COVID-19: A DIGESTIVE DISEASE!
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ABSTRACT
Since the first case of CoVID-19 pandemic has been reported in Wuhan in China, evidence of associated severe acute respiratory syndrome is well established and the disease is accepted as a primarily respiratory infection. However, current available data are supporting a gastrointestinal tropism with great implications at multiple levels in the course of this disease. The gastrointestinal tract appears in the heart of the strategy for management of infected patients from diagnosis to post-recovery isolation policies. This review highlights the digestive aspects of CoVID-19.

Keywords: ACE2, CoVID-19, Digestive, Endoscopy, Fecal transmission, Liver, Prognosis.

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INTRODUCTION
The 2019–20 coronavirus pandemic is associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). First identified in the city of Wuhan in Central China, CoVID-19 -which is the acronym of "coronavirus disease 2019"- was declared as a Public Health Emergency of International Concern in January, 30 2020 [1] and then characterized by World Health Organization as a pandemic on 11 March 2020. All ages are susceptible. Human to human contamination by the virus is well established by WHO [2]. CoVID-19 is primarily a respiratory infection with tropism to human airway epithelial cells [3] where the cellular receptor ACE2 is abundantly present [4, 5]. Mild or severe Pneumonia and acute severe respiratory illness are frequent respiratory complications [6]. The first commonly known agents of virus transmission are droplets generated by symptomatic patients in close contact when coughing, sneezing or talking [7, 8]. Are all of those elements mean that the gastroenterologists are not directly concerned by the CoVID-19 pandemic?

It’s certainly not true, and many studies assessed the impact of coronavirus disease on the gastrointestinal system at multiple levels. Firstly, it has been shown that patients with CoVID-19 might present atypically gastrointestinal symptoms at the onset of the disease when respiratory complaints are still absent [9, 10]. Also, strong data support fecal-oral transmission of CoVID19 [8]; it is currently admitted as a potential route of virus spread. Third level is that some authors associate concurrent gastrointestinal (GI) symptoms to the severity of the disease [11]. Last point is the detection of presence of virus ARN present in feces samples even after an apparent recovery phase [12]. Considering all those findings, the gastrointestinal tract appears in the heart of the strategy for management of patients with CoVID-19 from diagnosis to isolation policies. CoVID-19 outbreak raises also issues related to protection of healthcare providers in endoscopy.
rooms and sterilization of endoscopy tubes. This review will focus on the aspects of the “digestive” CoVID-19 disease.

Epidemiology and current status of the pandemic!

Coronavirus disease 2019 (COVID-19), first reported in December 2019 in Wuhan in China, has reached a pandemic level. The causative agent is SARS-COV2, from the Coronaviridae family, is characterized by a high mutation potential and elevated mortality rate [13]. The number of CoVID-19 confirmed cases has reached more than 3.04 million cases in 185 countries as of April 27, 2020 leading to 211,000 deaths [14].

GI symptoms in CoVID-19:

While respiratory symptoms are typically major complaints in patients with CoVID-19, many patients reported gastrointestinal symptoms like diarrhea, vomiting and abdominal pain initially or during illness course [15 - 17]. In first reports from Wuhan city, 2–10% of patients had gastrointestinal complaints [18 - 20]. At the beginning of outbreak in Iran, doctors reported an unusual increase by 20% of the admissions in gastroenterology department; the patients reported diarrhea, vomiting abdominal pain and melena [10] and common therapeutic agents were unusually inefficient. They were all tested positive for SARS-CoV 2 [10].

GI symptoms are associated with coronaviruses and in outbreak of 2002–03, diarrhea was present in 16–73% of patients with SARS [21]. The mechanism of gastrointestinal tropism is explained by the affinity to ACE2 abundantly expressed in the glandular cells of gastric, duodenal, and rectal epithelia [22]. ACE2 - which is a membrane protein and inactivator of angiotensin II- is used by SARS-CoV2 as cell entry receptor [4]. The complex SARS-CoV2-ACE2 is endocytosed inducing release of pro-inflammatory cytokines and cellular damages. The invasion of enterocytes expressing ACE2 by SARS-CoV-2 causes malabsorption, unbalanced intestinal secretion leading to diarrhea [23]. Furthermore, the coronavirus 19 itself may be at the origin of disorders of the intestinal flora [25].

