Management of Patients affected by EoE and other Eosinophilic Gastro-Intestinal Disorders during Coronavirus disease (COVID-19) pandemic.

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Introduction

In March 2020, COVID-19 disease became pandemic and, nowadays, represents a worldwide problem. Clinicians have to deal with this new entity, and continuing to provide the best care to patients with other diseases. In this setting, it is challenging to know if common indications dispensed to our patients remain valid .

The aim of this document is to provide a support for clinicians to make decisions about the management of eosinophilic gastrointestinal disorders (EGIDs). Information contained in this manuscript are produced by a team of experts on EGIDs, after revision of the available literature and collective discussion. We think that sharing these information can help clinicians to offer the best treatment to their patients, especially to those at higher risk of SARS-CoV-2 infection, in particular those with ongoing immunosuppressive therapy.

This document should be considered as an additional guidance and not substitutive of statements provided by international medical authorities such as the World Health Organization, the European and US Center for Disease Prevention and Control and Official National health care authorities, that must be prioritized.

As the knowledge on COVID-19 is rapidly increasing, also these recommendations could be updated or changed in parallel.

What are the EoE and the other Eosinophilic Gastrointestinal Disorders?

The Eosinophilic Gastro-Intestinal Diseases (EGIDs) is a group of disorders characterized by symptoms of gastro-intestinal dysfunction and eosinophilic inflammation of a segment of the digestive tract, without other causes of eosinophilia. The most common disorder, is represented by Eosinophilic Esophagitis (EoE) that involves the esophagus. Eosinophilic Gastroenteritis (EGE), affecting stomach and/or small bowel, and Eosinophilic Colitis (EC) localized in the large bowel, are the other two entities.

The Covid-19 pandemic

The Coronavirus disease 2019 (COVID-19) is an ongoing pandemic, firstly identified in December 2019 in Wuhan (China). It is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Data published so far have shown that the infection runs mildly in about 80% of cases, but unfortunately, 14% of them develop severe disease and 6% experience critical illness.[1]

From an epidemiological point of view, the effects of the infection change according to the age of the affected person. The estimated mean mortality is about 2.3%, 0.2% between 10 and 40 years and more than 10% above 80y.o. patients. Children under 10y.o. seem to have lower risk of serious course or complications. The male gender presents a slightly increased risk. Smokers seem to have higher susceptibility to COVID-19, probably due to tobacco-related increased gene expression of the angiotensin converting enzyme (ACE-2), the entry receptor for this virus.[2]

Respiratory symptoms as dry cough, dyspnea and fever, are the most frequent clinical manifestations, but other district could be involved, including digestive system.[3]

Gastrointestinal manifestation of COVID-19

The SARS-CoV-2 virus uses the ACE-2 protein as a receptor, which is present not only in the respiratory epithelium but also in the gastro-enteric mucosa. So, as reported in other Coronavirus infections, gastrointestinal symptoms in COVID-19 are not uncommon (3-79%). They included anorexia (40-50%), diarrhea (2-50%), vomiting (4-70%), nausea (1-30%), abdominal pain (2-6.0%) and gastrointestinal bleeding (4-13.7%).[4–8]

With the exclusion of the non-specific symptom anorexia, diarrhea was the most reported, with a mean duration of 4.1 ± 2.5 days.[4] These symptoms may be present before and after the diagnosis, with and without respiratory symptoms. Some studies highlighted a higher proportion of gastrointestinal symptoms in severe patients compared to non-severe ones, but these data seem mostly related to anorexia.

Several studies demonstrated the presence of SARS-CoV-2 RNA in stool or anal/rectal swabs for a period ranging from 1 to 12 days and in 23% cases fecal excretion persisted after sputum excretion ends.[4] This aspect implicates that virus abundance in stool and stability in the environment, would arise the oro-fecal way as a possible way of transmission, with a cascade of considerations that could be applied on this (eg “Is rectal swab test necessary before discharge?”, “Could the toilet plume be a generator of infective aerosols?”).

Are EGIDs patients at higher risk for COVID-19 infection and severe course?

With the worldwide spread of COVID-19 and more than one million people affected, it is unavoidable that also patients with EGIDs have to deal with this pandemic.

As far as we know, patients with EGIDs are not at higher risk of COVID-19 infection or worst outcomes themselves. However, there are no data concerning this COVID-19 pandemic in EGIDs or studies from other Coronavirus outbreak as the Severe acute respiratory syndrome (SARS) and the Middle East Respiratory Syndrome (MERS), suggesting an increased risk in EGIDs patients.

Risk factors that should be considered in this group of patients are the old age, quite rare in EGIDs, and the presence of other comorbidities. Pathologies such as cardiovascular disease, diabetes, chronic respiratory disease, hypertension, malnutrition and cancer, have a significant impact on the course and the severity of the disease.[9]

Anyway, general measures released by international and national healthcare authorities should be strictly respected by EGIDs patients. Hand washing, avoiding mouth, eyes and nose contact, using mask and gloves, staying at home as much as possible, minimizing contact with other people, maintaining at least 1-2m distance one from each other, avoiding crowed places are good measures to prevent SARS-CoV-2 infection. It is important to ensure application of all the possible precautions to avoid contagion. For all the details, patients should refer to the specific national and regional regulations.

