an intestinal expression of angiotensin conversion enzyme 2 protein, suggests a possible fecal-oral transmission for SARS-CoV-2. Furthermore, gastrointestinal (GI) symptoms are common in COVID-19 patients including watery diarrhea, vomiting—particularly in children—nausea, and abdominal pain.

Pathogenesis of SARS-CoV-2 infection presents significant similarities to those of some immune-mediated diseases, such as inflammatory bowel diseases or rheumatoid arthritis, leading to the hypothesis that targeted therapies used for the treatment of immune-mediated disease could be effective to treat (and possibly prevent) the main complications of COVID-19.

In this review, we synthesize the present and future impact of SARS-CoV-2 infection on the gastrointestinal system and on gastroenterology practice, hypothesizing a potential role of the “gut-lung axis” and perhaps of the gut and lung microbiota into the interindividual differential susceptibility to COVID-19 disease.

Finally, we speculate on the reorganization of outpatient gastroenterology services, which need to consider, among other factors, the major psychological impact of strict lockdown measures on the whole population.

Key Words: immune-mediated disease, lung-gut axis, microbiota, immunomodulators

INTRODUCTION

The new pathogenic virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was recently identified as the causative agent of the novel acute respiratory disease named coronavirus disease 2019 (COVID-19) that started in the Hubei Province, China, and rapidly spread around the world.^{1,2}

SARS-CoV-2 belongs to the β -CoV family and is enveloped by the spike glycoprotein trimmer (S) and the hemagglutinin-esterase (HE); it is characterized by a high infectivity: respiratory droplets and direct contacts represent the main form of transmission.³

Despite being considered mainly a respiratory disease, it has now become clear that COVID-19 can have a direct impact

Received for publications May 29, 2020; Editorial Decision June 17, 2020.

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Specific author contribution: FS, GI, and AA designed the project. FS, GI, GP, LRL, LMV, VP, YR, and IB performed the literature research and wrote the manuscript. DP, MN, GC, YR, GC, AG, and AA also contributed to literature research and to revise critically the manuscript. All authors reviewed and approved the final draft of the article before submission. AA oversaw the project and guarantees for the integrity of the work.

Conflicts of interest: FS: advisory board for Abbvie, Janssen, MSD, Sanofi, Takeda. GP received consultancy fees from Alphasigma. VP is in scientific advisory board of Actial Farmaceutica Srl, Italy. DP received speaker fees from AbbVie, MSD, Takeda and Janssen, Pfizer. GC: consultant for and food and beverage compensation from Cook Medical, Boston Scientific, and Olympus. AG reports

personal fees for consultancy for Eisai S.r.l., 3PSolutions, Real Time Meeting, Fondazione Istituto Danone, Sinergie S.r.l. Board MRGE, and Sanofi S.p.A, personal fees for acting as a speaker for Takeda S.p.A, AbbVie, and Sandoz S.p.A, and personal fees for acting on advisory boards for VSL3 and Eisai. IB: consultant for Apollo Endosurgery, Cook Medical, and Boston Scientific; board member for Endo Tools; research grant recipient from Apollo Endosurgery; food and beverage compensation from Apollo Endosurgery, Cook Medical, Boston Scientific, and Endo Tools. AA: consulting and/or advisory board fees from AbbVie, Allergan, Amgen, Biogen, Bristol-Myers Squibb, Celgene, Celltrion, Ferring, Gilead, Janssen, Lilly, MSD, Mylan, Pfizer, Samsung Bioepis, Sandoz, Takeda; lecture and/or speaker bureau fees from AbbVie, Amgen, Biogen, Ferring, Gilead, Janssen, MSD, Mitsubishi-Tanabe, Nikkiso, Pfizer, Sandoz, Samsung Bioepis, Takeda; and research grants from MSD, Pfizer, Takeda. All the other authors have no potential conflicts of interest to disclose.

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doi: 10.1093/ibd/izaa181
Published online 28 July 2020

on the gastrointestinal system which, in turn, might play a role in the pathogenesis of the disease.⁴ Furthermore, the pandemic itself and the lockdown measures to slow it could drive major changes in social behaviors and health care assistance that might affect patients with digestive diseases.

In this review, we focus on the current evidence of the relationship between SARS-CoV-2 and the gastrointestinal system; we outline the main implications on the management of patients with digestive diseases; and we try to prefigure the possible “gastrointestinal scenarios” we are about to face in the upcoming months.

