







REVIEW ARTICLE

COVID-19 in gastroenterology: Where are we now? Current evidence on the impact of COVID-19 in gastroenterology

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Abstract

Background: The COVID-19 pandemic has created unprecedented challenges in all fields of society with social, economic, and health-related consequences worldwide. In this context, gastroenterology patients and healthcare systems and professionals have seen their routines changed and were forced to adapt, adopting measures to minimize the risk of infection while guaranteeing continuous medical care to chronic patients.

Objective: At this point, it is important to evaluate the impact of the pandemic on this field to further improve the quality of the services provided in this context.

Methods/Results/Conclusion: We performed a literature review that summarizes the main aspects to consider in gastroenterology, during the pandemic crisis, and includes a deep discussion on the main changes affecting gastroenterology patients and healthcare systems, anticipating the pandemic recovery scenario with future practices and policies.

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INTRODUCTION

Since the emergence of the SARS-CoV-2 virus in December 2019,¹ the COVID-19 pandemic has spread globally with far-reaching consequences on every echelon of society. As of 20 April 2021, COVID-19 has infected over 140 million people and claimed at least 3 million lives.² Controlling the pandemic has been at the forefront of the World Health Organization (WHO) and international communities. As countries implement public health reforms which reverberate through healthcare, social, education, travel, and economic sectors,³⁻⁶ the gastroenterology community has also been forced to accommodate sweeping adaptations.

Specific to gastroenterology, stakeholders affected by COVID-19 include patients, healthcare professionals (HCPs), researchers, societies, and health policy makers.⁷⁻⁹ On this setting, the susceptibility, monitoring, diagnosis, and treatment of patients with chronic gastrointestinal (GI) diseases are major concerns.¹⁰⁻¹² Regarding diagnosis, endoscopy is one of the most affected procedures and the impact of the decrease of procedures is yet to be determined.^{13,14}

Gastroenterologists have seen their clinical routine disturbed by the pandemic with adaptations in patients' management and evidence of burnout and mental health among HCP.^{10,15} Telemedicine became a reality,^{16,17} and team and scientific meetings were adapted to virtual format,¹⁸ as well as medical training and learning.¹⁵

The vaccination process is now a priority, and the conditions in which GI patients shall be managed must be clarified. This article intends to provide a global perspective on the major changes that have been affecting gastroenterology during the pandemic, while providing a deep discussion on their impact on patients, healthcare systems, and professionals, considering all the lessons learned and the management plan for the pandemic, in the next years.

COVID-19 AND THE ALIMENTARY TRACT—PATHOPHYSIOLOGY

SARS-CoV-2 infection is dependent on cell entry; this occurs via the binding of the viral spike protein to the angiotensin-converting enzyme 2 (ACE-2) receptor, and cleavage of S-protein by transmembrane serine protease 2 (TMPRSS2). Although expressed in the respiratory tract,¹⁹ ACE-2 and TMPRSS2 are highly expressed in the brush border of enterocytes and the evidence of SARS-CoV-2 intestinal infections highlights the potential influence of the gut inflammatory response.^{20,21} Indeed, multiple in vitro and in vivo animal studies showed that SARS-CoV-2 can enter and replicate in enterocytes.^{22,23} This has been confirmed in several human studies through detection of viral RNA, subgenomic RNA, antigens, and

virions in intestinal tissue samples. The prolonged detection of viral RNA in fecal samples, in about half of patients with COVID-19^{21,23,24} provides further evidence for the relation between SARS-CoV-2 and enterocytes. Viral RNA is detectable in stools, for a median time of 28 days, persisting for a mean of 11 days, after negative nasopharyngeal swab PCR testing.^{21,25-27} In some cases, peak concentrations were higher than those in pharyngeal swabs. The analysis of human excrements in sewage content are being considered as a strategy to estimate the prevalence of COVID-19 and evaluate emerging virus strains.²⁸ These evidences of the presence of SARS-CoV-2 in intestinal tissues and fecal samples have raised concerns about a potential fecal-oral transmission.^{21,29-31} According to histological analyses, the replication of SARS-CoV-2 in enterocytes causes tissue inflammatory infiltration, usually without major injury.^{21,23,32} The possibility of gut inflammatory response is supported by the occurrence of diarrhea and increased concentrations of calprotectin in stools of patients with COVID-19,³³ and high concentrations of enterocyte-specific cytokines (IL-18), in severe COVID-19 patients.^{23,34} Fecal microbiota analyses have shown a significant and prolonged effect of SARS-CoV-2 infection on dysbiosis, including depletion of commensals and selection of opportunistic pathogens, which correlate with inflammatory markers and disease severity.^{35,36}

Multiple largescale meta-analysis have reported GI symptoms and elevation of liver enzymes, in patients with COVID-19. This arises either as a result of SARS-CoV-2 infection or of adverse events caused by drugs.^{37,38} Diarrhea is the most common GI symptom (2%–16.5%); it can persist for 1–9 days and has been associated to viral RNA detection in stools.^{21,23,29} The mechanism of diarrhea is unknown and may involve changes in gut microbiota, gut epithelial inflammation, and release of virulent antigens.^{23,39} Other common GI symptoms include nausea, vomiting, anorexia, and abdominal pain, whereas rare cases of GI bleeding and ischemic injury have been reported.^{29,33,40} In a propensity-score matched study, COVID-19 patients had higher rates of GI complications including mesenteric ischemia, suggesting a different phenotype for COVID-19 when compared with conventional acute respiratory distress syndrome (ARDS).⁴¹ However, it remains inconclusive whether GI symptoms are related to severity of COVID-19.^{21,23,42,43} As GI signs may be present at the onset of the disease, COVID-19 may be considered as a differential diagnosis, even in the absence of respiratory symptoms.⁴⁴

