REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

Title:
COVID-19 and the digestive system: protection and management during the SARS-CoV-2 pandemic

Authors:
Javier Crespo , Julio Iglesias-García, Joaquin E. Hinojosa del Val, Federico García García , Ángel Gil de Miguel , Carlos Fernández Carrillo , Javier Ampuero , Enrique Pérez-Cuadrado Martínez

DOI: 10.17235/reed.2020.7128/2020
Link: PubMed (Epub ahead of print)

Please cite this article as:
Crespo Javier, Iglesias-García Julio, Hinojosa del Val Joaquin E., García García Federico, Gil de Miguel Ángel, Fernández Carrillo Carlos, Ampuero Javier, Pérez-Cuadrado Martínez Enrique . COVID-19 and the digestive system: protection and management during the SARS-CoV-2 pandemic. Rev Esp Enferm Dig 2020. doi: 10.17235/reed.2020.7128/2020.

REV 7128 inglés

DOI: 10.17235/reed.2020.7128/2020

COVID-19 and the digestive system: protection and management during the SARS-CoV-2 pandemic

Javier Crespo[1], Julio Iglesias-García[2], Joaquín Hinojosa del Val[3], Federico García García[4], Ángel Gil de Miguel[5], Carlos Fernández Carrillo[6], Javier Ampuero[7] and Enrique Pérez-Cuadrado Martínez[8]; on behalf of the COVID Group of the Sociedad Española Patología Digestiva (SEPD)

[1]Gastroenterology Department. Hospital Universitario Marqués de Valdecilla. Santander. [2]Gastroenterology Department. Complejo Hospitalario Universitario Santiago de Compostela. Santiago de Compostela, A Coruña. [3]Gastroenterology Department. Hospital de Manises. Manises, Valencia. [4]Microbiology Department. Hospital Universitario Clínico San Cecilio. Granada. [5]Medical Specialties and Public Health Department. Universidad Rey Juan Carlos. Madrid. [6]Gastroenterology and Hepatology Department. Hospital Universitario Puerta de Hierro Majadahonda. Majadahonda, Madrid. [7]Gastroenterology Department. Hospital Universitario Virgen del Rocío. Instituto de Biomedicina. Sevilla. [8]Gastroenterology Section. Hospital General Universitario Morales Meseguer. Murcia

Received: 13/04/2020

Accepted: 19/04/2020

Correspondence: Enrique Pérez-Cuadrado Martínez. Gastroenterology Department. Hospital General Universitario Morales Meseguer. Avda. Marqués de los Vélez, s/n. 3008 Murcia

e-mail: eperezcuadradom@gmail.com

All authors have taken part in the design and writing of the present paper.

Conflicts of interest: J. Ampuero and E. Pérez-Cuadrado Martínez have contributed to the writing of the manuscript without taking part in the editorial review process established in the publishing guidelines of Rev Esp Enferm Dig, in which the remaining associate editors did participate.

ABSTRACT

The purpose of this rapid review is to provide an update on the impact of SARS-CoV-2 infection on Gastroenterology and Hepatology departments, our patients, and our new way of working. The gastrointestinal tract and the liver are affected by SARS-CoV-2, especially in patients with immunosuppressive therapies. Patients with liver transplantation should be followed closely.

Digestive endoscopy is a high-risk procedure for the transmission of SARS-CoV-2. While the pandemic lasts, we must adapt its indications and promote protective measures for patients and healthcare professionals alike.

The COVID-19 pandemic has changed our priorities and the way we work, although we do not know what the repercussions will be after normality is reinstated.

Keywords: SARS-CoV-2. COVID-19. Endoscopy. Inflammatory bowel disease. Liver transplantation.

INTRODUCTION

The coronavirus family of viruses causes respiratory, gastrointestinal, and liver disease. In December 2019 a pneumonia outbreak was detected in association with a new coronavirus (SARS-CoV-2) in Wuhan (Hubei, China), and in January the first death was reported. A few days later the first case outside China was recorded. On January 30 and March 11 the World Health Organization (WHO) declared the outbreak a Public Health Emergency of International Concern, and then a Pandemic, respectively. On January 31 the first case was confirmed in Spain when 9,800 cases and 213 deaths had already been

reported worldwide (1), and the State of Alarm was declared on March 14 to manage a health crisis of global proportions (Fig. 1).

The goal of this review is to provide an update on the impact of SARS-CoV-2 on our specialty of Gastroenterology, on our patients, and on our new way of working.