COVID-19 AND GASTROINTESTINAL SYSTEM: CLINICAL ASPECTS

The pathognomonic symptoms of COVID-19 are cough, fever, and dyspnea. However, the disease can present a wider spectrum of clinical manifestations.⁵ Siddiqi and colleagues proposed a 3-phase model based on the observed symptoms to classify COVID-19. When the infection occurs (first stage), it typically presents with mild symptoms (malaise, low-grade fever, and dry cough). Some patients (up to 20%) develop atypical pneumonia (second stage), with high-grade fever, cough, dyspnea, and possibly hypoxia. Finally, a minority of patients progress to a third stage, characterized by a systemic hyperinflammatory state, that can lead to acute respiratory distress syndrome (ARDS), multi-organ failure, and death.⁶

Besides typical respiratory symptoms, other clinical manifestations have also been described, including gastrointestinal ones.⁴ Indeed, gastrointestinal symptoms had been associated with other coronavirus diseases, such as the 2002 SARS and the 2012 Middle East Respiratory Syndrome (MERS) epidemics,⁷ and diarrhea had been proposed as a possible prognostic factor for these diseases, even though no firm conclusions could be drawn.^{8,9}

In a recent systematic review, gastrointestinal symptoms were found in a broad range of SARS-CoV-2 patients. Anorexia was the most common symptom, reported in up to 40% of the patients, followed by other, more gastrointestinal-specific symptoms, including watery diarrhea (9.6%–16%), nausea and vomiting (6.6%–15.3%), and abdominal pain (5.7%–14.5%).¹⁰ Gastrointestinal bleeding has also been reported, but it is not clear whether it was directly caused by the infection or should be considered a secondary manifestation of systemic damage in critically ill patients.¹¹

Recent reports from Wuhan, China, demonstrated that 23% of COVID-19 patients presented with only digestive symptoms, 33% presented with both digestive and respiratory symptoms, and 44% presented with only respiratory symptoms.¹² Furthermore, it has been shown that gastrointestinal symptoms can sometimes precede respiratory involvement and be the first manifestation of the infection.¹³ These data suggest the possible need to include SARS-CoV-2 infection among the differential

diagnosis of acute diarrhea and/or vomiting, at least for the duration of this pandemic.

Notably, a recent review speculated about the possible role of diarrhea as a prognostic factor in COVID-19. No conclusive correlation was found: in some studies, gastrointestinal symptoms correlated with worse outcomes, whereas other findings suggested that no association was present.⁷

PATHOGENESIS OF SARS-COV-2 INFECTION: AN EMERGING ROLE FOR THE GASTROINTESTINAL TRACT

Angiotensin conversion enzyme 2 (ACE2) serves as the receptor used by the virus to enter human cells: the spike protein S binds to the receptor and mediates the fusion of the membranes. The process is regulated by the cell surface-associated transmembrane protease serine protease 2 (TMPRSS2), which operates in protein S cleavage and priming.¹⁴

ACE and TMPRSS2 are mainly expressed by type 2 pneumocytes¹⁵ but have also been found on intestinal cells.^{16,17} SARS-CoV-2 is believed to infect ACE2-expressing cells, triggering them to produce inflammatory mediators which lead to immune cells activation. Consequently, these cells release cytokines (such as interleukin [IL]-2, IL-6, IL-17, and tumor necrosis factor [TNF]), which mediate local and systemic manifestations of COVID-19¹⁸ (Fig. 1).

Viral RNA has been detected in fecal samples from up to 50% of COVID-19 patients, thus the possibility of a fecal-oral transmission for SARS-CoV-2 has been advanced.¹⁹ In the study from Xiao et al, SARS-CoV-2 RNA duration time in the stool ranged from 1 to 12 days, and about 25% of patients still had positive fecal samples after oral and nasopharyngeal swab negativization¹⁶; similar results were also found in pediatric cohorts.^{20,21} These studies suggest that fecal-oral route is at least possible for SARS-CoV-2 and might even last longer than “conventional” salivary droplet transmission. However, in a study conducted by Wolfel et al, although viral RNA was found in the stool samples of the patients, the presence of infectious SARS-CoV-2 was not detected, thus questioning the actual capability of the virus to be transmitted via a fecal-oral route.²²

Various etiopathogenetic hypotheses have been advanced to explain the occurrence of diarrhea in COVID-19 patients including loss in enterocytes absorption capability,²³ microscopic inflammatory gastrointestinal mucosal damage, and an impaired function of ACE2, which has a recognized role in maintaining gut homeostasis.²⁴ Endoscopy performed on a COVID-19 patient with diarrhea did not show macroscopic mucosal alterations, but microscopy examination revealed the presence of numerous lymphocytes infiltrating the lamina propria.¹⁶ Furthermore, in a recent letter, Effenberg et al reported higher levels of

