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Review article

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COVID-19 - MORE THAN RESPIRATORY DISEASE: A GASTROENTEROLOGIST'S PERSPECTIVE

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Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV2) outbreak is the most dramatic event since World War II. Originating as a cluster of unexplained cases of pneumonia, it turned out that this viral disease termed COVID-19 is not only a respiratory infection, but a systemic disease associated with a number of extrapulmonary complications. One of the medical disciplines that is strongly affected by this viral infection is gastroenterology. COVID-19 causes in some patients typical symptoms of enteritis such as diarrhea or abdominal pain. There is also evidence that this infection may lead to liver and pancreatic injury. Since the SARS-CoV2 virus was detected in stool, a fecal-oral route of transmission is possible. Moreover, viral receptor angiotensin converting enzyme 2 (ACE2) is highly expressed in the gastrointestinal tract and enables the invasion of the gastrointestinal epithelium as demonstrated *in vitro* and *in vivo*. COVID-19 pandemic has an impact on the daily practice and the workflows in endoscopy leading to a dramatic decrease of screening and surveillance procedures. COVID-19 impacts the therapy of patients with inflammatory bowel disease (IBD), particularly those using high doses of corticosteroids, immunosuppressive agents and biologics. Patients with preexisting liver disease, especially metabolic associated liver fatty disease (MALFD) with fibrosis or liver cirrhosis, are at high risk for severe COVID-19. As long as no active vaccine against SARS-CoV2 is available, gastroenterologists have to be aware of these problems that affect their daily routine practice.

Key words: *SARS-CoV2, pandemic, COVID-19, gastrointestinal manifestations, anti-inflammatory therapy, gut microbiota, endoscopy, inflammatory bowel disease, liver disease*

INTRODUCTION

In December 2019 in Wuhan (China), the first cases of "mysterious" pneumonia have been reported by health authorities. A novel beta-coronavirus named severe acute respiratory syndrome (SARS)-CoV2 was identified as the cause of the disease termed COVID-19. The SARS-CoV2 infection spread rapidly from China to almost all countries worldwide leading to the greatest pandemic outbreak since the Spanish flu in 1918. The World Health Organization (WHO) declared COVID-19 as a global pandemic on March 11, 2020 (1).

SARS-CoV2 as a member of the beta-coronaviruses is an enveloped single stranded positive sense RNA virus with an average diameter of 60 – 149 nm. SARS-CoV2 shares up to 80% sequence homology with severe acute respiratory syndrome coronavirus (SARS-CoV) and 50% with Middle East respiratory syndrome coronavirus (MERS-CoV), respectively (2). All these three viruses originated in bats as a natural reservoir and jumped to humans *via* different intermediate mammal hosts such as pangolin, civet and camel, respectively (3) (*Fig. 1*).

The development of the pandemic occurred in three stages: viral transmission from the intermediate reservoir to the humans; human-to-human transmission, and pandemic outbreak. The number of infections and death toll are daily increasing dramatically and the true numbers are undercounted (4). The recent updated evidence indicates that almost 4,923,969 persons were infected and 320,790 patients died from this infection. SARS-CoV2 infection represents the most dramatic human and health crisis since the World War II and places unprecedented strain on the health care systems worldwide. For control of the pandemic, different strategies have been developed such as the "Chinese approach" (very strict isolation of cities and individuals); flatten the curve (Germany; involving different levels of isolation, social distancing, using face masks in the public and widespread virus testing), and herd immunity (Sweden) (3).

CLINICAL SYMPTOMS OF SARS-CoV2 INFECTION

Human-to-human transmission occurs mainly through the respiratory tract, by droplets, respiratory secretions, and direct contact. The incubation period for the virus is between two and 14 days. The spectrum of SARS-CoV2-induced clinical manifestations ranges from asymptomatic cases through symptoms of common cold (headache, dry cough, fatigue, fever), progressing in some patients to interstitial pneumonia complicated by acute respiratory distress syndrome with a high mortality rate (5) (*Fig. 2*). The number of asymptomatic cases is significant, ranging