Implications of digestive symptoms:

In comparison with patients without CoViD-19 digestive symptoms, the presence of CoVID-19 GI manifestations was associated to longer discharge delay and laboratory evidence of prolonged coagulation and higher liver tests [23, 25]. It was also established that abdominal pain is significantly associated with increase of the disease severity and may be considered as a clinical predictive factor of severe forms [25]. In some studies, diarrhea was also mostly reported in patients with severe disease [11]; nausea, vomiting and diarrhea were significantly frequent in the group of patients who had acute respiratory distress syndrome and required mechanic ventilation [26]. This clinical association was not significant in other studies [19, 16].

Detection of Viral ARN in feces and Evidence of fecal oral transmission of CoVID-19

In the first US case of novel CoViD 19, the patient presented diarrhea at illness day 6 and stool samples collected a day later were tested positive by rRT-PCR [27] confirming the presence of the virus particles in feces and highlighting the possible fecal transmission. Presence of viral RNA in feces has been reported in many studies even during recovery period of CoViD-19 pneumonia [22, 28, 29]. It was suggested that survival period of viral particles was longer in gastrointestinal system than in respiratory [29]. Regarding those findings, it was important to assess about risk of fecal transmission in order to reduce the spread of disease and prevent contamination of patients’ healthy family members and gastroenterologists when performing therapeutic or diagnosis endoscopies. Ong et al. established the risk of transmission in patient’s environment by collecting samples from
patient’s bathroom and toilet area. Samples from the toilet bowl’s surface, the sink (internal bowl) and the door handle detected the presence of SARS-CoV-2 while results were negative after cleaning [29, 30]. Toilets with poor sanitation may be a source of fecal oral transmission. Sharing toilets with CoVID-19 patients is not recommended even after discharge and recovery; they should be isolated in the following 14 days [29, 31]. It raises also the risk of contamination in asymptomatic patients and in pre-symptomatic period before respiratory symptoms are evident [29, 32, 33]. If there is no screening strategy, the failure to detect early this group of patients may contribute to continuous spread of the disease. For hospitalized patients, Xiao et al recommend PCR-test in feces routinely and maintain of transmission-based rules if results are still positive [22].

**Implications in endoscopy room:**

Gastroenterologists are required to establish clear algorithms and list of patients to reschedule. Unless in emergency cases (like acute gastrointestinal bleeding, acute cholangitis, foreign body retrieval...), endoscopy procedures should be postponed [34]. A list of prioritized procedures should be established. A screening of patients with risk of infection is recommended prior to endoscopy. Issues that should be investigated when patient is admitted are: recent travel to a high-risk area, medical history of recent fever, cough or dyspnea, or contact with an infected patient [23]. In Wuhan, screening CT scan was regularly performed before endoscopic procedures. Some centers opted for screening by IgM/IgG [35, 36]. The screening strategy model is certainly related to technical feasibility regarding accessibility and cost.

Considering the persistent fecal positivity by RT-PCR in recovering CoVID-19 patients, the timing of endoscopy is an issue. In this group of patients, except urgent cases, it seems preferable to perform that endoscopy at least 2 weeks after convalescence [35]. Some authors suggested stool testing as a risk stratification parameter [35].

If available, an isolated room with negative pressure should be dedicated to endoscopy [23, 35]. Wear of personal protective equipment (PPE) by gastroenterologists and nurses is mandatory. Staff members should be limited to minimal necessary for patient care and safety in order to minimize risk of healthcare exposure and optimize use of PPE. Other measures are recommended for patients with urgent indications for endoscopy including: reduce overcrowding and waiting times, wearing surgical masks and respect of hands hygiene rules and social distancing with at least 1 to 1.8 meters between patients in waiting rooms [35].

Like SARS CoV1, SARS CoV 2 is an enveloped virus inactivated by disinfectant agents with antiviral activity [23, 35, 37]. According to this, current protocols and existing guidelines seems efficient in reprocessing of scopes and endoscopic accessories [35, 38]. High level disinfection is indicated for scopes and sterilization for “critical” accessories [23, 39]. All surfaces in endoscopy room should be deeply cleaned daily with general disinfection.