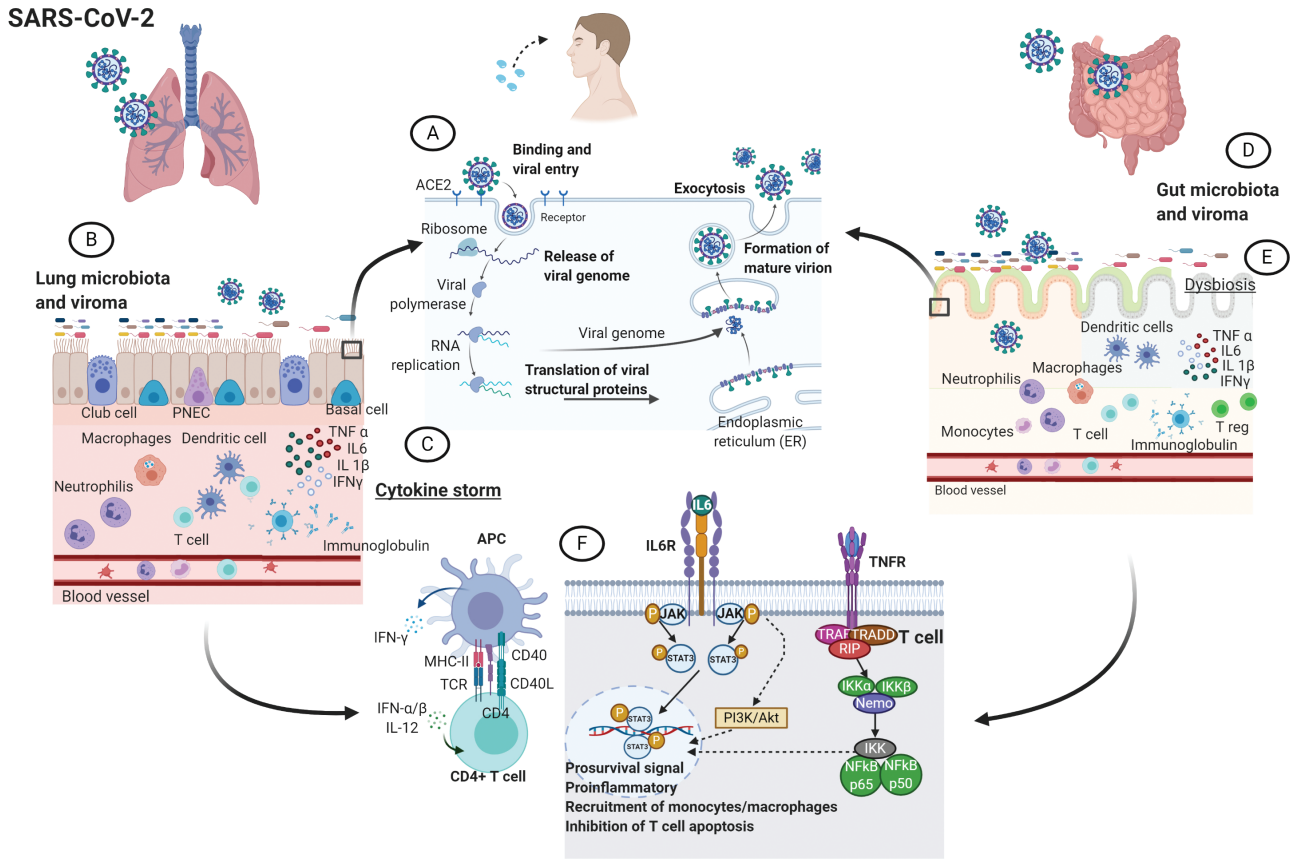


FIGURE 1. The lung-gut axis in COVID-19. Both lung and gut epithelium expresses the ACE2 receptor, recognized by SARS-CoV-2 to entry in the host cells where the virus starts to replicate (A). In the lung (B), once the virus has entered the cells, it prompts immune system activation characterized by pro-inflammatory cytokines and immune cell recruitment. If viral clearance is not sufficient, the immune response further progresses toward a cytokine storm syndrome (C). In the gut (D), the virus targets the cells and elicits the immune response in a similar fashion, although it is not yet clear whether the magnitude of the inflammatory response reaches the same level of the lung. Possibly, the immune response could lead to a dysbiosis (E) with a propagation of the pro-inflammatory state. Antigen presenting cells (APCs) are involved in the activation of the immune system in response to various exogenous triggers (F) from virus and bacteria: COVID-19 can activate inflammatory pathways that present some similarities with some immune-mediated diseases, such as IBD or rheumatoid arthritis. Abbreviations: IFN, interferon; IKK, inhibitory kappa B kinases; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; PNEC, pulmonary neuroendocrine cells; RNA, ribonucleic acid; STAT, signal transducer and activator of transcription; TNFR, tumor-necrosis factor receptor; TRADD, TNFR1-associated death domain protein; TRAF, tumor necrosis factor receptor-associated factors; T reg, T regulatory cell; NEMO, NF-κB essential modulator.