Do EGIDs therapies modify the risk of SARS-CoV-2 infection or worse outcomes of COVID-19 disease?

Most of EGIDs patients have EoE and among them, the majority are treated with PPIs and topical steroids. On the contrary, some of the EGIDs patients are taking immunosuppressive/ immunomodulating therapies, as systemic steroids, antimetabolites and biologics, that could potentially increase the risk of infection and/or complications related to COVID-19. Anyway, regardless of the type of treatment, the first recommendation to patients is to not modify their current therapy.

Drugs as PPIs, and swallowed topical steroids are safe and should be continued considering that they do not increase the risk of infection. Basing on available data, mostly derived from EoE and IBD patients, these drugs do not have systemic immunosuppressive action.

Budesonide has a low systemic bioavailability, thanks to high first-pass hepatic metabolism. Patients with an ongoing treatment with these drugs should continue it.

Considering oral systemic steroid therapy (prednisone/prednisolone) evidence is less clear. Steroid therapies boost the risk of viral, fungal and bacterial infections and some studies highlighted also an

increased rate of mortality related to these events. Thus, during COVID-19 pandemic, this kind of treatments could potentially increase the risk of contagion and/or worsen the outcome of SARS-CoV-2 infection. However, it should be also considered that oral steroids are usually used in cases of severe EGIDs, and their discontinuation may cause the recurrence of the disease with the logical consequence of increasing the risk of infection in a sick patient. Given these considerations, the continuation of systemic steroid, especially at high doses, should be carefully evaluated, taking into account risks and benefits. Treatment with steroids should be gradually discontinued if the patient presents a stable disease since a long time. When this is not possible, due to the severity of the disease or because of steroid dependency, steroids should be tapered to the lowest dosage able to maintain the remission of the EGIDs. Another possibility is to shift to a low bioavailability steroid. In parallel, patients must undergo all the possible measures in terms of self-isolation, avoiding contacts with people at risk and wearing protective equipment.

Immunomodulators such as thiopurines and methotrexate tend to inhibit the immune response. An increased risk of viral infections is the most frequent aspect related to these therapies, but also opportunistic bacterial and fungal infections can occur, mostly when intermediate/high dosage are used or in combination with steroids and/or biologics. Even if discontinuation is not suggested, it could be considered when these therapies are associated with significant myelosuppression. Anyway, immunosuppressed patients do not seem to have a higher risk of COVID-19 worse outcome due to their immunosuppressed state. Moreover, it should be considered that the complete washout from immunosuppressive therapies such as azathioprine and methotrexate require months, so the discontinuation is not useful in the short term.

Monoclonal antibodies are an effective class of drug useful in some EGIDs with severe course or non-responders to conventional therapies. They block specific molecules involved in the inflammatory response, offering a targeted and focused effect compared to steroids and immunosuppressant. Biologics are associated with a higher risk of fungal or mycobacterial infections. Combination therapy of biologics with other drugs further increase this risk. Discontinuation is not advisable as a preventive measure to avoid contagion. Moreover, the washout period of biologics is counted in months, so their discontinuation is not associated to a rapid recovery of the immune system. A tailored decision with temporarily suspension based on specific risk of COVID-19 infection and recurrence/progression of EGIDs, should be taken. If ev infusion is scarcely accessible, postponing infusion to 4-8 weeks may be reasonable and does not seem to significantly increase the risk of relapse.

In case of confirmed or suspected COVID-19 infection, temporarily suspension of immunosuppressive/immunomodulatory treatments should be considered. As the majority of cases

of COVID-19 present mild course, in this setting, there is no reason to stop EGIDs therapy. When moderate to severe symptoms are present, discontinuation is advisable in order to avoid possible worsening of the disease course or interactions with other treatments. Anyway, single case evaluation and assessment of risk should be done and therapeutic management could not be generalized. For patients who do not require hospitalization, a carefully monitoring by telemedicine is advisable to prevent complications.

A new prescription of immunosuppressant therapy or a strengthening in dose of an ongoing immunosuppressive therapy should be delayed, if possible. If the patient requires the introduction of a immunosuppressant therapy, SARS-CoV-2 test should be included in the screening.[10]

Suggesting patients to a fast contact with the referring EGIDs center is mandatory in case of fever and other symptoms suggestive of COVID-19, or even in presence of EGIDs flare or recurrence.

Follow-up of patients and elective evaluations

Considering follow-up, avoiding ambulatory evaluations not strictly necessary is recommended. The available data elucidate that a high percentage of patients have been infected in hospitals. Also healthcare operators have a higher rate of contagion compared to general population.[11] For this reason is desirable that EGIDs with an ongoing treatment with immunomodulators, avoid unnecessary hospital appointments, limit as much as possible to go outside of their home, take advantage of a home delivery service for medicines, have access to a dedicated phone number for necessities and undergo to a surveillance program by telemedicine.