INFECTION WITH SARS-CoV-2

The present pandemic has a fast spread rate and considerable morbidity and mortality when compared to the previous SARS-CoV (2002-2003) and MERS (2012) pandemics, which has prompted recourse to exceptional measures such as population confinement and social isolation (2) on a worldwide level, albeit evidence is limited regarding the epidemiological data thus far reported, coming primarily from China, the pandemic's origin (1-3). This pandemic has been underestimated from an epidemiological standpoint, and the rates of viral replication and lethality have far exceeded all expectations. Following contagion, the first detectable marker is viral RNA by PCR on nasopharyngeal exudate and sputum samples. IgM antibodies develop after 5-7 days, and IgG antibodies after around 14 days (3).

The basic reproduction number (R0) represents the rate of spread. Initial estimations of early outbreak dynamics at Wuhan (4) suggest a doubling time of infection cases of 6-7 days, and an R0 of 2.2-2.7, with an unexpected high rate of contagiousness. In this study all available information is collected about individual cases in China and the key epidemiological parameters, including the incubation period, using a design with 2 mathematical models that infer outbreak dynamics based on high-resolution data on domestic traveling and infection. The results obtained show that the early doubling time of the epidemic at Wuhan was 2.3-3.3 days, with a serial interval of 6 to 9 days, hence a mean R0 of 5.7 (95 % CI: 3.8 to 8.9). These data suggest that active vigilance, contact tracking, quarantine, and initial attempts at social distancing are necessary to stop viral transmission. However, this rate should decrease after infection expansion with a reduction in the number of susceptible healthy individuals. In order to avoid viral spread the best strategy would be massive rapid antigen testing of the transmitting population, but usefulness would be limited by low sensitivity (5). The Spanish *Red Nacional de Vigilancia de Salud Pública* (RENAVE) (6) identifies as more vulnerable population groups those consisting of individuals above 65 years of age, males, and patients with chronic

conditions. In these groups the required hospitalization rate is around 20 %, and 25 % of inpatients will be admitted to the ICU (intensive care unit) (7). Current containment and confinement measures have a positive impact on health but a negative impact from the economy perspective. New health care circuits have been established including telework and improvements in the general prevention of high-risk procedures for transmissible diseases.

Furthermore, the course of the pandemic is not comparable between countries as different denominators are used by each one of them. Lethality rate is difficult to estimate at the time of this writing because of multiple biases associated with the unknown total number of infection cases, and different criteria in the attribution of cause of death to COVID-19. Population-based seroprevalence studies will be necessary for the preparation of future control strategies that avoid confinement as much as possible (immunity passport). Antibody detection assays will estimate the immunity level of the population, as well as of each individual patient, using seroprevalence studies.

GUT INVOLVEMENT WITH SARS-CoV-2

The gastrointestinal epithelium is a potential target for this virus. Xiao et al (8) demonstrated the expression of angiotensin-converting enzyme 2 (ACE2), the primary receptor for SARS-CoV-2, and virus nucleocapsid in biopsy samples of gastric, duodenal, and rectal mucosa from infected patients.

General COVID-19 symptoms include fever, cough, dyspnea, headache, myalgia, and significant asthenia. Gastrointestinal symptoms are also common, including anorexia (25 %), diarrhea, nausea, vomiting, and abdominal pain, as well as anosmia and ageusia (9). However, diarrhea may be underdiagnosed since it usually develops early and is self-limited in the course of disease, its association with an eventual diagnosis of COVID-19 being challenging. Also, digestive symptoms may develop with no associated respiratory manifestations, which has significant epidemiological implications (10). The coexistence of gastrointestinal and respiratory manifestations might suggest greater severity based on clinical, laboratory, and radiological data, with greater need for mechanical ventilation, when compared to cases with respiratory manifestations alone (11), which is consistent with case reports of infection with SARS-CoV-2 (12). Although viral RNA

exhibits higher levels in the feces (which later may disappear) than in samples from the respiratory tract, neither viral stool cultures have been achieved, nor has been fecal-oral transmission irrefutably ascertained (9).

ENDOSCOPY AND COVID-19

Upper GI endoscopy -gastroscopy, echoendoscopy, enteroscopy, and ERCP (endoscopic retrograde cholangiopancreatography)- is a high-risk procedure because of the presence of SARS-CoV-2 in nasopharyngeal exudate, whereas lower GI endoscopy is deemed a moderate-risk procedure because of the more protracted presence of the virus in stools (9). The general principles of endoscopy recommendations include identifying patients at risk of having COVID-19 (Table 1), protecting patients and professionals, particularly in high-risk situations, during endoscopy (Fig. 2), and organizing endoscopy unit activities and infrastructures to preserve the highest quality for endoscopic procedures.