fecal calprotectin levels in hospitalized COVID-19 patients with diarrhea compared with patients who never reported it.²⁵ However, although these 2 reports might suggest that SARS-CoV-2 can directly target the gastrointestinal system, no definitive conclusion can be drawn based on these results.

Finally, alterations in liver function tests during COVID-19 have been reported.⁵ Indeed, ACE2 was found on hepatocytes and cholangiocytes, although to a lesser extent compared with lungs and intestine. Thus, SARS-CoV-2 could theoretically target liver cells.²⁶ Nevertheless, a causative role for SARS-CoV-2 cannot be inferred based on these findings because fluctuations of aminotransferases are often recorded in patients with systemic viral infections and actually reflect systemic inflammatory activation rather than direct viral damage (a phenomenon referred to as “bystander hepatitis”).²⁷ A recent

study conducted on 115 hospitalized COVID-19 patients did not find any significant difference in liver function tests when comparing COVID-19 with other forms of pneumonia, thus suggesting that liver impairment might not be a prominent feature in COVID-19.²⁸

SIMILARITIES AND DIFFERENCES WITH OTHER IMMUNE-MEDIATED DISORDERS

Immune-mediated diseases are conceived as multifactorial diseases whose pathogenesis relies on a complex interplay between genetic predisposition and environmental factors; in this context, infections have been widely advocated as potential triggers for the activation of immune-mediated diseases.²⁹ After the removal of the initial trigger, activated immune cells still continue to actively participate in damage production and

disease progression; this establishes a vicious circle of abnormal inflammation and tissue damage that perpetuates disease activity^{30,31} (Fig. 1).

COVID-19, especially in its later and more severe stages, is characterized by a significant dysregulation of immune cells.³² Neutrophilia has been associated with a higher risk for ARDS and death.³³ Furthermore, studies on peripheral blood mononuclear cells have revealed some intriguing results: though all T-cell subtypes were numerically reduced, such a decrease was more prominent in memory and regulatory T cells. Interestingly, a correlation between disease severity and the levels of inflammatory biomarkers was observed, with a sharp rise in IL-1, IL-2, IL-6, IL-8, IL-13, IL-17, and TNF,^{1,34} when comparing mild and severe patients. These findings are consistent with the notion that the severe forms of COVID-19 depend upon an immune-mediated process characterized by a systemic hyperinflammatory state.

During SARS-CoV-2 infection, an escalating transition from mild to severe immune activation can be observed, with a progressive rise of proinflammatory cytokines.⁶ Neutrophils accumulate at the site of infection, where they wield antiviral functions but, at the same time, contribute to the propagation of the immune response. If viral clearance is inadequate, their unceasing activation sets off the progression towards a hyperinflammatory state. As a matter of fact, unfavorable outcomes in COVID-19 have been associated with an exaggerated immune response to SARS-CoV-2: a cytokine storm syndrome can develop, leading to ARDS and multi-organ failure.^{35,36} Novel pathogenic hypotheses can be formed in regard to the prevention and treatment of the immune-mediated disease caused by SARS-CoV-2 infection. Notably, the cytokines overexpressed in the most advanced stages of COVID-19 are not directly involved in virus clearance.³⁷ This led to the hypothesis that targeted therapies used for the treatment of immune-mediated diseases could prove effective to treat and—possibly—prevent the main complications of COVID-19. Interleukin-6 inhibitors have been proposed and used with encouraging results.³⁸ Furthermore, baricitinib, a Janus kinases (JAK) 1 and 2 inhibitor, has been conceived as another viable treatment. The role of the different JAKs in the response to viral infections is not fully understood. Even though JAK 2 inhibition could potentially reduce viral entry within the host cells, JAK 1 inhibition might lead to a further reduction in viral clearance.^{39,40}