Subacute or chronic diarrhea have been observed in 0.9%–10.5% of patients suffering from post-acute COVID-19.^{24,45,46} The subacute and long-term consequences of COVID-19 on the GI system, including post-infectious irritable bowel syndrome (IBS), are still being studied (NCT04691895). A population-based survey, including 2704 people from 33 countries, revealed that 5% of respondents

developed IBS-like symptoms during the first 3 months of the COVID-19 pandemic. Patients with IBS prior to the COVID-19 pandemic (11%) reported significantly worse emotional, social, and psychological well-being, compared with non-IBS respondents.⁴⁷

GI symptoms can also be a consequence of the socio-cultural changes that emerged during the COVID-19 pandemic. In fact, lockdowns and social distancing are modifying behaviors that are being associated with unhealthy eating habits, decreased physical exercise, decreased patient interactions with medical services, increased anxiety and alcohol consumption (or relapse in abstinent patients). All these events may have negative impact on GI and liver health⁴⁸⁻⁵⁰ and are important to re-emphasize to our patients.

COVID-19 AND GASTROENTEROLOGY PRACTICE

The COVID-19 pandemic has disrupted our medical routines and impacted a wide variety of medical activities, resulting in an exponential increase of telemedicine.^{51,52} A US study revealed that, during the pandemic, 94% of GI/hepatology visits were virtual via telemedicine, compared to only 5% 2 weeks before the onset of COVID-19.⁵²

Overall, the pandemic is affecting general Gastroenterology services with impact on patients, HCPs, and policy makers.⁵³ Outpatient care has evolved, and patients have seen their appointments delayed and their visiting rights restricted.

Healthcare systems were forced to implement measures to minimize the risk of virus spread: the services were reconfigured with changes affecting patients' triaging, healthcare personnel (redeployment, "shielding" of vulnerable HCP), medical and technical training, and Protective Personal Equipment (PPE). All this in a changing policy environment with tremendous pressures on policy makers to issue guidance on the pandemic and to manage the vaccination process.

COVID-19 IN IBD

The increased susceptibility of IBD patients, per se, to infections was a matter of debate even before the pandemic crisis.^{54,55} This increased risk can be modulated by many factors including medications such as steroids, immunosuppressive, or biologic therapies.⁵⁶

Despite previous evidence, both physicians and patients have been facing challenges while unveiling how to adapt to COVID-19.⁷ Reassuringly, IBD patients do not appear to be at increased risk of SARS-CoV-2 infection compared to the general population.⁵⁷⁻⁶¹ The discussion has been focused on the overexpression of the ACE-2 receptor in the colonic mucosa and its downregulation in the small bowel.^{62,63} Available data seem to indicate that factors such as IBD phenotype, disease location, or the degree of mucosal inflammation do not influence the risk of infection. Although IBD does not increase risk of transmission, certain classes of treatments seem to be associated with increased severity and mortality from COVID-19.^{64,65}

The outcome of the infection and factors affecting the risk of infection with SARS-CoV-2 are somehow conflicting. Data from the SECURE registry, a prospective, international, and collaborative database, showed that the sex-standardized mortality ratio was similar to that of the general population,⁶⁶ but updated data suggested that mortality in IBD might be higher (data not published).⁶⁷ However, a separate multicenter analysis of 232 patients did not find differences in hospitalization or mortality risk.^{68,69} In this context, the risk of severe COVID-19 in patients with IBD (defined as ICU admission, use of mechanical ventilation, or death) seems to be driven by the same risk factors as in the general population. While age appears to confer additional prognostic risk as in the general population, this risk is not increased in IBD per se,^{64,66,70,71} as observed in subjects with concomitant non-IBD comorbidities.^{58,64,66,70}

However, some factors demand particular attention. It has been demonstrated, across different cohorts, that steroids increase the risk of infection and that active disease should be considered as a risk factor.^{66,68,70} In addition, thiopurines have been identified as the major responsible for the increased risk of viral infections in IBD patients.^{54-56,72} The SECURE-IBD registry found that thiopurines either as monotherapy or in combination with anti-TNF inhibitors were associated with more severe disease.⁷³ Some authors have also reported an increased risk of severe disease among patients with ulcerative colitis (UC)^{60,70,74} and in those receiving aminosalicylates,⁶⁶ but these observations need further validation in population-based studies. No further concerns have been reported with the remaining drugs, including small molecules like tofacitinib and biologics like ustekinumab and vedolizumab.^{73,75-77}

In spite of available evidence, management of IBD during COVID-19 remains heterogenous.^{78,79} To harmonize management, societies, including European Crohn's and Colitis Organisation, the International Organisation for the study of Inflammatory Bowel Disease, and the American Gastroenterological Association, have published best practice recommendations for managing IBD during COVID-19.^{8,80,81} The use of biologics can be optimized with the following recommendations: (i) consider subcutaneous administration on new patients to reduce burden and contacts; (ii) avoid elective switching from infliximab infusions to subcutaneous anti-TNF formulations, as it may increase the risk of relapse; (iii) consider withholding immunomodulator therapy to reduce infection risk in patients on combination therapy and deep remission in older patients; (iv) adopt therapeutic drug monitoring to guide decisions; (v) consider withholding anti-TNF therapies for 2 weeks in patients in contact with a COVID-19 patient; and (vi) consider withholding biologics in SARS-CoV-2 positive and/or COVID-19 patients.

In addition, the British Society of Gastroenterology adapted the guidelines for acute severe UC, by means of a RAND panel, to face the challenges of the pandemic.⁸² The panel recommended that: (i) patients should be isolated during hospital stays; (ii) intravenous hydrocortisone shall be used with caution in patients with COVID-19 pneumonia; (iii) colectomy shall not be delayed; and (iv) prophylactic

anticoagulation post-discharge is appropriate in patients with a positive SARS-CoV-2 swab.