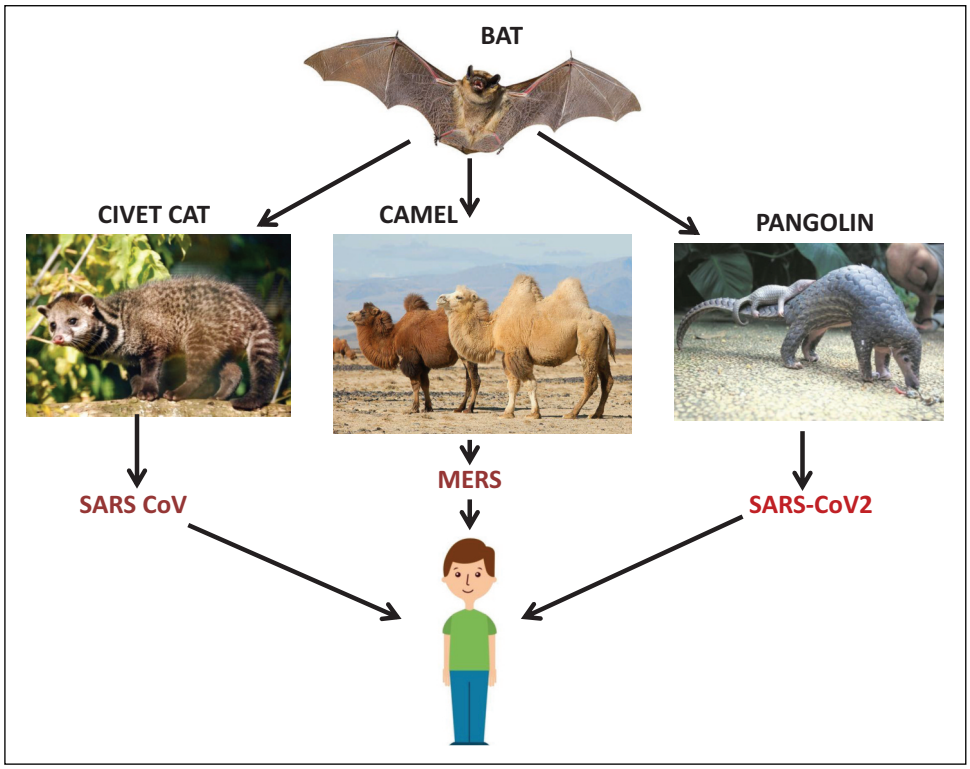

Fig. 1. Possible transmission of beta-coronaviruses, SARS CoV, MERS and SARS-CoV2 from bats to humans *via* intermediate hosts.

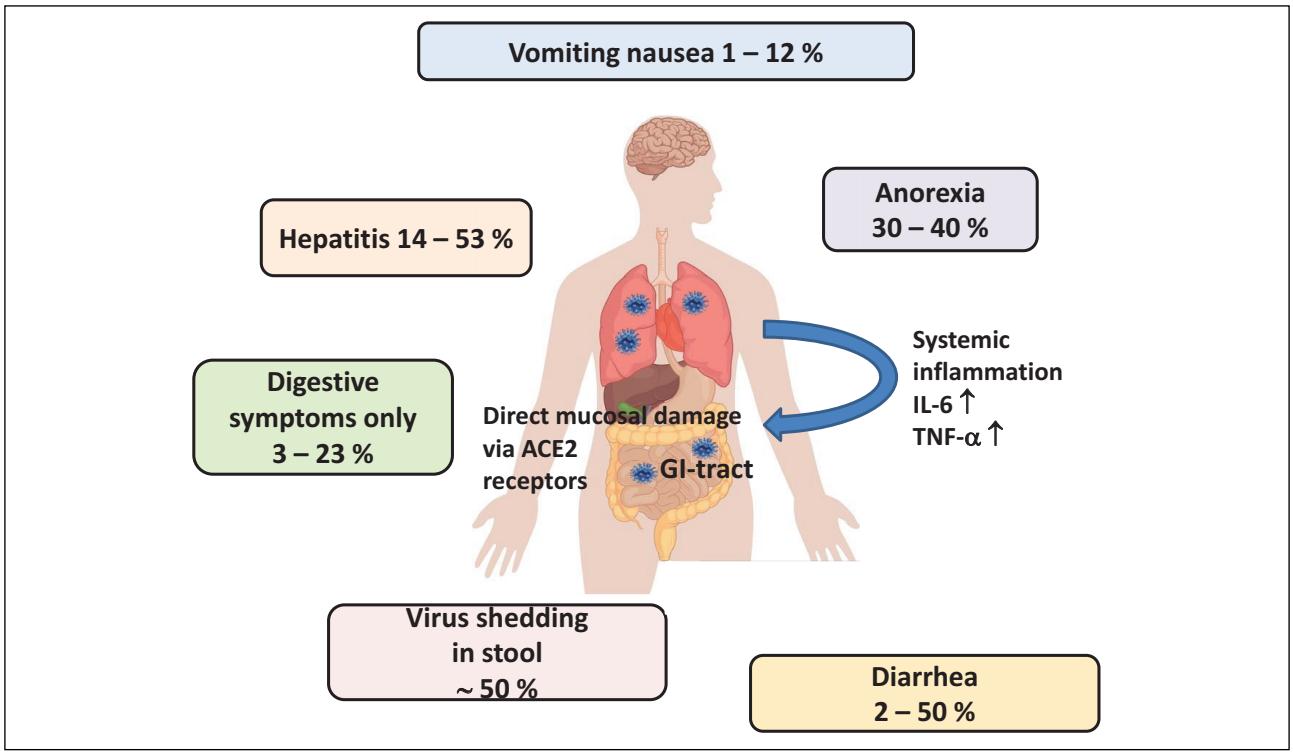

Fig. 2. Gastrointestinal and hepatic manifestations of SARS-CoV2 infection in humans.

between 20% and 50%, making the tracing of this disease very difficult (6). Moreover, SARS is already infectious before first symptoms appear (7). Therefore, the asymptomatic carriage of the virus could act as an important source of ongoing transmission.