The cytokine repertoire induced by SARS-CoV-2 infection in complex COVID-19 presents significant similarities with those of some immune-mediated diseases, characterized by an aberrant activation of innate and adaptive immunity, possibly sustained by genetic or microbial predisposition^{31,41} (Fig. 1). A fascinating consideration comes from the recent report of isolated cases of Kawasaki disease (KD) with concurrent COVID-19 pediatric infection.⁴² The cause of KD remains unknown, but various studies have described an association

between viral respiratory infections and KD, ranging from 9% to 42% of patients with KD testing positive for a respiratory viral infection in the 30-days leading up to diagnosis of KD.⁴³ The immune system plays a pivotal role in the pathogenesis of KD,⁴⁴ and severe refractory cases of KD can benefit from treatment with immunomodulator agents.⁴⁵

The putative link between SARS-CoV-2 infection and the onset of Kawasaki disease gives rise to the question about the actual extent of the mutual influences between the virus and the immune system. In this regard, the case of IBD is particularly interesting, given that the virus can exert a tropism on intestinal cells. ACE2 and TMPRSS2 were found to be upregulated in inflamed intestine of IBD patients.^{46,47} These findings might hint at an augmented susceptibility to SARS-CoV-2 in IBD patients. On the other hand, it has been suggested that the soluble form of ACE2, whose serum concentrations are elevated in IBD,⁴⁸ might exert a protective role against the infection by acting as a competitive receptor for the virus; soluble ACE2 is obtained through proteolytic cleavage, mediated by a protease (ADAM17) upregulated in active IBD.⁴⁹

Despite some remarkable similarities, COVID-19 remains a very distinct entity from immune-mediated diseases (Table 1). First of all, COVID-19 has a definite etiologic agent, whose opportune and timely clearance is associated with disease resolution. Furthermore, the cytokine overproduction is generally abrupt and restricted in duration. Finally, limited information is available regarding immune cells involvement in COVID-19, whereas the major role of these cell types has been widely described in immune-mediated disorders.^{31,41}

THE LUNG-GUT AXIS AND THE POSSIBLE ROLE OF GUT MICROBIOTA

Gut microbiota seems to play a fundamental role in the maturation and regulation of the immune system, with intestinal bacteria and their metabolites providing local and systemic signals to immune cells; vice versa, the immune system exerts a major influence on microbiota composition and functions.⁵⁰

Despite being numerically smaller compared with gut microbiota, lung microbiota share the same main microbial phyla and relative abundance.⁵¹ Bacterial colonization of the respiratory tract has been implicated in the maturation and homeostasis of the lung immune system,⁵² and an association between lung microbiome dysbiosis and clinical manifestations of pulmonary disorders has been reported.⁵³

Recent evidences have postulated a bidirectional relationship between the 2 microbiota.⁵³ Fecal microbiota transplantation (FMT) was proved to have an impact on lung microbiota composition.⁵⁴ Furthermore, it has been observed that gut-resident innate lymphoid cells, implicated in repair functions, can move to the lung under inflammatory stimulus.⁵⁵ Lastly, a 2-way communication through the lymphatic system, involving both bacteria and their metabolites, has been documented.^{56–58}

TABLE 1. Similarities and Difference Between COVID19 and Other Immune-Mediated Disorders

	COVID-19	IMMUNE-MEDIATED DISEASES (eg, IBD, RA)
Virus infection and clearance	✓	⊘
Genetic, immune, and environmental predisposition	?	✓
Severe immune activation	✓	✓
Rise of proinflammatory cytokines	✓	✓
Endothelial, epithelial, and other nonimmune cells	✓	✓
Gut microbiota involvement	?	✓
ARDS and multi-organ Failure	✓	⊘
IL-6 inhibitors and JAK inhibitors	?	✓
Acute mortality and morbidity	✓	⊘

The ensemble of the relevant connections between the intestine and the lung, including gut and lung microbiota, their intercompartment crosstalk, and gut and lung immune system crosstalk with local or long-reaching interactions, has been called the “gut-lung axis.”⁵³

This axis has already been implicated in several diseases, with some interesting findings regarding viral respiratory infections reported in murine models, where a Th17-mediated modulation of gut microbiota composition has been observed.⁵⁹ Furthermore, impairment of gut microbiota was found to be associated with more severe forms of respiratory influenza in mice, in which microbiota-derived signals were able to exert their effects on lung stromal cells and keep epithelial cells in an IFN-primed state, inducing an antiviral state in nonimmune cells.⁶⁰ It could be argued that the composition of gut microbiota can have an impact on the immune response against some viral respiratory agents and, thus, on the outcome of the disease. Therefore, a putative role for the gut-lung axis in the modulation of the pathophysiology of SARS-CoV-2 infection and the subsequent immune activation can be hypothesized (Fig. 1).