Regarding the daily care of these patients, telemedicine has now arrived in the field of IBD, with new tools and devices that will enable the development of the forthcoming models of patients care.^{83,84} The reduction of endoscopic procedures resulted in a maximum decrease of 46.3% in new diagnoses and in a decrease of 25.5% in indefinite and low-grade dysplasia diagnoses.⁸⁵

In terms of monitoring, noninvasive biomarkers have been included as targets of IBD management, in the recent STRIDE-II recommendations.⁸⁶ In this setting, it is expected that the implementation of remote monitoring, with PROMS and point of care tests, will become more widely utilized in the upcoming years⁸⁷ (Figure 1).

COVID-19 IN LIVER AND PANCREAS

COVID-19 related liver injury

Within the liver, ACE-2 is expressed predominantly in cholangiocytes (59.7% of cells) and to a lesser extent, hepatocytes (2.6% of cells).⁸⁸ Liver injury associated with COVID-19 is typically hepatocellular in nature with transaminitis.^{89,90} Possible causative mechanisms include: direct hepatocytotoxic effect of SARS-CoV-2, liver engorgement from increased pulmonary pressure, drug-induced liver injury, or ischemic hepatitis.⁹¹ Two recent meta-analyses showed that the prevalence of “COVID-19 acute liver injury” in hospitalized patients was about 24%–27%, and that 2% of patients developed chronic liver disease (CLD). Acute liver injury was associated with poor outcomes and was found in 45% of patients with severe COVID-19 and in 20% of non-severe COVID-19 patients.^{89,90} An important sidenote here is that the definitions of “severe COVID-19” or “acute liver injury” were heterogeneous across studies. Of note is

also the increase of mortality and liver disease severity associated with the decrease of liver transplantation procedures due to patient's vulnerability, scarcity of deceased donor organs, and to imposed restrictions to decrease virus transmission.^{92,93}

Chronic liver disease

The overall mortality rate for COVID-19 is estimated at 0%–2% in CLD patients,^{89,90} with risk factors comprising cirrhosis, alcohol-related liver disease (ALD), increasing age, obesity, and diabetes. Patients with metabolic-associated fatty liver disease (MAFLD) may also be at higher risk.⁹⁴ As expected, rates of acute-on-chronic liver failure (ACLF) and severe COVID-19 disease course increase with the stage of liver disease, according to the Child-Pugh classification.⁹⁴

In the setting of the pandemic, the lack of physical activity, mental health issues, and increased alcohol consumption can contribute to the increase of ALD and MAFLD burdens.⁹⁵

Liver transplant recipients and autoimmune hepatitis

Immunosuppression is associated with increased risk of acquiring SARS-CoV-2. A recent study showed a hospital admission rate of 84% in liver transplant recipients, and a mortality rate of 20%, with respiratory failure as the most prevalent cause of death.⁹⁶ However, studies highlighted the possible protective effect of calcineurin inhibitors and potential deleterious effects of mycophenolate mofetil.^{96,97} The protective effect of immunosuppressants may be due to mitigation of the cytokine storm. In a European/American retrospective study of 110 patients with autoimmune hepatitis (AIH), patients with COVID-19 were not at increased risk for worse outcomes with an overall all-cause mortality rate of 10%, and 22% for

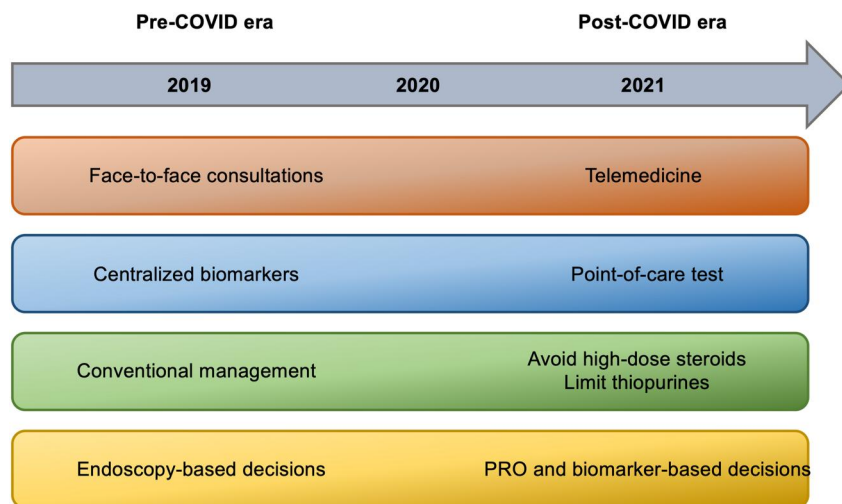


FIGURE 1 Main changes on the management of IBD patients during the COVID-19 pandemic. IBD, inflammatory bowel disease; PRO, patient reported outcomes

hospitalized patients.⁹⁸ In this study, 92% of patients were on immunosuppressants. The authors concluded that immunosuppression was protective for liver injury and did not predispose to a more severe disease course.⁹⁸

COVID-19 and the pancreas

Even though causality cannot be confirmed, pathophysiological findings seem to indicate that the pancreas is affected by COVID-19.⁹⁹ In fact, ACE-2 receptor is expressed in the exocrine and endocrine pancreas^{100,101} and SARS-CoV-2 infects and replicates in pancreatic cells.¹⁰²

