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### GASTROINTESTINAL MANIFESTATIONS OF COVID-19 INFECTION

*In case of the severe acute respiratory syndrome – caused by the COVID-19 viral infection – gastrointestinal involvement seems to be among the most important extrapulmonary manifestation. Its significance beyond different symptoms is underlined by the fact, that ACE2 receptors are available in different segments of the gastrointestinal tract, with changing density, that may play a role in the activation as well as the spread and dissemination of the infections. The different digestive organs show different involvement, the most frequent symptoms are diarrhoea, nausea, loss of appetite, dysgeusia – loss of smell –, and anorexia. It is important to emphasize, that digestive complaints and respiratory symptoms are not always accompanying each other and may also differ in time course. The most important aspects are discussed below.*

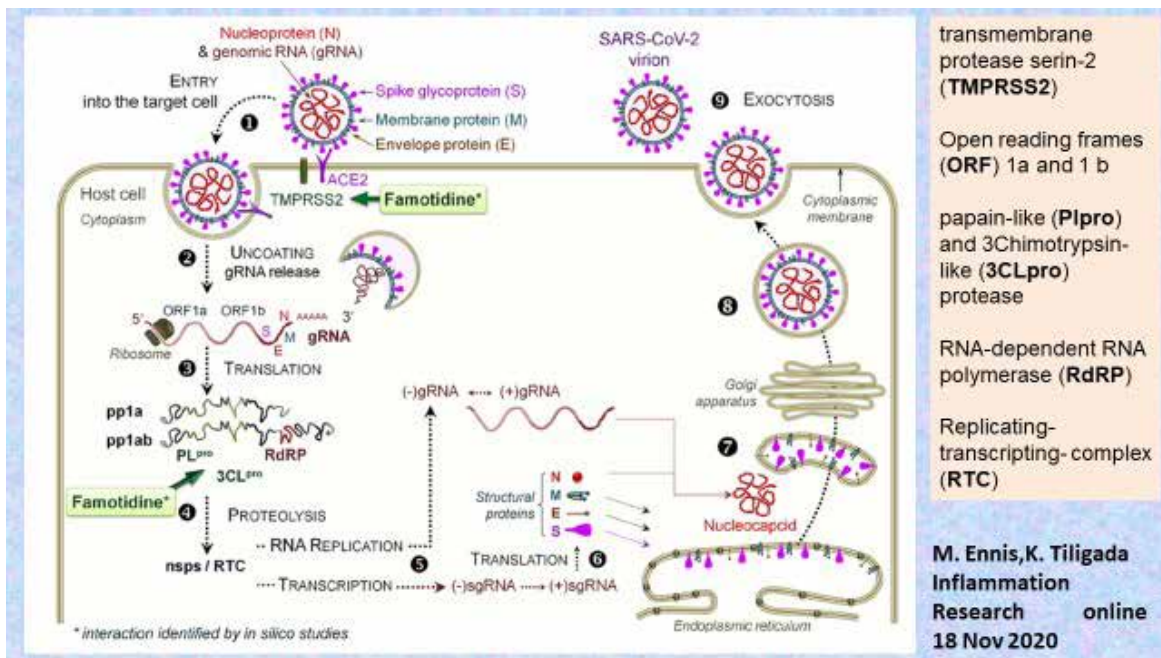
#### Introduction

The COVID-19 disorders caused SARS-CoV-2 virus was declared by WHO as pandemic in March 2020. The SARS-CoV-2 is a single-stranded RNA virus, and the name comes from the words „serious acute respiratory syndrome”. This virus is member of the family of coronaviruses, similarly to the virus caused an epidemic in 2002 to 2004 in China and to the virus caused epidemic in the Middle East in 2012, named MERS. The new virus is in close relation with viruses can be found in bats, therefore the possibility of zoonotic origin is rather probable (1). As it was experienced during the last one-and-half year, this virus is highly infectious, mainly in form of aerosol, entering the respiratory tract, but could also be isolated from the faeces of patients, although faeco-oral spreading has not been proved yet.

#### Gastrointestinal manifestations

The predominant symptoms are of course respiratory, according to large cohorts, 71% of patients admitted to hospitals have fever, cough is present in 68,9% accompanied by dyspnea in 71,2%, further frequent symptoms are myalgias, joint pain, headache, chronic fatigue, then follow abdominal complaints, like pain, cramps, nausea, diarrhoea, vomitus. Around 30 % of patients suffer from digestive complaints, mainly along with respiratory symptoms, only 4% of patients were found to have solely gastrointestinal problems. (2).