If patients have to come to hospital for unpostponable evaluation or therapeutic infusion/ procedure, intervention in order to minimize risk of contagion should be taken. All scheduled patients should be called the day before by healthcare personnel to confirm the appointment and should answer to a series of questions focused on the identification of a possible SARS-CoV-2 infection. A dedicated phone line should be available to patients to inform the healthcare personnel of any change in their clinical status. The day of the evaluation, a first checkpoint out of the hospital entrance should screen possible infected patients with questions (cough, fever, shortness of breath and myalgia in the previous 2 weeks), body temperature evaluation and exclusion of possible contacts with people with suggestive symptoms. In the day hospital unit and in the outpatient clinic, patients should maintain at least 2 m distance one to each other, avoiding gatherings. The use of surgical masks and gloves by patients is suggested.

Elective endoscopic procedures

Digestive endoscopy must be considered as a procedure at risk of virus transmission to health care personnel, both for the upper and lower tract. Reasons are related to aerosolized particles and possible oro-fecal transmission. Moreover, also healthcare workers should be considered at high risk to be affected by SARS-CoV-2 and may transmit infection to patients. For these reasons it is advisable to suspend ordinary outpatient evaluations, limiting access to emergencies or non-deferrable evaluations. Also in this contest, an accurate anamnesis and triage with specific questionnaires asking to declare any respiratory symptoms, contacts with people affected by COVID-19, is mandatory for a correct stratification of patients and a rapid identification of any suspicious cases. In suspected or confirmed cases, it is essential that the patient wears the surgical mask until the beginning of the examination.

Continuity of care with Telemedicine

With COVID-19 outbreak all the elective evaluations have been postponed when possible. Even if this is a good way to deal with SARS-CoV-2, the interruption of elective procedures and routine follow-up controls has caused disorientation and anxiety among patients.

Telemedicine has emerged as a critical technology that could play an important role in the management of patients in this setting it could help clinicians to keep in contact with patients, avoiding complications related to loss of follow-up and limiting the risk of transmission of COVID-19 among patients, families, and clinicians. Chinese centers have already tested the efficiency of this approach in this pandemic.[7]

It is advisable to encourage telemedicine and telephonic consultations, in order to reduce access to hospitals, to assure follow-up and monitoring of known patients, to prolong therapeutic continuity of medicines in order to minimize unsolved medical needs of our patients.

Secure EoE/EGIDs registry

COVID-19 pandemic has a severe impact on the management of chronic disease, as for EGIDs patients. There is a need to understand if the way clinicians manage these diseases have to change. A rapid accumulation of data of COVID-19 infections in this subgroup of patients is therefore mandatory in order to allow the development of specific clinical and therapeutic recommendations.

A platform to collect information on patients with a previous diagnosis of EGIDs, with highly suspected or confirmed COVID-19 infection, can be found by clinicians at the following link: https://redcap.clalit.co.il/redcap/surveys/?s=PHLW7EC8WD . We encourage practitioners world-wide to report all cases.

References

1. Risk assessment on COVID-19, 25 March 2020. Available at: https://www.ecdc.europa.eu/en/current-risk-assessment-novel-coronavirus-situation. (Accessed: 1st April 2020)
2. Cai, G. Bulk and single-cell transcriptomics identify tobacco-use disparity in lung gene expression of ACE2, the receptor of 2019-nCov. *medRxiv* 2020.02.05.20020107 (2020). doi:10.1101/2020.02.05.20020107
3. Pan, L. *et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study*.
4. Tian, Y., Rong, L., Nian, W. & He, Y. Review article: Gastrointestinal features in COVID-19 and the possibility of faecal transmission. *Aliment. Pharmacol. Ther.* (2020). doi:10.1111/apt.15731
5. Jin, X. *et al.* Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut* gutjnl-2020-320926 (2020). doi:10.1136/gutjnl-2020-320926
6. Wong, S. H., Lui, R. N. & Sung, J. J. Covid-19 and the Digestive System. *J. Gastroenterol. Hepatol.* **n/a**, (2020).
7. Mao, R. *et al.* Implications of COVID-19 for patients with pre-existing digestive diseases. *Lancet Gastroenterol. Hepatol.* **0**, (2020).
8. Gu, J., Han, B. & Wang, J. COVID-19: Gastrointestinal manifestations and potential fecal-oral transmission. *Gastroenterology* **0**, (2020).
9. Wu, Z. & McGoogan, J. M. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases from the Chinese Center for Disease Control and Prevention. *JAMA - J. Am. Med. Assoc.* (2020). doi:10.1001/jama.2020.2648
10. Zingone, F. & Savarino, E. V. Correspondence Viral screening before initiation of biologics in patients with inflammatory bowel disease during the. *Lancet Gastroenterol. Hepatol.* **1253**, 30085 (2020).
11. Wang, D. *et al.* Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA - J. Am. Med. Assoc.* **323**, 1061–1069 (2020).