In the early stages of the pandemic, a few studies reported increased levels of lipase and amylase, in COVID-19 patients (9 of 52 patients) with severe pneumonia.¹⁰³ This evidence led to the hypotheses that COVID-19 infection could directly result in acute pancreatitis (AP). The publication of reports on cases of COVID-induced pancreatitis corroborated that theory.¹⁰⁴⁻¹⁰⁶ However, in most cases, lipase levels were less than three times higher than the upper limit-of-normal (ULN), and patients showed no typical symptoms of pancreatitis. Thus, these reports lacked specificity for the diagnosis of AP.^{107,108} Also on this setting, a US multicenter study reported hyperlipasemia in 12.1% of hospitalized COVID-19 patients; in this study, 2.2% of patients presented lipase levels three times higher than the ULN and no patient developed AP.¹⁰⁹ Comparable data were reported in Asian¹¹⁰ and German patients,¹¹¹ and in other US study.¹¹² However, a large retrospective study analyzed 48,012 patients who were admitted during the COVID-19 pandemic. Some 189 had evidence for AP and, 32 from this cohort were COVID-19 positive. In patients with COVID-19, the cause of AP was more often undetermined.¹¹³ Moreover, in a prospective study from China, 12.6% of patients with COVID-19 pneumonia developed AP, which was a risk factor for severe illness and mortality.¹¹⁴ These findings were confirmed by a large prospective UK study that determined COVID-19 as a risk factor for severe AP, with worse clinical outcome.¹¹⁵

To conclude, increased amylase or lipase levels might not be associated with AP in COVID-19 and may be a consequence of concurrent clinical conditions. There is no evidence for a COVID-19-induced AP.^{99,116,117}

COVID-19 AND ENDOSCOPY

The largest challenge during the first wave of the COVID-19 pandemic was the high asymptomatic carrier rate, along with the lack of effective means to detect the virus.

Even though the incidence of asymptomatic cases varies across studies (from 1.6% to 56.5%), it has been early recognized that these patients are potentially infective.¹¹⁸ It became clear that, although endoscopy is a high-risk aerosol generating procedure, the adoption of protective measures reduces infective transmission.¹¹⁹⁻¹²¹ This

improved with the availability of nasopharyngeal antigen testing, followed by rapid point of care tests, although false negative rates remain high.

Anyway, the first wave led to a marked decrease in endoscopy activity as elective procedures were curbed to minimize footfall and hospital transmission. The redistribution of HCP and lack of PPE were initial contributory factors. Several societies worldwide were quick to issue guidance on prioritizing activity and patient risk stratification for procedures.¹¹⁹⁻¹²¹ This marked reduction in activity (to 10%-15% of pre-COVID-19) included also cancer screening procedures.¹³ The selective control of indications for GI endoscopy led to an increase in cancer detection rate per procedure and to a concerning decrease in colorectal cancer diagnosis (of 72% in the United Kingdom and 50% in the United States).^{13,122} In the United Kingdom, colorectal and esophageal cancer deaths will increase 15% and 6%, respectively, in the next 5 years.¹²³

After the first wave, endoscopy departments faced the challenges of reconfiguring services to adapt, revert to pre-pandemic levels of activity, and address waiting list backlogs (Table 1). Patients were discouraged to attend hospitals and started avoiding healthcare contacts (and/or having access difficulties), given that the risk of contracting COVID-19 was perceived as high, outweighing the risk of a delay in cancer diagnosis.¹²⁴ Since the start of the pandemic, overall cancer diagnoses decreased in the United States, not meaning that the actual incidence of cancer has dropped. Undiagnosed cancers summed up with those that were deprioritized to preserve clinical capacity for COVID-19 patients, with delayed surgeries and less frequent chemotherapy and/or radiotherapy, are matter of serious concern.¹²⁵ The impact of these tendencies is predictable if we acknowledge that even a slight 3-month delay in cancer diagnosis (especially T2-T3) may have significant impact on survival.¹²⁶ For instance, model predictions indicate an excess of 10,000 deaths from breast and colorectal cancer, in the next decades.¹²⁵

At this point, with all the lessons learned, and with vaccination under way with good results in most countries, gastroenterologists and health providers shall assure that:

- (a) Cancelled and delayed procedures are resumed, through review of waiting lists and adequate prioritization
- (b) Individuals perceive the risks of postponing cancer screening/diagnostic procedures
- (c) Screening programs are resumed, at least by non-invasive methods, if endoscopic capability is low
- (d) Training programs for physicians and technicians are resumed with minimum impact to trainees

The impact of these measures will be further improved by proper patient education programs that are being adapted to the digital format in many hospitals.¹²⁷

The pandemic had also a negative impact on endoscopy training worldwide.^{128,129} The decrement of case volume, PPE shortage, exclusion from endoscopy procedures, or redeployment to another clinical area were the main challenges that endoscopy trainees had to

TABLE 1 Adaptative measures in endoscopic units

Adaptative measure	Comment
Pre-procedure	
Change in patient indications	Emergent and urgent indications in first wave; return to pre-COVID-19 activity, with re-triage and prioritization of patients
Triage of symptoms/signs of infection, high-risk contacts, and travel to high-risk areas	Universal; 2–3 days before endoscopy and at admission
Limitation of family members at the hospital	Possible difficult communication. Phone contact policy with relatives is useful
Pre-procedural swab testing	Significant healthcare burden and costs; not universally adopted, but may be useful depending on the local phase of the pandemic and resources
Linear flow of patients throughout units	Strict social distancing rules; minimization of time spent in departments
Procedure	
Limitation of staff members in the endoscopy suit	Impact in training
Protective personal equipment use; appropriate donning and doffing	According to local policy/guidelines
Barrier protection	Not universally adopted but in development (transparent aerosol boxes, plastic shields); questionable benefit if other protective measures are strictly followed
Negative pressure rooms	For procedures in COVID-19 positive patients/high-suspicion patients pending results
Post-procedure	
Enhanced cleaning procedures	According to local policy/guidelines
Routine high-level disinfection	Minimal/null risk of transmission through endoscopes after high-level disinfection
Procedural room downtime	Depending on patient COVID-19 status, room volume, changes per hour
Post-procedure patient tracking/contact	Tracking of contacts

face.^{128,130} The substantial reduction of hands-on opportunities disrupted further endoscopy skills development. Additional concerns stemmed from the potential endoscopy training prolongation and from the lack of institutional support for trainees' emotional health care.^{128,131,132} All this has been translated into growing frustration, anxiety (52.4%), and even burnout (18.8%), among endoscopy trainees.^{128,131} These conclusions became a call for prompt reorganization of the training path by involving societies, endoscopy units, and course directors.¹³³