ACE2 on the enterocytes serves as regulator of dietary aminoacids uptake and has been implicated in gut immune and microbial homeostasis; it has been shown that its activation, under the regulation of tryptophan, leads to the production of antimicrobial peptides.²⁴ Even though we do not know the exact implications of SARS-CoV-2 on the intestine,

given that ACE2 is recognized by the virus, it is possible to hypothesize that its occupancy might inhibit its regulatory activity and produce intestinal dysbiosis; furthermore, it has been shown that ACE2 expression is downregulated by SARS-CoV-2,⁶¹ which could further contribute to limit ACE2 functions. Regardless of the exact mechanism, if SARS-CoV-2 is able to produce intestinal damage, the possibility of gut dysbiosis and augmented intestinal permeability needs to be taken into account. Such conditions might have an impact on lung diseases through 2 possible mechanisms: the translocation of bacteria and their metabolites or the migration of activated immune cells.^{57, 62, 63} Indeed, a study suggested a correlation between the composition of gut microbiota and the outcome of critically ill patients with ARDS: intestinal bacteria seemed to have an influence on the evolution of these patients, due to a gut-to-lung bacterial translocation secondary to increased gut and alveolo-capillary permeability.⁶⁴ Whether these findings are valid for COVID-induced ARDS remains unknown.

To date, there is no direct evidence supporting the notion that acting on the gut-lung axis might exert an effect on the course of SARS-CoV-2 infection. However, this remains a fascinating hypothesis due to the possible implications in clinical practice. Of note, the only report linking the gut-lung axis to COVID-19 have been Chinese guidelines recommending the use of probiotics in severe COVID-19 patients to preserve intestinal homeostasis and avoid bacterial infection.⁶⁵

PRESENT CLINICAL IMPLICATIONS FOR GASTROENTEROLOGISTS

Outpatient Services and Endoscopy

The outbreak of the COVID-19 pandemic had a dramatic impact on the organization and execution of every clinical activity. Given their close contact with patients, health care professionals are at great risk of being infected, with an estimated prevalence up to 10% in the most affected regions.⁶⁶ The significant prevalence of gastrointestinal symptoms¹⁰ and the possibility of a fecal-oral transmission¹⁶ entail that gastroenterologists may be deeply involved; furthermore, non-COVID-19 patients with preexisting digestive diseases still need appropriate and timely care during the pandemic. Therefore, the utmost effort has been made since the beginning of the emergency to provide essential care for both COVID-19 and non-COVID-19 patients while keeping health care professionals safe.

Health care professionals' workflows had to be entirely reconsidered: outpatient services, especially for patients on chronic immunosuppressive therapy, have been redesigned by providing waiting rooms that can guarantee social distancing, strictly scheduled accesses, preventive nasal swab in case of suggestive symptoms, and prioritizing access to nondeferrable patients. Additionally, telemedicine tools have been massively implemented.⁶⁷

Endoscopists are at high risk from inhalation of airborne droplets, mucosal contact, and potential fecal-oral transmission. The European Society of Gastrointestinal Endoscopy and the European Society of Gastroenterology and Endoscopy Nurses Associated (ESGE/ESGENA) produced a detailed position statement for the COVID-19 pandemic, listing urgent (nondeferrable) and nonurgent (requiring a case-by-case evaluation) procedures. Patients risk stratification of being infected by SARS-CoV-2 is needed for scheduled GI endoscopy activities: in cases of high risk or confirmed infection, adequate PPE is required.⁶⁸ Reprocessing of flexible endoscopes and accessories should be performed according to published guidelines, with use of viricidal agents recommended.⁶⁹

In spite of expert opinions and society recommendations, deciding whether or not to postpone an endoscopy is not always unambiguous, particularly in IBD, where endoscopic findings can guide patients' management.⁷⁰ Nondeferrable colonoscopies should be performed in cases of new diagnosis confirmation, severe flares, subacute obstructions, and worsening of cholangitis and jaundice in a patient with known primary sclerosing cholangitis.⁷¹ However, no clear indication is available for those endoscopies that cannot be considered urgent but may be associated with unfavorable consequences if rescheduled in the long term, such as colorectal cancer surveillance, efficacy assessment of therapies, and postoperative recurrence evaluation in Crohn's disease.