In a Chinese publication in 20 % of the patients, diarrhoea was the first symptoms, lasting sometimes for 2 weeks, with daily 5-6 loose stools. Fever appeared in two third of the patients, who in general appeared some days later and the disease lasted somewhat longer. In the faeces the virus could be isolated or demonstrated by PCR in more than 70% (3). In certain observations the faecal viral positivity persisted beyond the respiratory symptoms. On the other hand, in some cases the viral positivity in the faeces was not accompanied by any digestive symptoms (4). As further complaints, anosmia – loss of smell – in 52,7% and dysgeusia – loss of taste – in 43,9% were observed (5). Very probably a cause for these is neuropathy provoked by COVID-19 infection in the olfactorial epithelium, where angiotensin convertase 2 receptors are available for viruses entering the region of bulbus olfactorius. The exact mechanism of the viral invasion is well known and shown on the figure, with the most important components listed on the right side.



From: Ennis M – Tiligada K: Histamin receptors and COVID-19. Inflammation Research <https://doi.org/10.1007/s00011-020-01422-1>

The spike protein on the surface of the virus connects to the ACE 2 receptor, where the type 2 transmembrane serin protease (TMPRSS2) will cleave the receptor and activate the spike protein, thus the virus enters the target cell, and the infection completes. In the lung this process leads to the hyperimmune reactions of the host, the cytokine storm, occurring as systemic inflammatory response syndrome (SIRS). In the digestive tract the mechanism of infection is very similar, as ACE-2 receptors and connected viral nucleocapsid proteins could be demonstrated in the mucosa of stomach, duodenum and rectum respectively (6), and as it has already been mentioned the virus could be identified in the stool of great percentage of COVID-19 patients. This fact otherwise proves also, that gastric acid – especially if pH >3 cannot destroy the virus itself! The presence of ACE 2 receptors was also studied in the colon mucosa and terminal ileum mucosa of patients suffering from inflammatory bowel disorders, where its density showed some parallelism with disease activity (7).

Among the symptoms in the upper GI tract, superacidity is less common, esophageal involvement is unusual, probably because of the small number of ACE2 receptors found in the mucosa of the esophagus, if compared with intestinal tract. On the other hand, loss of appetite, anorexia is rather common, the causes however might be more complex, nausea attached to toxic conditions, general fatigue, side effects of several drugs – analgesics, antipyretics – can also play a role. And severe loss of bodyweight in patients on prolonged ventilation was rather common. Among the first clinical observations at the beginning of the pandemic, it was stated, that those taking famotidine – a modern H2 receptor antagonist – because of any other cause at the beginning of their COVID-19 infection showed less aggressive course of the disease. Such observation among those taking proton pump inhibitors could not be confirmed (8). Exact and convincing explanations for this are yet awaited. Both clinical studies and laboratory investigations have started.

Along with the beginning of the pandemic, several practical questions arose, regarding the controls and continuous treatment modalities of those patients suffering from chronic, progressive diseases that would need regular clinical controls! Among disorders of the digestive system a typical example for this problem is the way of treatment those with inflammatory bowel disorders – ulcerative colitis and Crohn's disease.

Obviously, compliance with isolation rules, but necessity of combined and complex forms of treatment in order to maintain longer lasting clinical and endoscopic remission was a difficult task. Especially because hospitalization, or a surgical intervention because of a severe relapse could lead to several difficulties. To give correct answers for these questions an international SECURE-IBD registry was initiated. The first publication elaborating the data of the first 525 involved patients confirmed a mortality rate of only 3%, with risk factors as age, steroid treatment and comorbidities, however biologic monotherapy seemed not to increase the risk of a severe course (9). A next analysis of data of 2280 patients confirmed, that regarding the necessity of intensive therapy, need for ventilation and mortality the steroid treatment of IBD was of highest risk. 19 % of the patients on previous steroid treatment had a more severe COVID-19 disease course, while among those on anti-TNF monotherapy or anti-interleukin 12/23 therapy the percentage of severe course turned out to be only 2-3% (10). It seems that IBD in remission with a correct treatment – including also immunosuppressive drugs – is not accompanied with higher risk of COVID-19 infection.