So far, the visible changes regarding endoscopy training are strongly related to the translocation of endoscopic education to on-line platforms, shifting the focus to cognitive skills development.¹³³ Learning resources were developed and released on the websites of the major GI and endoscopy societies. In addition, trainees can have close contact with experts and access to public discussions, during interactive webinars or conferences, which also became a new virtual reality. Also, podcast series created by journals (Endoscopy, GIE) are gaining popularity. Social media platforms (Twitter and LinkedIn) opened new learning and sharing opportunities, including international collaboration and experience sharing.¹³⁴

However, patient-based endoscopy exposure for technical skills development remained the greatest concern for endoscopy trainees.¹³⁵ The emergence of international and national position

statements on GI endoscopy, during COVID-19 pandemic, led to the adaptation of endoscopy units, providing safety along with high-quality procedures performance.¹³⁶ The increment of endoscopy case volume, with prior-to-procedure testing, along with vaccination and adequate PPE, may allow incorporating advanced fellows back into the endoscopy room.¹³³ Adaptative strategies have included: simulation-based teaching programs,¹³⁷ non-technical skills teaching, resilience training and emotional support for staff and trainees, distance mentorship, proposals to move away from emphasizing minimum procedure numbers toward competency-based curricula backed by competency assessment tools.¹³⁷ As examples of simulators, we highlight Endoscopic Retrograde Cholangiopancreatography and Endoscopic ultrasound, that are being used as alternatives for upper and lower GI endoscopy and advanced procedure.

COVID-19 VACCINES: WHERE ARE WE NOW?

SARS-CoV-2 vaccines are the key for pandemic control. The vaccines approved by US Food and Drug Administration and European Medicines Agency are based on two new platforms: mRNA vaccines and adenovirus vector-based vaccines (Table 2). At least three other vaccines are under evaluation: a protein subunit-based vaccine, an

TABLE 2 Commercialized and under evaluation SARS-CoV-2 vaccines (EMA)

Manufacturer/ Vaccine	BioNTech/Pfizer BNT162b2 (US) ¹³⁸	Moderna mRNA-1273 (US) ¹³⁸	Oxford/AstraZeneca ChAdOx1 Vaxzevria (UK) ¹³⁹	Johnson & Johnson Ad26.CoV2.S (US) ¹⁴⁰	Sputnik-V (JNJ- 784436735) GamCovid-vac (Russia) ¹⁴¹	CureVac/CvnCoV (Germany, US)	Novavax NVX- CoV2373 (US) ¹⁴²
Platform	mRNA; encoding a genetically modified SARS-CoV-2 spike protein (lipid nanoparticle)	mRNA; encoding a genetically modified SARS-CoV-2 spike protein (lipid nanoparticle)	Non-replicating; defective chimpanzee adenovirus vector, Ad5 containing SARS-CoV-2 spike protein	Non-replicating; incompetent adenovirus vector, Ad26, encoding a full-length SARS-CoV-2 spike protein	Heterologous; recombinant adenovirus-based vaccine (rAd): rAd type26 (first shot), rAd type5 (second shot)	mRNA; encoding a genetically modified SARS-CoV-2 spike protein;	Protein subunit; recombinant nanoparticle vaccine
Storage conditions	-80°C to -60°C; 2-8°C for 5 days; Room temperature 6 h after reconstitution	-25°C to -15°C up to 6 months; 2-8°C for 30 days; Room temperature; for 24 h and 6 h after reconstitution	+2°C to 8°C for 6 months	2-8°C for 3 months; 6 h refrigeration after reconstitution	-18°C (liquid form) for up to 6 months; 2-8°C (freeze dried) for up to 6 months	2-8°C for 3 months; Room temperature for 24 h	2-8°C for 6 months; 24 h at room temperature
Dose	30 µg	100 µg	5 × 10 ¹⁰ viral particles	5 × 10 ¹⁰ viral particles	10 ¹¹ viral particles per dose for each recombinant adenoviruses	12 µg	5 µg of protein and 50 µg of Matrix-M adjuvant
Dosage	Two doses, 3 weeks apart (from 3-12 weeks apart)	Two doses, 4 weeks apart	Two doses, 4 weeks apart; (12 weeks apart great efficacy)	One dose versus two doses; 0,28 days apart	Two doses, 3 weeks apart	Two doses, 30 days apart	Two doses, 3 weeks apart
Age	>16	≥18	≥18	>18	>18	-	18-59
Efficacy	95% against symptomatic Covid-19 after two doses	94.1% against symptomatic Covid-19, ≥14 days after second dose	66.7% against virologically confirmed symptomatic Covid-19 disease ≥14 days after two doses; when the two doses ≥12 weeks apart efficacy 81.3% (standard dose) and 80.0% (low dose plus standard)	72% in the United States; 64% in South Africa—neutralizing antibody responses	91.6% PCR—Covid-19 confirmed ≥21 days of first dose	Ongoing study (HERALD phase 2b/3 trial in Europe and Latin America)	Ongoing study PREVENT Phase 3 trial on United States and Mexico
Efficacy against severe disease/hospitalisation	RCT—not reported; Israeli real-world data ¹⁴³ ; 92%/87%	100%	100%/100% (>21 days after the second dose) ¹⁴⁴	NA	100% against moderate to severe COVID-19 ¹⁴⁵	NA	NA
Trial phase published	3	3	3	1,2	3	-	1,2
Approval EU	Yes	Yes	Yes	Yes	Under evaluation EMA	Under evaluation EMA	Under evaluation EMA

Abbreviation: EMA, European Medicines Agency.