Clinical Management of Gastrointestinal Diseases and Fecal Microbiota Transplant

Immune-mediated diseases, patients undergoing chemotherapy, and transplant patients raise some concerns for a theoretically higher risk of infectious diseases. Given the paucity of evidences currently available, a cautious attitude in prescribing immunomodulators is generally advisable; however, a protective role for these patients has been theorized. Interleukin-6 inhibitors are currently used to treat COVID-19 complications³⁸; furthermore, observational studies reporting no severe cases in IBD patients living in epidemic areas might suggest that this population is actually at lower risk,^{72, 73} and immunomodulators may have played a role in these observations. The preliminary data from the Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD) registry have shown that increasing age, ≥ 2 comorbidities, systemic corticosteroids, and sulfasalazine or mesalamine represent risk factors in IBD patients for severe COVID-19. The results on aminosalicylates are indeed surprising: they could depend on some unrecognized confounding factors or the biological activity of the drug, but no clear interpretation is possible to date.⁷⁴

Corticosteroids, the mainstay for the treatment of many immune-mediated diseases, have been associated with worse outcomes in influenza pneumonia⁷⁵ and with a reduction of viral clearance in patients with SARS⁷⁶ and MERS.⁷⁷ Current evidences seem to point against their use in COVID-19, as their administration was associated with higher mortality, longer hospitalizations, and a higher risk for secondary bacterial infections.⁷⁸ Furthermore, the SECURE-IBD study showed that systemic corticosteroids significantly increased the risk for hospitalization, need for intensive care, and death.⁷⁴ Consequently, steroid prescription should be cautiously weighted in non-COVID-19 patients, and prednisone ≥ 20 mg/day should be avoided.⁷⁹

Thiopurines reduce the number and function of activated T cells³² and have been associated with an increased risk for viral infections.⁸⁰ To date, there is insufficient evidence to conclude that thiopurines might actually increase the risk of SARS-CoV-2 infection. Because they still continue to exert their immunosuppressive effect for weeks after cessation,⁸¹ dose reduction and therapy discontinuation are not currently recommended.⁷⁹

Calcineurin and mammalian target of rapamycin inhibitors are not associated with major concerns of infections.⁸² Indeed, mammalian target of rapamycin inhibition has been associated with possible antiviral activity,⁸³ and calcineurin inhibition was reported to suppress coronaviruses replication.⁸⁴ Treatment withdrawal is not recommended; however, due to the possible interactions with some antiviral agents, a dose adjustment or suspension could be required in the case of SARS-CoV-2 patients being treated with specific drugs.²⁷

Anti-TNF agents are associated with an increase in infectious risk⁸⁵; however, TNF might exert a pathogenetic role in

severe cases of COVID-19 because it can cause increased expression of ACE2 and lymphocyte death.⁸⁶ Tursi et al reported the case of a young man with IBD treated with adalimumab who developed COVID-19 and quickly recovered.⁸⁷ In the SECURE-IBD registry, anti-TNF agents did not seem to affect the course of COVID-19, whereas combination therapy (anti-TNF and thiopurines) was associated with worse outcomes.⁷⁴ Continuation of anti-TNF treatment is currently recommended⁷⁹; furthermore, adalimumab is under study as a treatment for cytokine storm syndrome in COVID-19.⁸⁸ Conversely, the use of combination therapy should probably be discouraged, at least in those patients with other risk factors for severe COVID-19.

Vedolizumab and ustekinumab are not associated with an increased risk for viral infections,^{89,90} and their continuation is currently recommended.⁷⁹ Vedolizumab is a gut-selective agent that prevents lymphocytes homing; in a phase 1 clinical trial, its use in human immunodeficiency virus (HIV)-positive patients did not increase the viral load.⁹¹ Ustekinumab targets the p40 subunit common to IL-12 and IL-23, thus blocking Th1 cells priming and Th17 cells activation. The suppression of the Th17 response might theoretically contribute to mitigate COVID-19 cytokine storm, but this approach has never been tested.³²

The blockade of the JAK pathways leads to a wider suppression of cytokine-mediated responses. JAK 1 and 3 inhibition downregulates IFN γ , which has a role in viral clearance³⁷ and has been associated with an increased risk for herpes-zoster infection.⁹² Conversely, JAK 2 inhibition has been proposed as a therapeutic strategy for COVID-19.⁹³ No definitive conclusions on tofacitinib (JAK 1 and 3 inhibitor) can be drawn in respect to SARS-CoV-2: discontinuation is not currently recommended,⁷⁹ but initiation in epidemic areas should be avoided, unless appropriate alternatives are not available.⁹⁴

Another interesting case could be made for fecal microbiota transplant (FMT), a clearly known effective treatment for recurrent *Clostridium difficile* infections.^{95,96} In December 2019, the consensus report on stool banking for microbiota transplantation was released, where specific recommendations about stool donor screening were made.⁹⁷ Given the increasing evidence of a potential gastrointestinal involvement in SARS-CoV-2 infection and the possible existence of a fecal-oral route of transmission, several measures have been updated to assure the best safety possible against COVID-19 transmission through FMT.