Very likely, a great part of the infected population remains asymptomatic, which includes both patients and health workers. Although standard tests (PCR) are highly specific, some have limited sensitivity (approximately 70 % according to commercial kits) and variable availability. Despite these limitations, screening for SARS-CoV-2 infection is recommended both for endoscopy unit staff (regularly, though intervals have not been established as yet) and patients with indications for GI endoscopy. In all cases optimizing and complying with safety recommendations as established by health authorities is highly advisable.

Adapting indications for endoscopic procedures

- Postponement of non-urgent indications according to two different scenarios during the pandemic:
    - *A:* Unit conditioned by a moderate-low workload in association with the pandemic, where standard care activities are maintained (particularly medical-surgical therapies) for patients with cancer, complex chronic disorders, inflammatory bowel disease (IBD), and liver transplant (LT).
    - *B:* Unit with a high workload in association with the pandemic, where all non-urgent health care activities had to be called off.

Table 2 list the types of technique that could be used in scenarios A and B, and those who should be delayed until the end of the pandemic.

Endoscopic procedure

Human resources

- Minimize contact between staff members. Only the essential personnel for the procedure must remain in the room (physician, nurse, assistant, and anesthetist when required).
- Staff members with COVID-19 symptoms must not work, even if an initial PCR test is negative, until negativity is confirmed. This also aplies to their contacts.
- Set up differentiated work teams (endoscopist, nurse, nursing assistant) for periods of 7-15 days, avoiding their coming together in time and place.

Patients

- Appointments: patients will be called up the day before their endoscopy to perform a checklist, which will be repeated on the day of the procedure; questions will deal with presence of symptoms (cough, shortness of breath, fever), and close contact with confirmed SARS-CoV-2 cases. The patient will be scheduled for the procedure if all responses are negative; should one or more be positive, the indication will be reassessed on a case-by-case basis, and the examination will be delayed.
- In endoscopy listings intervals between appointments will be longer to prevent overcrowding in the waiting room, where measures will be taken to maintain social distancing.
- Patients shall attend accompanied at most by only one person, who will not enter the unit unless specific help is required of him or her.
- Access to the endoscopy unit: a surgical mask and gloves will be placed on the patient (hand washing with hydroalcoholic solution if no gloves are available), and body temperature will be measured.

Protective measures during endoscopy

They will vary according to patient risk (13-15) (Table 1). When risk is moderate using the following is mandatory: disposable gloves and cap, face protection (16) (screen and mask or goggles and mask (type: surgical, N95/FFP2/FFP3)), body protection (scrubs + overcoat +/- waterproof lab coat) and appropriate footwear (clogs exclusively for in-hospital use); for high-risk patients the following must be added: double gloves (inner pair of the surgical, longer type), and single-use shoe covers (17-20).

When negative pressure (ideally) is not available the room should be well ventilated for at least 1 hour between one COVID patient and the next, or for 30 minutes if they are COVID-negative. It seems reasonable to place positive cases at the end of the agenda, though they should be ideally examined in a dedicated room whenever possible (21).

Processing of endoscopes, expendable materials, and endoscopy room cleaning

The recommendation by scientific societies is that endoscopes and reusable expendable materials undergo the standard reprocessing and disinfection procedures with bactericidal, mycobactericidal, fungicidal, and virucidal properties, which minimizes transmission risk for any type of virus. Channel cleaning brushes must be single-use, and plastic connections to the aspiration system must be discarded. Endoscopes must travel to the cleaning area already leaving the room inside a closed container (for instance, a plastic bag); once in the disinfection room they must immediately undergo manual washing before being introduced into the automated washing system.

Surfaces having been in contact with the patient, patient secretions or staff members must be cleaned and disinfected using bleach or sodium hypochlorite solution containing 1000 ppm of active chlorine. Waste residues must be eliminated and managed according to the relevant regulations in force, and a differentiated circuit should be available to this end (14,15,18,19).

INFLAMMATORY BOWEL DISEASE (IBD)

Preliminary data on patients with IBD and SARS-CoV-2 infection, as those in the Secure IBD registry, currently including 582 patients, do not demonstrate a higher risk for this infection (22).