adenovirus-based vaccine and other mRNA vaccine (Table 2). Data from Phase 3 clinical trials (BNT162b2, mRNA-1273, and ChAdOx1 nCoV-19), that included almost 100,000 adults, showed that mild local injection site reactions (pain, swelling, redness) and systemic features (fatigue, headache, chills) were common, but not serious, for most vaccines.^{138,139,146} So far, except for rare thrombotic events associated with adenovirus AstraZeneca vaccine,^{147,148} rare reports of cerebral venous sinus thrombosis, and low level of platelets associated with Johnson & Johnson vaccine,¹⁴⁹ no major side effects were reported for these vaccines. Even though, additional data and new statements from the regulatory agencies, concerning thrombotic events and vectorial vaccines, are expected to be published soon. Meanwhile, the Johnson & Johnson vaccine is temporarily suspended in the United States, South Africa, and European Union, following a recommendation of the US Centers for Disease Control and Prevention,¹⁵⁰ and several European countries suspended the administration of the AstraZeneca vaccine, in some groups of the general population, such as people below 60 or 55 years of age.

Despite these concerns, vaccine effectiveness seems to be the key concern, rather than safety. All the entities and experts recommend COVID-19 vaccination for IBD patients,¹⁵¹⁻¹⁵⁵ including those who had anaphylaxis following biologic treatment.¹⁵¹

In addition, the British Society of Gastroenterology and the British Association for the Study of the Liver recommend that patients with CLD, AIH, and those with liver transplants shall be vaccinated for COVID-19, with one of the available vaccines.¹⁵⁶

COVID-19 vaccination data in special populations, such as patients with IBD, pregnant and breastfeeding women, and immunosuppressed patients, are scarce and consist mainly of experts' opinions, and position statements from regulatory agencies and safety surveillance reports.

At this point, it is vital to understand if immunosuppressive agents mitigate or even prevent side effects related to vaccine immunogenicity, in IBD patients.¹⁵⁷ In fact, COVID-19 vaccines efficacy might be reduced in IBD patients treated with immunosuppressants, biologicals, or corticosteroids. Several studies found that patients with COVID-19 infection, treated with infliximab, have a blunted anti-SARS-CoV-2 response,^{158,159} that is further reduced with concomitant immunomodulator use.¹⁵⁸ However, a blunted response does not equate to vaccine failure. This effect was not observed with vedolizumab.¹⁶⁰ Another concern is the possibility of an accelerated waning of protective antibody titers, in patients treated with immunosuppressants, as verified with common vaccines (hepatitis B, measles, pertussis).¹⁶¹⁻¹⁶³ In this context, the International Organization for the study of Inflammatory Bowel Disease advises that maintenance therapies should not be withheld.⁹ Thus, patients shall be vaccinated as soon as possible¹⁵⁵ and, whenever possible, the vaccine should be administered to stable patients, before the start of immunosuppression and under a dose of corticosteroids lower than 20 mg of prednisolone a day (or equivalent), as systemic corticosteroids are known to have immunosuppressive effect above this dosage.¹⁶⁴ This does not exclude the need to consider comorbidities, age, health condition, and risk exposition to COVID-19,

prior to vaccine administration. With the objective of guiding physicians worldwide, we, herein, propose a flow-chart for SARS-CoV-2 vaccination, in IBD adult patients (Figure 2).

Regarding other GI diseases, the European Association for the Study of the Liver considered that patients with CLD, significant fibrosis, hepatobiliary cancer, and those who have had or await liver transplantation are prime candidates for receiving the COVID-19 vaccines, as all other highly vulnerable people.¹⁶⁵

Recent concern has been raised about variants of SARS-CoV-2 that may escape current vaccines, as changes in SARS-CoV-2 spike can alter neutralization sensitivity and reduce vaccine efficacy.^{166,167} New SARS-CoV-2 variants are emerging rapidly, such as B.1.1.7, B.1.351, and P.1 lineages, and it is critical to understand if antibody responses induced by current vaccines remain effective. Despite all the uncertainty, in real-world, COVID-19 vaccines seem to be effective when the process is carried out with efficiency. For instance, Pfizer and BioNtech announced a reduction of 94% of symptomatic and asymptomatic infections, in Israel.¹⁶⁸

DISCUSSION

This article presents an overview of COVID-19 in Gastroenterology, the lessons learned so far, in the scope of this specialty, as well as implications to the future¹⁶⁹ (Figure 3).

It is now clear that GI manifestations are common in COVID-19 patients, but without established relation with disease severity.²⁰ These manifestations can be further aggravated by the reduction of patients' contact with medical services and by the sedentary lifestyle adopted by the majority of the population, during lockdowns.

GI patients, as others, have been also affected by the reduction of the frequency of medical attendances, with a wide range of consequences, such as progression or decompensation of chronic diseases, late diagnosis of complications, and failure in monitoring medical treatments. In this setting, we highlight, with great concern, the difficulties concerning viral hepatitis control as defined by WHO, that aimed at a reduction of newly infected persons and related mortality by 90% and 65% respectively, by 2030. The pandemic crisis is affecting the achievement of this goal mainly by decreasing diagnosis, access to treatment and harm reduction programs.¹⁷⁰

In this scenario, telemedicine was explored to mitigate the effects of the pandemic on the care provided to chronic GI patients and allowed medical monitoring in a remote format.¹⁷ We predict that, considering its recent developments and indicators, such as reduction of costs and administrative burdens, telemedicine can remain a valid strategy for IBD patients, in combination with conventional visits, both for continuous care and procedure's monitoring (Figure 3).¹⁶ However, it is mandatory to observe how telemedicine will evolve and impact the whole management, while guaranteeing individual accessibility.⁸³ An important aspect to consider, in this transition phase, is patient's satisfaction. In fact, virtual appointments are still viewed as distant contacts and may not fulfill the needs of older and less favored patients.

