Gastroenterology during COVID-19 pandemic: FISMAD recommendations

The end of 2019 has been marked by the emergence of a new coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which caused an outbreak of viral pneumonia (COVID-19) in Wuhan, China. At present SARS-CoV-2 is widespread all over the world causing an increasing number of infections and deaths. On March 11th, 2020, the World Health Organization (WHO) declared the infection a pandemic.

What we know:

- Fever and respiratory symptoms (cough, shortness of breath or dyspnea) are the most common clinical manifestations.
- The virus SARS-CoV-2 uses the receptor angiotensin-converting enzyme 2 (ACE2) to enter human cells which was found to be highly expressed not only in respiratory tract, but in gastrointestinal epithelial cells too.
- A significant proportion of SARS-CoV-2 patients has diarrhea, nausea, vomiting and/or abdominal pain even before or without respiratory symptoms (2-18%).
- The time from onset to admission is greater among patients with digestive symptoms than among those without. Moreover, as the severity of the disease increases, digestive symptoms become more pronounced
- It is recommended monitoring patients with initial GI distress, as the monitoring will allow for earlier detection, diagnosis, isolation and intervention.
- Although direct droplet and airborne transmission during procedures that generate aerosols are the main routes of transmission, fecal excretion with environmental contamination might contribute to viral transmission as well.
- Viral RNA is detectable in stool of patients with suspected coronavirus (29-53%); it is now clear that the virus sheds into the stool.
- Viral gastrointestinal infection and potential fecal-oral transmission can last even after viral clearance in respiratory tract.
- Prevention of fecal-oral transmission should be taken into consideration to control the spread of the virus.

COVID-19 and MICROBIOTA

- Although some studies have shown that - by modulating intestinal microbiota - it is possible to reduce enteritis and ventilator-associated pneumonia, at the moment there isn't any clinical evidence that the same procedure might play a therapeutic role in the treatment of COVID-19.
- Targeting gut microbiota could be a new therapeutic option or an adjuvant therapeutic choice.
- In early February both the China's National Health Commission and the National Administration of Traditional Chinese Medicine recommended probiotics in

patients with severe COVID-19 infection in order to prevent possible secondary bacterial infections. This position proves that the Chinese Government and the medical staff recognized the important role of gut microbiota in COVID-19 infection.

- Currently available data shows a reduction of Lactobacilli and Bifidobacteria in Covid-19 infections.

FAECAL TRANSPLANTATION

- SARS-CoV-2 can be transmitted with stool for a long period. This might be a considerable problem in case of fecal transplantation. In order to prevent SARS-CoV-2 transmission, it is necessary to review the current screening measures.
- Before each donation, physicians should evaluate whether the donor presents any sign of infection. Should this be the case, they should either be rejected or tested with RT-PCR assay for SARS-CoV-2.
- In endemic countries, the RT-PCR assay should be performed to all donors. Alternatively, donor stools should be preserved and quarantined for 30 days before use, and released only if the donor has not developed symptoms.
- Biobanks should check the health status of the donor before using frozen feces, according to local epidemiology, to avoid further potential spread of SARS-CoV-2.

COVID-19 and LIVER INJURY

- A liver disfunction during COVID-19 infection has been reported. The most common feature (14-53%) is represented by elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) accompanied by slightly elevated bilirubin levels, with normal levels of gamma- glutamyl transferase (GGT). In severe cases it is possible to observe lower levels of plasmatic albumin (2.6 – 3.09 g/dL), in particular during the second week of infection.
- The liver injury occurs more often in the severe COVID-19 infection than in the mild case. More than one mechanism can lead to liver injury during COVID-19 infection. Current evidences suggest that the COVID-19, as the SARS-CoV, uses the ACE-2 receptor to infect its target cells; this receptor is highly expressed in the cholangiocytes, to a comparable level of alveolar type 2 cells in the lung, while is less expressed on hepatic cell surface. These findings suggest that the liver injury that occurs in the COVID-19 infected patients could be caused by the direct damage by the virus to the bile duct cells, rather than liver cells. Another mechanism suggested is the drug-induced hepatotoxicity related to the antiviral therapies (such as Lopinavir/Ritonavir combination), antibiotics and steroids. The role of the inflammatory cytokines storm and the hypoxic damage, secondary to the lung disfunction, have also been suggested to explain the liver injury, in particular in the severe cases of COVID-19 infection.
- Currently, few data are available regarding the outcome of the COVID-19 infection and the immunosuppression related to liver transplantation. Those patients have

to be closely monitored due to the known higher rate of infection due to the iatrogenic immunosuppression. Quin J. et al. described a case of a perioperative COVID-19 infection in a young liver transplant recipient; the authors underlined the therapeutic paradox in these patients: an insufficient immunosuppression can lead to organ rejection, while excessive immunosuppression can result in more severe infection, including the COVID-19 infection. A donors and recipient screening for COVID-19 is advisable to prevent procedure related complications and the spread of the COVID-19 infection.