Regarding biopsy specimen, the French Society of Digestive Endoscopy (SFED) recommended the use of formal in order to inactivate the virus in samples sent for histological study [40]. Tele-health is a good option for patients’ follow-up; it’s an opportunity to notify the development of recent CoVID-19 symptoms in the 14th days following endoscopic procedure and if yes, advise the staff who was possibly in contact with the infected patient [35].

**CoVID-19 and gut microbiome:**

The place of gut microbiome in the CoViD-19 digestive disease has been highlighted by some authors. In some patients, a decrease in probiotics such as Lactobacillus and Bifidobacterium was reported suggesting an intestinal microbial dysbiosis [41]. Nutritional aspects are important in corrections of digestive disorders in CoVID-19. As a part of "Four-Anti
and Two-Balance" strategy, medical staff in Zhejiang Hospital recommended use of prebiotics or probiotics for regulation of intestinal micro-ecological balance, correction of intestinal microbiota disorders and prevention of secondary infection induced by bacterial translocation [41].

Lactobacillus plantarum is largely used in food and medical industries as probiotic microorganism [42]. With its probiotic properties, the strong antiviral activity against coronavirus infection in porcine epithelial cell of the intestine was demonstrated. IFN-λ3 in Lactobacillus plantarum suppresses enteric coronavirus infection in epithelial cells of intestine of piglets which could be an option for oral therapeutic antiviral agent [43]. Prescription of probiotics may be with great support to the immune system against the virus. A preprint suggested the role of bacteria Prevotella in CoVID-19 pandemy, but there is no clear evidence regarding this.

Liver manifestations in CoVID-19 disease:

Many studies have reported liver impairment in CoVID19 patients suggesting that SARS-CoV2 may affect hepatocytes and hepatic functions [24, 45, 47]. Authors reported elevated levels of alanine aminotransferase and aspartate aminotransferase with prolonged coagulation in infected patients [24, 45] with increased incidence of abnormal liver function in severe forms of the disease [24, 45] with increased incidence of abnormal liver function in severe forms of the disease [24, 45] with increased incidence of abnormal liver function in severe forms of the disease [24, 45]. A Chinese team from Shaanxi region concluded that critical illness was an independent risk factor for hepatic damage [46]. Liver injury might be explained by the abundant presence of ACE2 receptor in cholangiocytes [47] indicating a direct action on ACE2-positive hepatocytes responsible of hepatic dysfunction. Some authors suggested that mechanism of COVID-19 may be direct liver injuries due to a viral hepatitis [45], but post-mortem liver biopsies from infected patients showed microvesicular steatosis, -which is commonly found in case of sepsis [48]-, without viral inclusions in the liver [49]. Clinicians should pay special attention to patients with pre-existing liver disease. Because ACE2 gene is on the chromosome X, Pirola CJ et al. suggested clinical differences in the evolution of the disease in male patients with chronic liver disease compared to women [50]. Since ACE2 is expressed in low levels in the liver of women, severe liver injury may be prominent in men [50, 51].

CONCLUSION

There is no doubt that CoVID-19 is primarily a respiratory infection with a spectrum of complication leading to death. But, in SARS CoV2, digestive symptoms may be inaugural and associated with longer discharge and severe presentations of the disease. Viral ARN is present in feces of asymptomatic patients and hepatic and intestinal viral tropism is established because of the abundance of ACE2 receptors. Oral fecal transmission is a potential route of continuous virus spread even after recovery of pneumonia. Regarding all those elements, CoVID-19 is also a digestive disease with highly implications on prevention and management strategy.

ABBREVIATIONS:

SARS-CoV2: severe acute respiratory syndrome coronavirus 2.
ACE2: angiotensin-converting enzyme II.
GI: gastrointestinal.
CT: computed tomography.
IFN: interferon.

DECLARATION OF INTERESTS: None
KEY POINTS:

1- The gastrointestinal tract appears in the heart of the strategy for management of patients with CoVID-19 from diagnosis to isolation policies.
2- Digestive symptoms may be inaugural and associated with longer discharge and severe presentations of the disease.
3- Oral fecal transmission is a potential route of continuous virus spread even after recovery of CoVID-19 pneumonia.
4- Hepatic and intestinal viral tropism is the result of the presence of ACE2 receptors. ACE2 repartition may explain sexual dimorphism in CoVID-19.

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