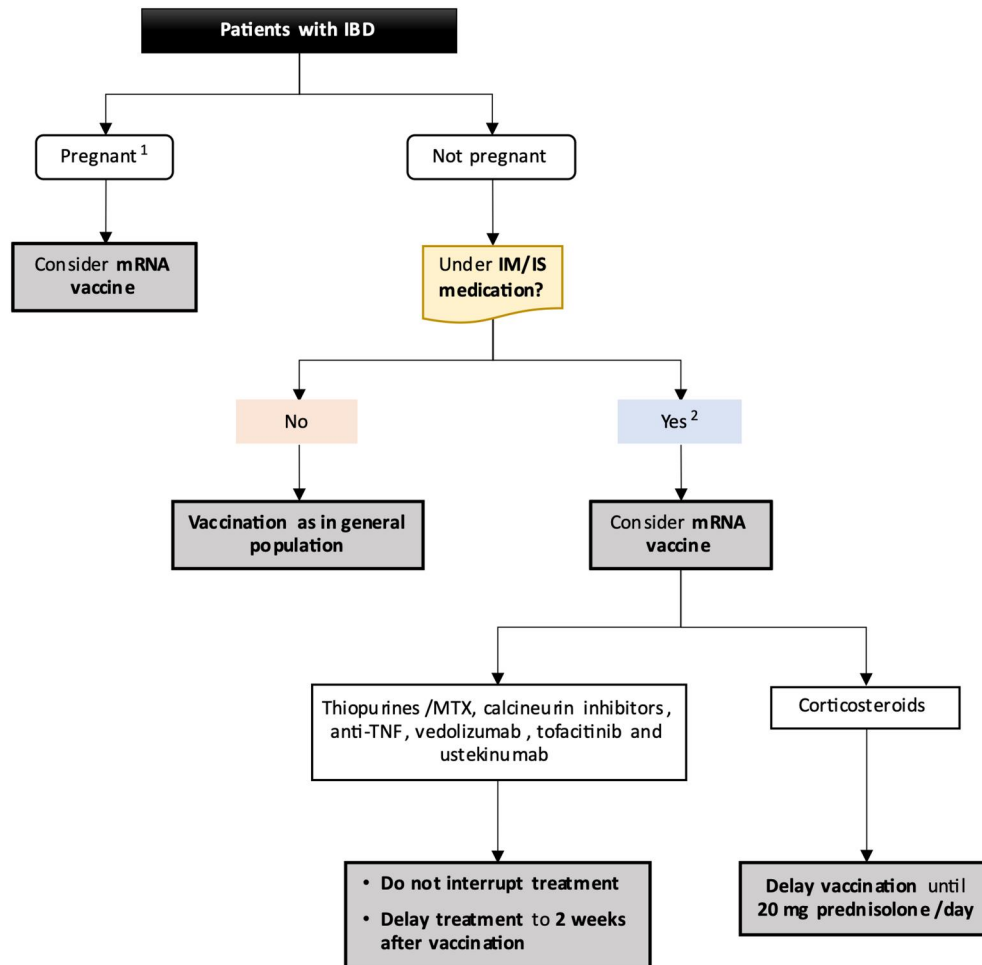


FIGURE 2 COVID-19 vaccination in inflammatory bowel disease patients. ¹Case-by-case decision according to comorbidities and risk exposure. ²Within this group of patients: (1) possibility of reduced protection, (2) vaccination not precluded, (3) vaccine booster may be needed, and (4) consider check antibodies after vaccine

One year after the beginning of the COVID-19 pandemic, it is clear that IBD does not confer an increased risk for COVID-19, per se. However, we can identify risk factors, including medications such as thiopurines, that should be considered in the risk stratification. As caregivers, we must adapt and individualize our clinical practice and treatment strategies based on best available evidence, careful appraisal of risk and benefit and acceptability to patients.

Recent evidence shows that liver injury is associated with severe COVID-19 and poor outcomes. However, clear definitions or cut-offs for liver biomarkers, to determine the prognosis of these COVID-19 patients, have not been defined yet. Patients with cirrhosis have higher risk of poor outcome, which increases with the stage of liver disease. Liver transplant patients are more frequently admitted to the hospital; however, the course of COVID-19 disease seems to be mild. The current recommendation for AIH patients is to maintain immunosuppression. In the case of liver transplant recipients, calcineurin inhibitors seem to protect against severe COVID-19, while it may be advisable to taper or withhold mycophenolate mofetil.

Despite all the concerns around endoscopy, current evidence shows that the negative impact of the reduction of procedures during the pandemic surpasses the risk of contracting COVID-19.¹²⁶ After some readjustments, it seems that endoscopy is back on track, to levels similar to those of the pre-COVID-19 era, with new (and perhaps better) habits, allowing the continued provision of safe and valuable procedures (Figure 3).¹⁷¹ Considering that endoscopy is a core diagnosis and treatment modality for GI pathology, these readjustments are vital. Even though, the widespread use of point-of-care testing to cohort patients, may obviate the need for aerosol generating procedure PPE and room turnover precautions.

Overall, the scientific and medical communities are also concerned about the impact of COVID-19 on medical education and training.^{15,130} Several tools have been developed and implemented to provide long distance classes and training, and despite all the associated advantages, the lack of hands-on training will impair skills development. Moreover, this loses the element of social interactivity, which is not only important for feedback and learning, but also emotional support, which can affect emotional health.^{130,131} It is