During acute COVID-19 infection moderate elevation of liver enzymes – transaminases – may occur, but autopsy experiences confirmed, that liver damage was in majority due to shock or MOF, but no signs of special viral hepatitis were observed. On the other hand, however, in cases of chronic liver disorders rapid deterioration, ACLF-like syndrome could be observed, and risk of mortality in Child B and C patients could rise by 60 % (11). During pandemic several other problems regarding chronic liver patients had to be discussed, such as increasing consumption of alcohol, use of drugs, reduced controls of disease progression – among others regular checking of esophageal varicose veins – radical reduction of the number of organ donors and transplantations. Regarding a new drug for the treatment of COVID-19 infection, remdesivir, it was found, that it's use might cause complications if the liver transaminases are substantially elevated (>5x UNL) (12). The use of a dexamethason increases the risk of Hepatitis B virus relapse (13). On the other hand, no higher risk of COVID-19 infection among those living with transplanted liver could be confirmed (14).

The occurrence of acute pancreatitis is not typical during COVID-19 infection, if elevated pancreatic enzymes are observed, it is probably part of the multi-organ failure (MOF) condition. Interestingly camostat mesylate, used as serin protease inhibitor in Japan for the treatment of acute pancreatitis is able to also inhibit TMPRSS2 and thus might also inhibit the viral penetration in the human respiratory epithel, studies in progress (15).

Upper gastrointestinal bleedings do not occur more frequently in COVID-19 infected patients, interestingly neither the number of stress ulcers among patients on ventilation did not increase, but that is probably the result of widely used proton pump inhibitors (16). Lower gastrointestinal bleedings in forms of haemorrhagic colitis, or ischaemic colitis were described in some patients, and it is possible, that the relatively frequently observed elevation of d-dimer values might accompany not only microembolisation in the lung but also mesenteric ischaemia (17).

In general, the number of endoscopic investigations and among them digestive endoscopy reduced dramatically during the first months of epidemic! The general fear of dissemination and the rapid growing of the overload of hospitals made this understandable, however also the questions arose, how many important investigations will delay leading to irreversible progression of tumorous disorders! The management of urgent endoscopic investigations had to be performed with very special caution, since during upper endoscopy the aerosol formation is strong and doctors, assistants, nurses, other patients have to be defended from the danger of infection! On the other hand, really urgent cases have to be solved immediately. Therefore, different endoscopic societies developed guidelines for how to make distinction between more and less risky endoscopic procedures as well for the more precise categorization of urgency! The most urgent cases are severe upper gastrointestinal bleedings, infective cholangitis caused by stone in the common bile duct, tumorous obliterations in the digestive tract, foreign body in the esophagus, causing obstruction, well defined suspicion for malignancy and finally all cases for urgent surgical interventions (18). It is clear, that during urgent endoscopy in addition to the use of FFP 2/3 mask the use of face shield, headgear, double

cape, footbag and double protective gloves is important. However, this needs a very disciplined way of for the organization of dressing and undressing. The members of the team may communicate less easily, and due to inconveniences have to be changed after maximum 3 hours (19)! Different forms of breath tests leading to aerosol formation were also not performed in several institutions, to defend the assistants and reduce the danger of dissemination, but it needs the development of new methods to replace the diagnostic needs. For the performance of elective, routine endoscopic procedures a good possibility is the negative PCR test immediately – 24-48 hours – before the procedure. It is important to emphasize, that colorectal screening colonoscopies in case of FOBT positivity should be continued to avoid irreversible delays in the detection of early-stage tumors!

As last, drugs used during the treatment of COVID-19 disease may also have gastrointestinal side effects, such as antibiotics, anti-inflammatory drugs may contribute to diarrhoea, may also cause elevation of liver enzymes etc. Steroid and dexamethason treatment in intensive care units may cause upper gastrointestinal bleedings due to erosions and ulcers, for the prevention the use of proton pump inhibitors is recommended, despite those observations that found less aggressive course of COVID-19 infection in patients taking histamin 2 receptor antagonist – famotidine –, but for the prevention of bleeding from stress ulcers, PPI is the proper solution. From this group of drugs the least interactions are awaited by using pantoprazol or rabeprazol. Along with SARS-CoV-2 infection changes in the bacterial flora of the gut, dysbiosis has also been observed, but the use of probiotics could not show any benefit (20).

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