In an inflamed gut intestinal ACE2 is overexpressed, particularly in Crohn's disease, which represents an additional virus entry route (23). However, ACE2 has two distinct functional forms, a larger one with a transmembrane structural extracellular domain, and a soluble one that circulates freely in small amounts and competes with the membrane receptor for SARS-CoV-2 binding; this isoform is up-regulated in patients with IBD and might contribute to limiting infection.

There is currently no evidence suggesting that infection may trigger flare-ups; patients who become infected while in clinical remission will most likely remain in clinical remission. However, caution is advisable since during the influenzavirus A pandemic, without gastrointestinal involvement, infection was certainly associated with mild flares during the first week of viral infection, particularly in patients with ulcerative colitis (24). Furthermore, the clinical course of COVID-19 in patients with IBD does not seem to be worse than in the general population (25), maybe because of their being younger and having greater adherence to general protective measures, albeit special attention must be paid for prevention to the smokers subgroup given their higher susceptibility to COVID-19 as tobacco enhances ACE2 gene expression in the gut and also diminishes ciliary clearing in the respiratory epithelium as well as other factors. Risk groups are listed in table 3.

Treatments with oral/topical mesalazine, locally released corticosteroids (budesonide, beclomethasone), antibiotics for bacterial overgrowth or perianal disease, antidiarrheals (loperamide), or bile salt chelators (cholestyramine resin) may be maintained and are not deemed to increase infection risk.

In case of a close contact with COVID-19 patients with IBD must comply with general recommendations regarding isolation, and are advised to consult with their IBD unit. In principle they will not be instructed to discontinue medication. Patients on immunomodulators (IMM) (26) should undergo stringent social distancing and strict monitoring to rule out signs/symptoms suggestive of infection.

Patients with IBD and COVID-19 shall be advised to discontinue or taper steroids (particularly if dose > 20 mg/day). Patients with positive SARS-CoV-2 testing, with COVID-19 and on IMM with thiopurines (azathioprine, mercaptopurine), methotrexate, calcineurin inhibitors (cyclosporine, tacrolimus) or mycophenolate, because of the washout period, should temporarily interrupt these medications, particularly in case of

severe infection. Similarly, patients on treatment with biologics such as anti-TNFs (infliximab, adalimumab, golimumab), ustekinumab, and vedolizumab (although no interaction with general immunity is to be expected given its gut-selective mechanism of action) should delay dosing in case of mild infection, and discontinue dosing in case of severe infection. However, in patients with IBD in remission infected with SARS-CoV-2 without COVID-19 biologic therapy delays and IMM discontinuation may be considered on a case-by-case basis.

As regards JAK inhibitors (tofacitinib), they tend to inhibit immune responses to viral infection, and have the advantage of a short half-life; therefore, should the need arise to discontinue medication because of infection, patients will rapidly recover their immunity. These drugs should be withdrawn during infection, and their reintroduction should be considered at 14 days after hospital discharge. However, they should not be newly indicated except when alternatives are unavailable.

In stable patients on combined therapy (biologic + immunosuppressant) monotherapy will be considered. Which agent should be discontinued remains undefined, but keeping the biologic is the suggested option. The decision may vary in case of treatment start with IMM. Whenever possible during the COVID-19 pandemic, treatment should be postponed according to individual risk.

It is recommended that each monographic IBD unit develop a screening plan for SARS-CoV-2 infection among their patients, particularly those on IMM.

COVID-19 AND HEPATOLOGY

A total of 14 %-50 % of patients with COVID-19 exhibited impaired ALT and AST levels (27). These findings may be accounted for by direct effects on hepatocytes, facilitated by ACE2 receptor expression; by hepatotoxicity secondary to antiviral drugs such as lopinavir/ritonavir; and by inflammation itself as mediated by the immune system (e.g., cytokine storm) (28).

Preliminary results from 5 hospitals in Madrid suggest that high transaminase levels represent a marker of clinical severity (unpublished data). In fact, AST rises mainly early in the course of disease, and exhibits a strong predictive value for poor prognosis in contrast with ALT and GGT, whose elevations occur later and are nonspecific. The influence of SARS-CoV-2 infection in patients with advanced fibrosis or cirrhosis remains

unknown, hence a number of registries and clinical studies have been set in motion (29,30).

In autoimmune liver disease (ALD) the clinical management of IMM medication is of concern; in the presence of infection after a diagnosis with ALD, caution should be exerted in starting prednisone or other IMM, and the risk-benefit ratio should be assessed on a case-by-case basis (31).