- Between 2-11% of COVID-19 infected patients has an underlying chronic hepatic disease. The real impact of the COVID-19 infection and mortality rate has to be strictly evaluated and monitored over time in these patients, as they have lower immune function and worst outcomes from acute respiratory distress syndrome than the rest of the critically ill population, as previously demonstrated for the SARS-CoV infection.

COVID-19 and Inflammatory Bowel Disease

- In order to avoid the spreading of SARS-CoV-2, also people affected by IBD have to follow the behavioral rules provided by the Institutions.
- The higher risk groups are listed below:
  - Adults over 60, especially men.
  - Individuals with underlying pathologies such as heart disease, lung disease (including asthma), diabetes, chronic kidney disease, chronic liver disease, endocrine and metabolic disorders, neurological, neurologic and neurodevelopment conditions; the group doesn't include inflammatory bowel disease.
  - Pregnant women or women who had a recent pregnancy.
  - Individuals with weakened immune system.
- As smokers are more likely than non-smokers to contract the COVID-19, more attention should be given to this group of patients. This is probably related to the fact that tobacco increases the gene expression of angiotensin converting enzyme (ACE 2), i.e. the binding receptor for the virus.
- Since COVID-19 might manifest itself with gastrointestinal symptoms, in case of suspected flare-ups, it is recommended to evaluate the possibility of an atypical infection by SARS-CoV-2.
- It is recommended to encourage telemedicine in order to reduce hospital admissions and to prolong the time of administration for stable patients treated with biologics.

<u>Measures for IBD patients</u>

- Patients should not change the existing therapy on their own, since the drugs used for IBD avoid any bowel inflammation, prevent complications and reduce hospital admissions.
- Patients treated with mesalamine, or other aminosalicylates, do not need to take any additional precautions more than what the Authorities have recommended.

- Patients on immunosuppressants or biologics/biosimilars are encouraged not to travel and gather in crowded places.

Updates and recommendations regarding drugs used for IBD treatment

- The start of immunomodulator/immunosuppressive therapy should be postponed on an individual risk assessment.
- Patients in therapy with steroids (prednisone/prednisolone) have to take further precautions, such as avoiding travels, movements and interpersonal contacts. Moreover, tapering the dose, whenever possible, is recommended.
- Immunomodulators like thiopurines tend to inhibit the body's immune response to viral infections, but their use should not be suspended.
- In patients treated with biologics, such as adalimumab, infliximab, golimumab, ustekinumab and vedolizumab, the adjustment of the therapy depends on the risk of infection, relapse risk and progression of the bowel disease.
- Immunomodulators and biologics have a rather long half-life; therefore, their interruption is not useful in the immediate future.
- It is possible to postpone the administration of biologics to patients with a stable disease for more than 1 year. More specifically, if fecal calprotectin and other biomarkers are normal, the administration of infliximab can be postponed for a period of not more than 10 weeks, while vedolizumab can be postpone for not more than 4-8 weeks. However, keeping the original schedule is still the best option.
- Randomized controlled trials, if already started, should be carried forward only for patients with no therapeutic alternative available. Moreover, patient access to hospital should be minimized.
- The switch from an intravenous therapy to a subcutaneous one is not recommended since it would increase the chance of losing response. However, if a patient needs to start a new therapy the subcutaneous drugs are preferred, in order to limit hospital accesses.
- It is unknown whether patients treated with biologics or immunosuppressant might have a worse development of the respiratory disease. The actual knowledge of COVID-19 does not suggest a suspension of the therapy, since the odds of a flare-up, even severe, are far higher than those of contracting a severe form of SARS-CoV-2.
- A Chinese group reported on The Lancet their experience (from Jan 2020 to early Feb 2020): they suspended the administrations of biologics and immunosuppressants to the 318 patients enrolled in the Chinese Regional Medical Center for IBD in Wuhan. There are no data regarding the possible repercussion of the suspension on the history of the disease, but it is a fact that none of the patients resulted positive to SARS-CoV-2.