EMERGING NEEDS AND FUTURE IMPLICATIONS

The COVID-19 pandemic has changed priorities and forced a reorganization of several outpatient services and inpatients management. Furthermore, the strict lockdown measures have major psychological impact on the whole population, including children and adolescents, as they are abruptly experiencing a dramatic change in life habits, increased social isolation and subjective feelings of loneliness, and changed management

of deaths and comfort.⁹⁸ Moreover, diet habits are changing as well, as most subjects have gained weight during the lockdown. All these things will have an unpredictable impact on patients with gastrointestinal diseases, on health personnel involved in gastrointestinal services, and also on organizational schemes for the “post-COVID” era.

In an attempt to reduce hospital visits and minimize the contagious risk, considerable numbers of visits and procedures have been postponed. Prioritizing urgent patients is undoubtedly imperative, but the compelling focus on the strategies to reduce contagions could lead to an improper neglect of “stable” patients, thus exposing them to otherwise preventable risks in the long term. Some concerns about the possible long-lasting impact of this situation on cirrhotic patients have been recently raised. Early diagnosis and close monitoring of cirrhosis complications are crucial for their management; the consequences of missed identifications of early hepatocellular carcinoma, delayed screening endoscopies, and unperformed follow-up visits are expected in the following months.⁹⁹ Similar considerations could be made for IBD. Deep remission and treat-to-target strategies correlate with better long-term outcomes,⁷⁰ and tight control management is associated with reduced rates of disease progression and complications.¹⁰⁰ To what extent the current shift in the management of IBD can impact the natural history of the disease is unpredictable. We can reasonably expect that diagnostic and therapeutic delays have occurred since the beginning of the pandemic, and we will have to cope with their consequences in the near future.

We do expect an increase in the requests for gastrointestinal clinic visits and endoscopic procedures to make up for patients postponed during the pandemic. However, the risk of new cancer diagnosis because of delay of screening procedures (eg, colonoscopies) is not predictable. Additionally, intestinal infections by SARS-CoV-2 or pandemic-associated environmental changes may also lead to stress-related functional gastrointestinal disorders (eg, reactivation of IBS and postinfectious IBS).

Health personnel had to face the pandemic by reorganizing shift and schedules, patient-physician relationships, and education tasks. This will induce health personnel to participate more actively in the organization of the post-COVID-19 era. Hospital and services, in fact, will not be allowed to come back to former schedules as the post-COVID-19 era maintains the risk of a second peak of the pandemic. Furthermore, “space restrictions” to avoid assembling and the consequent reduction of the total number of patients entering the outpatient clinic will outstand the organization, web-based telemedicine, and the suitability of clinical procedures.

Conflicts of Interest: FS has served on the advisory boards for Abbvie, Janssen, MSD, Sanofi, and Takeda. GP received consultancy fees from Alphasigma. VP is on the scientific advisory board of Actial Farmaceutica Srl, Italy. DP received speaker fees from AbbVie, MSD, Takeda, Janssen,

and Pfizer. GC is a consultant for and has received food and beverage compensation from Cook Medical, Boston Scientific, and Olympus. AG reports personal fees for consultancy for Eisai S.r.l., 3PSolutions, Real Time Meeting, Fondazione Istituto Danone, Sinergie S.r.l. Board MRGE, and Sanofi S.p.A, personal fees for acting as a speaker for Takeda S.p.A, AbbVie, and Sandoz S.p.A, and personal fees for acting on advisory boards for VSL3 and Eisai. IB is a consultant for Apollo Endosurgery, Cook Medical, and Boston Scientific; is a board member for Endo Tools; research grant recipient from Apollo Endosurgery; and has received food and beverage compensation from Apollo Endosurgery, Cook Medical, Boston Scientific, and Endo Tools. AA has received consulting and/or advisory board fees from AbbVie, Allergan, Amgen, Biogen, Bristol-Myers Squibb, Celgene, Celltrion, Ferring, Gilead, Janssen, Lilly, MSD, Mylan, Pfizer, Samsung Bioepis, Sandoz, and Takeda; lecture and/or speaker bureau fees from AbbVie, Amgen, Biogen, Ferring, Gilead, Janssen, MSD, Mitsubishi-Tanabe, Nikkiso, Pfizer, Sandoz, Samsung Bioepis, Takeda; and research grants from MSD, Pfizer, Takeda. All the other authors have no conflicts of interest to declare.

ACKNOWLEDGMENTS

The authors wish to thank Alessia Leonetti for her support in proofreading the manuscript.

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