In patients diagnosed with ALD we should consider: a) minimizing prednisone dosing in patients on high doses, maintaining at least 10 mg/day; and b) reducing azathioprine or mycophenolate dosing, particularly in the presence of lymphopenia, fever, or a worsening of a pneumonia attributed to COVID-19.

Regarding LT, we must restrict consideration to patients with liver cancer or advanced-stage liver disease. Accordingly, current recommendations for LT in the setting of the present COVID-19 pandemic would include: a) emergency 0; b) MELD > 20; and b) hepatocellular carcinoma at risk of leaving the waiting list (WL). Once the indication has been settled, we must assess potential recipients to rule out symptoms consistent with, or direct contacts with COVID-19 within the previous three weeks, as well as potential donors.

Patients on the WL for LT must undergo diagnostic testing for SARS-CoV-2 infection using PCR assays on nasopharyngeal exudate samples and chest CT scans.

Providing information on an ongoing basis to patients on the WL is key to gain insight into the impact of the pandemic on potential LT delays because of deeply decreased numbers of donors, lack of usual resources, and infection risk (32,33).

In fact, it is obligatory to check on ICU bed and ventilator availability before LT. Patients with LT may have a prolonged, potentially more severe infection because of immunosuppressants, while on the other hand these drugs might alleviate the cytokine storm syndrome, which would be beneficial. Consequently, we must anticipate the potential impact of COVID-19 on the transplant community to avoid de serious outcomes of this infection. In any case, the decision to open or close LT programs is completely dynamic, and mostly depends on local conditions in terms of ICU availability, cumulative incidence of coronavirus infection, etc.

In transplanted patients who develop COVID-19 we should consider a reduction in mycophenolate or mTOR inhibitor (everolimus,sirolimus) doses when infection is mild,

and discontinuing these medications in severe cases, as well as a reduction in calcineurin inhibitor (tacrolimus, cyclosporine) doses. However, reducing or discontinuing immunosuppression is unnecessary for asymptomatic patients after LT.

With respect to the management of interactions between IMM and anti-COVID-19 therapies evidence is scarce, but lopinavir/ritonavir (potent inhibition of CYP3A4) have interactions with mycophenolate (only lopinavir/ritonavir), mTOR inhibitors, and calcineurin antagonists. In contrast, both tocilizumab and, most especially, remdesivir (two drugs typically reserved for serious infection) are free from relevant drug-drug interactions (34).

Finally, time to viral infection clearance might increase for immunocompromised patients, hence guidelines recommend a repeat PCR assay for SARS-CoV-2 at 5-10 days after antiviral therapy completion (35).

CONCLUSIONS

Onset gastrointestinal symptoms may be the only manifestation of COVID-19. Infection with SARS-CoV-2 may involve the gastrointestinal tract and occasionally the liver in patients with previously impaired immunity. Endoscopy is a high-risk procedure for SARS-CoV-2 transmission, and during the pandemic we must adapt its indications and promote protective measures for both patients and healthcare workers. Patients on WL for LT and transplanted individuals must be closely monitored.

The COVID-19 pandemic has modified our priorities and way of working, although we ignore what the impact will be after returning to normal.

COVID GROUP, SOCIEDAD ESPAÑOLA PATOLOGÍA DIGESTIVA (SEPD)

Alberca de las Parras F (H. Clíni Univ. Virgen de la Arrixaca. Murcia, Spain); Ampuero Herrojo J (H. Univ. Virgen del Rocío. Sevilla, Spain); Argüelles Arias F (H. Univ. Virgen Macarena. Sevilla, Spain); Domínguez-Muñoz E (Complejo Hospitalario Universitario. Santiago de Compostela. A Coruña, Spain); Fernández Carrillo C (H. Univ. Puerta de Hierro Majadahonda. Majadahonda, Madrid. Spain); García García F (H. Univ. Clín. San Cecilio. Granada, Spain); Gil de Miguel A (Universidad Rey Juan Carlos. Madrid, Spain); Hinojosa del Val J (H. de Manises. Valencia, Spain); Iglesias-García J (Complejo

Hospitalario Universitario. Santiago de Compostela. A Coruña, Spain); Pérez-Cuadrado Martínez E (H. Gral. Univ. Morales Meseguer. Murcia, Spain); Romero Gómez M (H. Univ. Virgen del Rocío. Sevilla, Spain); Sánchez-Yagüe A (H. Costa del Sol. Marbella, Málaga. Spain); and Vera Mendoza M (H. Univ. Puerta de Hierro Majadahonda. Majadahonda, Madrid. Spain).