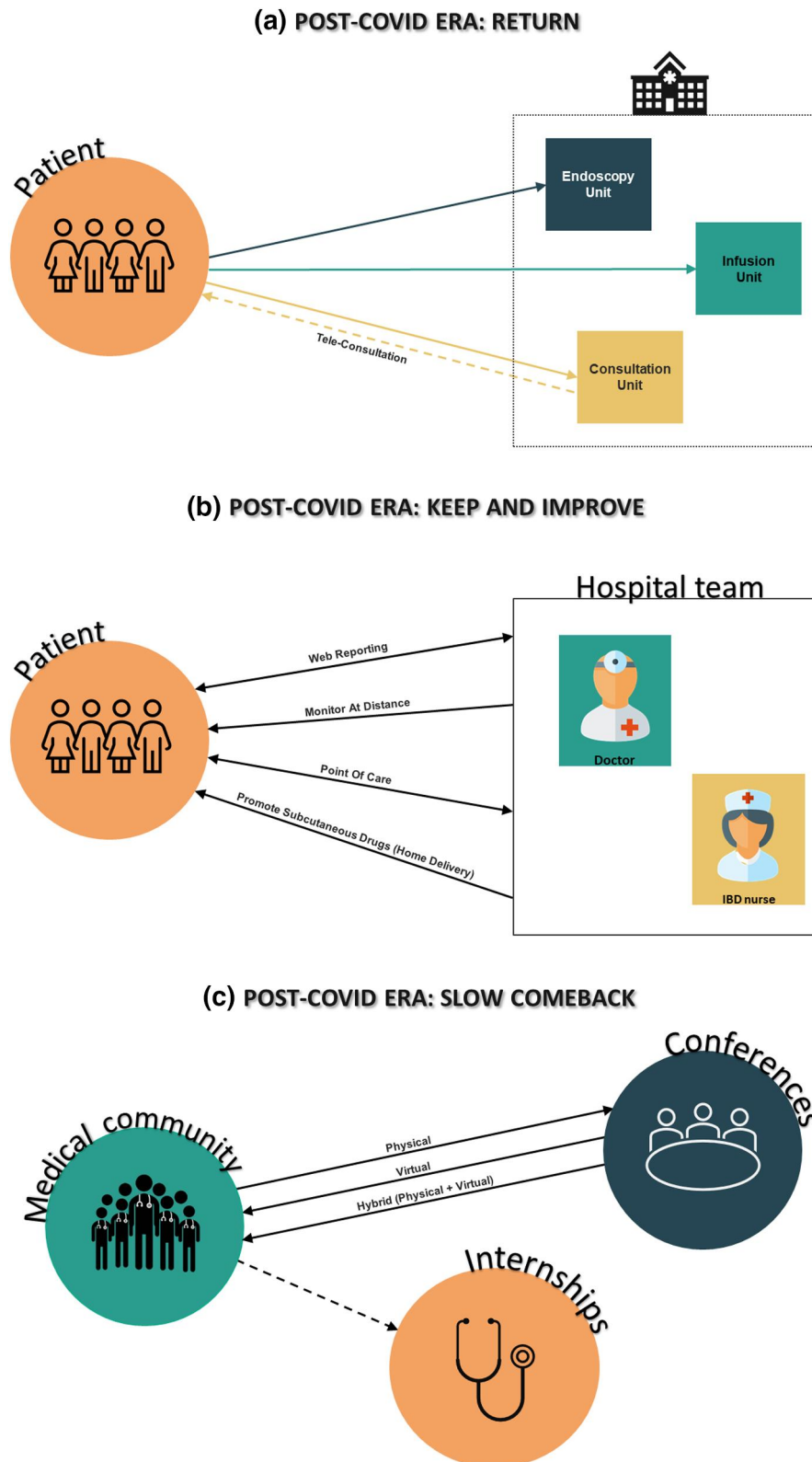


FIGURE 3 Gastroenterology in the post-COVID-19 era

hence important to maximize hands-on training opportunities and apply evidence-based interventions that optimize the endoscopy learning curve. Hybrid learning models may be the solution over the next years (Figure 3).

Researchers and scientists are also facing constraints regarding the discussion of research results. Conferences all around the world were adapted to virtual meetings with advantages in terms of cost, flexibility and accessibility.¹⁸ For instance, more than 1800

researchers, from 64 countries, attended the e-symposium “Vaccinology in the age of pandemics”. This is a good example of the importance of digital media technologies for scientific discussion, in this period of social and traveling constraints. We believe, from our experience in the GI area, that, after the pandemic, most scientific meetings will keep a virtual component (Figure 3). Although, we admit that virtual events cannot fully simulate the networking that is provided by regular science conferences, in which colleagues can discuss all the aspects of their research, in person. The pandemic has also fostered international research collaborations and the establishment of prospective databases, like SECURE-IBD, SECURE-Liver, COVID-HEP that are sources of important information for HCPs, policy makers, and patients.

At this point of the pandemic, researchers, physicians, and governments are focused on vaccination. Evidence shows that a careful evaluation of chronic GI patients regarding corticosteroids and immunosuppressants will guarantee safety and efficacy, during the vaccination process.¹⁵⁵ However, even if group immunity is achieved in some regions, general population shall be aware of the need to keep sanitary (hands washing and masks) and social distance rules, to further reduce the risk of SARS-CoV-2 dissemination. Anyway, the COVID-19 “vaccine passport” is being discussed worldwide with the objective of allowing for citizens who were vaccinated or who tested negative, or recovered from the virus, to travel between countries with minimum risks.

Future research will further increase the knowledge on SARS-CoV-2 and COVID-19 and guide patients' management. We highlight the need to clarify the role of the GI tract on severe COVID-19 forms and on virus multiplication, as well as post-COVID complications such as IBS and dysbiosis.

In conclusion, the pandemic crisis has created unprecedented challenges for gastroenterologists and GI patients. One year after the first lockdowns worldwide, the impact of COVID-19 on healthcare systems, disease's courses and diagnosis and on education and training were evaluated, and are herein discussed in detail, enabling supported decisions. We believe that we have gathered enough knowledge to assume that some of the adopted measures presented evident benefits, such as those related with telemedicine and online learning, while others showed to have negative impact in patients such as those related with endoscopic procedures and excessive reduction of medical attendances (Figure 3). Thoughtful decisions shall be now made regarding the transition to normality, in order to guarantee the best care possible for chronic GI patients, while taking advantage of the technological tools that can reduce disease burdens for patients and HCP and systems.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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