Therapeutic approach in COVID-19 positive patients

- Biologics and immunosuppressants should be suspended in patients affect by severe infection from SARS-CoV-2, while in other patients this precaution is not necessary.

Endoscopy and IBD

- Endoscopic procedures should be performed only in patients with moderate-to-severe intestinal symptoms, while regular endoscopic follow-up and screening should be postponed. It is important to guarantee rigorous hygiene conditions for every endoscopic procedure, as per national guidelines.

COVID-19 e CELIAC DISEASE

- There are no studies that specifically analyze the risk for people affected by the celiac disease.
- They are not part of high risk groups, however around 30% of celiac patients might have hyposplenism; since this condition is not normally evaluated, in order to prevent any accentuated risk these patients are recommended to follow the established guidelines for people with an higher risk of infection.

COVID-19 and COLORECTAL CANCER SCREENING

- COVID-19 epidemic is causing a reorganization and redefinition of the services provided by the regional health system. Therefore, according to the Italian National Observatory of Screening (ONS), while it may be necessary to reduce the screening tests of first level (fecal occult blood test), it is important to always carry out the second-level diagnostic process among people who tested positive to the first-level tests. With this regard, it is important to consider that an effective screening program is primarily based on the possibility to promptly treat all the positive cases detected with the colonoscopy. However, in the emergency scenario of Covid-19, the access to surgery may not be guaranteed. Surveillance colonoscopies should be postponed according to physician recommendations.
- As the COVID-19 emergency scenario evolves on a daily basis posing new challenges to the health system, the existence of the conditions to provide the screening service across the country may change and thus need to be closely monitored.

COVID-19 and GASTROINTESTINAL ENDOSCOPY

- Endoscopy is a risky procedure of exposure and subsequent infection of healthcare personnel. This risk is not limited to upper endoscopy procedures, because of the possible several routes of SARS-CoV-2 transmission: person-to-person, respiratory droplets, aerosol generated during endoscopy and the possible fecal-oral transmission. This could be even more relevant given that the virus transmission can occur during the incubation period in asymptomatic patients.
- To prevent the transmission of the virus in endoscopy centers and to promote a rational use of personal protective equipment (PPE), we summarize and recommend the following infection prevention and control workflow in digestive endoscopy during current pandemic.

Risk stratification and patient management

- GI endoscopy units should strongly consider temporarily postponing elective, non-urgent endoscopy procedures, according to local human resources and local policies that may depend on the regional/national guidance regarding the pandemic. The indications include:
    - upper gastrointestinal bleeding, acute cholangitis, foreign body, and obstructions.
    - care (initial diagnosis, biopsy, staging, palliation of biliary and luminal obstruction) of cancer patients may also be considered urgent.
- Accurate triage (medical history, contacts with suspicious or confirmed cases of COVID-19) 1 day prior to endoscopy (by phone preferably) and on the day of endoscopy.
- All patients entering in the endoscopy unit should be invited to wear surgical mask. The high risk patients should wear surgical mask and gloves, until the beginning of the exam.
- Check the patient's body temperature before entering in endoscopy.
- Consider contacting patients at 7 and 14 days to ask about any new diagnosis, or development of COVID-19 symptoms.

LOW RISK patient	No symptoms (e.g., cough, fever, shortness of breath, diarrhea) No history of contact with COVID-individual
HIGH RISK patient	Presence of symptoms with no history of contact with COVID-19-positive individual No symptoms but contact with COVID-19-positive individual At least one symptom + contact with COVID-19-positive individual

Table 1. Risk stratification for potential COVID-19 infection in patients requiring gastrointestinal endoscopy

Standard precautions for healthcare professionals

- Stocks of standard and enhanced Personal Protection Equipment (PPE) are limited and need to be prioritized. To conserve PPE and limit potential exposure, only essential personnel should be present in the endoscopy room.
- Work at individual working station and avoid sharing workstation items and equipment.
- Hand hygiene (water and soap or alcohol-based hand rub) during patient care

respecting the 5 fundamental moments and when the hands are visibly dirty or contaminated.
- During assistance, avoid touching surfaces to prevent both contamination of clean hands by environmental surfaces and the transmission of pathogens from contaminated hands to surfaces.
- Respiratory hygiene: cough by covering your mouth with a disposable handkerchief to be thrown as soon as possible (immediately after: hand hygiene) or, in its absence, coughing inside the crease of the elbow. Make the hydroalcoholic solution for hand hygiene easily available in all care settings.
- Contaminated waste and endoscopic devices should be disposed of using the specific local regulations related to high-risk waste
- The minimal composition of a set of PPE for personnel in endoscopy should be modified based on risk stratification.