ACKNOWLEDGEMENTS

The following associate editors of the Editorial Committee of *The Spanish Journal of Gastroenterology (Revista Española de Enfermedades Digestivas)* have taken part in the review of the manuscript:

Álvarez Delgado A (H. Gral. de la Santísima Trinidad. Salamanca, Spain); Cienfuegos JA (Clínica Universidad de Navarra. Pamplona, Spain); Fernández Rodríguez C (H. Univ. Fundación Alcorcón. Alcorcón, Madrid. Spain); Fernández Salazar L (H. Clín. de Valladolid. Spain); Espinel Díez J (Complejo Asistencial Universitario. León, Spain); Gómez Rodríguez R (Complejo Hospitalario de Toledo. Toledo, Spain); González Suárez B (H. Clínic. Barcelona, Spain); Hernández Ramírez V (H. Álvaro Cunqueiro. EOXI. Vigo. Spain); Herrero Santos JI (Clínica Universidad de Navarra. Pamplona. Spain); Herreros Martínez B (H. Marina Baixa de la Vila Joiosa. Alicante. Spain); López Serrano P (H. Univ. Fundación Alcorcón. Alcorcón, Madrid. Spain); Martínez Montiel P (H. Univ. 12 de Octubre. Madrid. Spain); Pérez-Cuadrado Robles E (H. Georges Pompidou. Paris, France); Pérez Roldán F (H. Gral. La Mancha-Centro. Ciudad Real, Spain); Valle Muñoz J (Complejo Hospitalario de Toledo. Toledo, Spain); and Betés Ibañez MT (Clínica Universidad de Navarra. Pamplona, Spain).

REFERENCES

1. Wu Y, Mc Googan JM. Characteristics of an Important Lessons from the Coronavirus Disease 2019 (COVID-19). Outbreak in China Summary of a Report

of 72314 Cases form the Chinese Center for Disease Control and Prevention. JAMA 2020;323(13):1239-42. DOI: 10.1001/jama.2020.2648

2. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395(10229):1054-62. DOI: 10.1016/S0140-6736(20)30566-3

3. Jin Y, Wang M, Zuo Z, et al. Diagnostic value and dynamic variance of serum antibody in coronavirus disease 2019. Int J Infect Dis 2020. DOI: 10.1016/j.ijid.2020.03.065

4. Emerging infectious diseases. Available from: https://wwwnc.cdc.gov/eid/article/26/7/20-0282_article?deliveryName=USCDC_333-DM25287

5. European Centre for Disease Prevention and Control. An overview of the rapid test situation for COVID-19 diagnosis in the EU/EEA. Available from: https://www.ecdc.europa.eu/en/publications-data/overview-rapid-test-situation-covid-19-diagnosis-eueea

6. Actualización n.º 64. Enfermedad por el coronavirus (COVID-19). Centro de Coordinación de Alertas y Emergencias Sanitarias. Available at: https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov-China/documentos/Actualizacion_64_COVID-19.pdf

7. Fei X, Meiwen T, Xiaobin Z, et al. Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology 2020 (in press). DOI: 10.1053/j. gastro.2020.02.055

8. Xiao F, Tang M, Zheng X, et al. Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology 2020. DOI: 10.1053/j.gastro.2020.02.055 [in press].

9. Cheung KS, Hung IF, Chan PP, et al. Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples from the Hong Kong Cohort and Systematic Review and Meta-analysis. Gastroenterology 2020. DOI: 10.1053/j.gastro.2020.03.065

10. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020. DOI: 10.1001/jama.2020.1585

11. Jin X, Lian JS, Hu JH, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut 2020 Mar 24. DOI: 10.1136/gutjnl-2020-320926

12. Leung WK, To KF, Chan PK, et al. Enteric involvement of severe acute respiratory syndrome-associated coronavirus infection. Gastroenterology 2003;125:1011-7. DOI: 10.1016/S0016-5085(03)01215-0

13. Recomendaciones generales de la Sociedad Española de Patología Digestiva (SEPD) y la Asociación Española de Gastroenterología (AEG) y sobre el funcionamiento en las unidades de endoscopia digestiva y gastroenterología con motivo de la pandemia por SARS-CoV-2 (18 de marzo). Rev Esp Enferm Dig 2020;112(4):319-22. DOI: 10.17235/reed.2020.7052/202

14. Endoscopy activity and COVID-19: BSG and JAG guiadance – update 03.04.20. Available from: https://www.bsg.org.uk/covid-19-advice/endoscopy-activity-and-covid-19-bsg-and-jag-guidance/

15. ESGE and ESGENA Position Statement on gastrointestinal endoscopy and the COVID-19 pandemic. Available from: https://www.esge.com/esge-and-esgena-position-statement-on-gastrointestinal-endoscopy-and-the-covid-19-pandemic/

16. Johnston ER, Habib-Bein N, Dueker J et al. Risk of bacterial exposure to the endoscopist's face during endoscopy. Gastrointest Endosc 2019;89(4):818-24. DOI: 10.1016/j.gie.2018.10.034

17. Zhang Y, Zhang X, Liu L, et al. Suggestions for infection prevention and control in digestive endoscopy during current 2019 COVID-nCoV pneumonia in Wuhan, Hubei province, China. Endoscopy 2020;52(4):312-4. DOI: 10.1055/a-1128-4313

18. World Endoscopy Organization (WEO) ALERT: Wuhan proposal for Safety in Digestive Endoscopy. Available from: http://www.worldendo.org/2020/02/05/weo-alert-wuhan-proposal-for-safety-in-digestive-endoscopy/

19. Recomendaciones de la Sociedad Española de Endoscopia Digestiva (SEED): Protección en Unidades de Endoscopia Digestiva frente al COVID-19. Available from:

https://wseed.org/images/site/guia_clinica/2020/RecomendacionesSEED_ProteccionUnidadesEndoscopia_Coronavirus.pdf 20. Sultan S, Lim J, Altayar O. AGA Institute Rapid Recommendations for Gastrointestinal Procedures During the COVID-19 Pandemic. Gastroenterology 2020. DOI: 10.1053/j.gastro.2020.03.072 [in press].

21. Repici A, Maselli R, Colombo M, et al. Coronavirus (COVID-19) outbreak: what the department of endoscopy should know. Gastrointest Endosc 2020 (in press). DOI: 10.1016/j.gie.2020.03.019

22. Kappelman MD, Brenner EJ, Colombel JF, et al. Surveillance Epidemiology of Coronavirus (COVID 19) Under Research Exclusion (SECURE IBD). 2020. Available from: http://www.covidibd.org

23. Monteleone G, Ardizzone S. Are patients with inflammatory bowel disease at increased risk for Covid-19 infection? J Crohns Colitis 2020;1-3. DOI: 10.1093/ecco-jcc/jjaa061

24. Ferreira CM. 1st Interview COVID-19 ECCO Taskforce. J Crohns Colitis. Available from: https://www.ecco-ibd.eu/images/6_Publication/6_8_Surveys/1st_interview_COVID-19%20ECCOTaskforce_published.pdf (published March 13, 2020.)

25. Mao, R. Liang J, Shen J, et al. Implications of COVID-19 for patients with pre-existing digestive diseases. Lancet Gastroenterol Hepatol 2020. Available from: https://doi.org/10.1016/S2468-1253(20)30076-5

26. IOIBD Update on COVID19 for Patients with Crohn's Disease and Ulcerative Colitis. Available from: https://www.ioibd.org/ioibd-update-on-covid19-for-patients-with-crohns-disease-and-ulcerative-colitis/ (2020)

27. Chau TN, Lee KC, Yao H, et al. SARS-associated viral hepatitis caused by a novel coronavirus: report of three cases. Hepatology 2004;39:302-10. DOI: 10.1002/hep.20111

28. Zhang C, Shei L, Wang FS. Liver Injury in COVID-19: Management and Challenges. Lancet Gastroenterol Hepatol 2020. DOI: 10.1016/S2468-1253(20)30057-1

29. Welcome to COVID-help.net. Available from: https://covid-hep.net/

30. Secure-Cirrhosis. Surveillance Epidemiology of Coronavirus (COVID-19) under Research Exclusion. Available from: https://covidcirrhosis.web.unc.edu/

31. AASLD. Clinical insights for hepatology and liver transplant providers during the COVID-19 pandemic. Released: 7 April 2020. Available from: https://www.aasld.org/sites/default/files/2020-04/AASLD-COVID19-ClinicalInsights-4.07.2020-Final.pdf