Precautions in the endoscopic room for low risk patients

- Use surgical masks (if FFP2 masks are not available).
- The decision to use a respirator mask should be based on local availability of respirators and COVID-19 prevalence, recognizing that asymptomatic patients may shed virus.
- Wear a waterproof disposable gowns and take it off before removing the gloves and leaving the endoscopic room.
- Wear protective eyewear: goggles or face shield.
- Wear shoe covers
- Keep your hair tied and always wear an hair net.
- Before leaving the room, always use alcoholic gel for hand disinfection or if possible wash your hands.
- Personnel handling patients must wear new gloves before leaving the endoscopic room and not remove the mask.

Further precautions in the endoscopic room for high risk patients

- Use respiratory PPE: FFP2 mask/FFP3 mask
- Use two pair of gloves

Putting on and removal of PPE must be done as recommended (https://www.cdc.gov/hai/pdfs/ppe/ppe-sequence.pdf), using the buddy system to confirm that the PPE is correctly in place for those who are not familiar with gowning up and down (Figure 1).

Figure 1: Protocol for putting on and removing PPE. Additional recommendation: wear shoe covers.

Role of the negative-pressure room

- Negative room pressure is an isolation technique used in hospitals and medical centers to prevent cross-contamination from room to room. This technique is used to isolate patients with airborne contagious diseases
- Despite ASGE suggestions to perform endoscopic procedures in a negative-pressure room, in most endoscopy facilities around the world, this is not available.
- It would be advisable to urgently equip at least one endoscopic room with a negative-pressure system to be used for all patients with respiratory symptoms.
- When this is not feasible, we recommend performing endoscopy on patients

who are high-risk or positive for SARS-CoV-2 in negative-pressure rooms located outside of the endoscopy department or at bedside, as long as this space is properly equipped to perform any endoscopic procedure safely and properly.

Reprocessing of endoscopes

- Enveloped viruses such as SARS-CoV-2 can easily be inactivated by commonly used disinfectants having virucidal activity (EN 14885).
- All endoscopes should be reprocessed with a uniform, standardized reprocessing procedure.
- Disinfectants used for must be as follows: bactericidal, mycobactericidal, fungicidal, and virucidal against enveloped and non enveloped viruses.
- Reuse of any disposable GI endoscopic device is strongly discouraged.
- The most significant HCP contamination occurs during precleaning of the endoscope in the procedure room due to splashing from the air/water button. Follow the protocol to turn off the processor when replacing the air/water button with the credit card button.
- When all currently reprocessing guidelines are strictly followed, the risk of transmission of any kind of viruses is extremely rare to nonexistent.
- Additional precautions should be taken in the reprocessing of equipment, such as FFP2/3 masks, after endoscopy in confirmed COVID-19 cases.
- It is recommendable to do training sessions and personnel meetings on the importance of strictly following endoscope reprocessing policy.

Decontamination rules for endoscopy rooms

- The virus can remain viable and infectious in aerosols for hours and on surfaces up to days.
- No data are yet available on the virucidal efficacy of chemical agents against SARS-CoV-2. Therefore, the recommendations are based on studies done for other coronaviruses. SARS coronavirus is stable in feces and urine for at least 1 to 2 days, thus surfaces may be a possible source of contamination.
- For the disinfection of surfaces and patient-care equipment, we recommend the use of 1:100 dilution of household bleach and water.
- After an endoscopic exam in a SARS-CoV-2 positive patient
    - o In the case of negative pressure rooms, it is recommended to wait about 30 minutes before allowing the next patient to access, as small particles can remain suspended in the air.
    - o In the absence of negative pressure rooms, it is advisable to ventilate the endoscopic room with cleaner air than the outside and to keep it empty for at least an hour.

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Useful LINK

- http://www.sied.it/coronavirus

Written by:

Anna Colombo, Alessandro Aversano Scuola di Specializzazione in MAD di Trieste

Sara Melissari, Gherardo Tapete Gastroenterologia di Pisa

Revised by:

Bastianello Germanà, Santino Marchi, Fabio Monica (FISMAD Committee)

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