32. Boettler T, Newsome P, Mondelli M, et al. Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper. JHEP Reports 2020. DOI: 10.1016/j.jhepr.2020.100113

33. Andrea G, Daniele D, Barbara A et al. Coronavirus Disease 2019 and Transplantation: a view from the inside. Am J Transplant 2020. DOI: 10.1111/ajt.15853

34. Grein J, Ohmagari N, Shin D, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. New Engl J Med 2020. DOI: 10.1056/NEJMoa2007016

35. Sociedad Española de Trasplante Hepático. Recomendaciones de la SETH frente a la infección COVID19 en receptores de trasplante hepático. Available from: https://www.sethepatico.org/docs/2020/Recomend_IMS_COVID_TH.pdf

Fig. 1. The spread of COVID-19: two months after the first death it involves the whole globe (adapted from: "The New York Times, March 4, 2020").

Fig. 2. Face protection in a COVID-19 patient during ERCP.

Table 1. Risk stratification in a patient about to undergo gastrointestinal endoscopy

Intermediate risk	• Any individual residing in an area of SARS-CoV-2 community transmission, WITH NEITHER respiratory symptoms NOR fever
High risk	• Any individual with respiratory symptoms or fever, with or without contact with a known case of SARS-CoV-2 infection • Patient with a POSITIVE diagnosis of SARS-CoV-2 infection

Table 2. Gastrointestinal endoscopy indication groups during the SARS-CoV-2 pandemic. *A:* Unit conditioned by a moderate-low workload associated with the pandemic, where standard care activities (most particularly medical-surgical treatments) are ongoing for

cancer and complex chronic patients, patients with inflammatory bowel disease (IBD), and patients with liver transplant (LT). *B:* Unit with a high workload associated with the pandemic, where all non-urgent standard care activities had to be discontinued

Group 1: Scenarios A & B	• Unstable GI bleeding and/or high transfusion requirement, where endoscopic therapy is feasible • Acute esophageal obstruction (foreign bodies, punctiform stenosis, cancer where a stent is needed) • Endoscopic therapy for perforations/leaks • ERCP (± EUS) for acute cholangitis/jaundice secondary to benigh/malignant biliary obstruction • ERCP (± EUS) for acute biliary pancreatitis and/or cholangitis with stones and icterus • Infected pancreatic collections/WON • Nutritional support deemed urgent for an inpatient (PEG/SNY) • Gastrointestinal obstruction, for decompression and/or stent placement
Group 2: Scenario A	• Stable GI bleeding • High suspicion of gastrointestinal, biliary, pancreatic cancer. • EMR/ESD for complex polyps/high-risk lesions • Suspected new-onset IBD • EUS for cancer staging/biopsy • Enteroscopy: bleeding with moderate transfusion requirement or suspected cancer (based on radiology and/or capsule endoscopy) • Variceal ligation in high-risk patients
Group 3: Postpone until end of pandemic	• Screening for digestive system cancer (colorectal, pancreatic) • Dilation for oligosymptomatic achalasia • Elective therapies (PEG, dilation, argon plasma coagulation, radiofrequency, ampullectomy, etc.) • Bariatric endoscopy

	• Low-risk follow-up: esophagitis, gastric ulcer healing, elective monitoring after any endoscopic therapy deemed effective and correct, stable IBD, Barrett's esophagus • Routine, non-urgent endoscopy for the small bowel • EUS for benign conditions: biliary dilation (no cancer suspected), uncomplicated lithiasis, subepithelial tumors, cystic pancreatic tumors without alarm signs, chronic pancreatitis • ERCP for lithiasis without cholangitis or jaundice, functioning stent replacement, chronic pancreatitis treatment • Capsule endoscopy of the small bowel and colon • Clinical trials

EMR: endoscopic mucosal resection; ESD: endoscopic submucosal dissection; PEG: percutaneous endoscopic gastrostomy; EUS: endoscopic ultrasonography.

Table 3. Risk groups in patients with IBD

1. Comorbidity (respiratory, cardiac, HBP, diabetes) and/or over 70 years of age
2. On treatment with IMM
3. Any age with one or more of the following criteria:
    - Moderately/severely active disease despite treatment with IMM
    - On treatment with prednisone 20 mg/day or equivalent (lower doses are deemed safe, although attempts should be made to reduce them)
    - Active disease with malnutrition
    - Recently initiated combination therpy (within 6 weeks)
    - Pregnancy (no specific recommendations are available; potential risk factor)