COVID-19 is a systemic disease; many infected patients show extra-pulmonary symptoms including diarrhea, vomiting, smell and taste dysfunction. In a recent publication by Zhou *et al.* including 254 patients with SARS-CoV-2 infection, 83%, 38,6% and 26% of the patients complained of fever, cough and gastrointestinal (GI) symptoms, respectively (8). The mortality rate ranged from 1 – 10% due to the development of fatal pneumonia. Especially older people and patients with comorbidities such as hypertension, diabetes mellitus and coronary heart disease have an increased risk for fatal clinical outcome (9). The disease may lead to a number of complications such as acute respiratory distress syndrome (ARDS), arrhythmia,

shock, acute kidney injury, skin manifestations, coagulation disorder (particularly pulmonary embolism), neurological complications, acute cardiovascular problems, liver dysfunction or secondary infections (10-15) (*Fig. 3*).

Compared to adults, children appear to be less affected by COVID-19. In the pediatric population, asymptomatic cases or a mild course of the disease are much more common (16). However, a concurrent development of Kawasaki disease in children with COVID-19 disease has been described recently (17). These reports shed a new light on the pathogenesis of COVID-19 disease among children showing a higher risk for autoimmune diseases.

DIAGNOSIS OF COVID-19

Currently, diagnosis of COVID-19 involves the molecular detection of SARS-CoV2 by real-time PCR of viral RNA obtained from the oropharynx or nasopharynx (18). In computerized tomography, the SARS-CoV2-induced interstitial pneumonia shows up as ground glass opacity and patchy infiltrates in the chest. However, it is difficult to differentiate between pneumonia caused by COVID-19 and other pneumonia on chest CT alone (19). The definitive diagnosis should be based on a positive medical history of the patient (direct contact to SARS positive person), positive RT-PCR test of nasopharyngeal and oropharyngeal swabs and typical CT findings in the lungs.

The seroconversion takes place on about the 4th day after infection with a consecutive rise of IgM and IgG antibodies that may be detected by an enzyme-linked immunosorbent assay (ELISA) based on the recombinant nucleocapsid protein of SARS-CoV2 (20).

COVID-19 THERAPY

Due to the lack of an effective antiviral therapy, particularly an effective vaccine, the treatment of COVID-19 focuses so far on symptomatic and respiratory support. Recently, different antiviral therapeutic approaches have been investigated in several studies. The potential therapeutics target different steps of the viral infection including 1) interfering with angiotensin converting enzyme 2 (ACE2) receptor (hydroxychloroquine and chloroquine), 2) premature termination of RNA transcription (remdesvir), 3) blockade of protein processing (lopinavir and ritonavir) and blocking of the "cytokine storm" (interleukin-1 (IL-1) receptor antagonist - anakinra, IL-6 receptor antagonist toclizumab) (21). For the time being, a final assessment of these therapies is not possible, however, remdesvir shows promising results in the context of shortening the period of mechanical ventilation and of stay at the intensive care unit (ICU) (22).

Another promising therapeutic approach is the use of plasma gained from convalescent carriers of SARS-CoV-2 containing neutralizing antibodies that led to the clinical improvement of patients critically ill with COVID-19 (23).

Since no vaccine therapy exists so far, a number of off-label medications have been tested in different observational studies to reduce the severity of COVID-19 infection. Some potential candidates for the adjuvant therapy of COVID-19 include melatonin, famotidine, dipyridamole, cholesterol-lowering fenofibrate and benzofibrate and finally sildenafil, the phosphodiesterase-5 inhibitor (PDE-5) (24).

Especially interesting candidates are melatonin and famotidine that are used in gastroenterology. Melatonin shows potent antioxidant and anti-inflammatory activities that may reduce the overproduction of proinflammatory cytokines ("cytokine storm") observed during COVID-19. Especially elderly persons would benefit from this therapy, as the endogenous melatonin production is age-dependent and significantly diminished in older individuals (25).

Famotidine is a histamine H_2 blocker approved for the treatment of the gastroesophageal reflux disease. Recent data demonstrated that this gastric acid suppressant has powerful effects on the immune system, reducing the inflammation and pathological clotting. A recent retrospective trial performed by

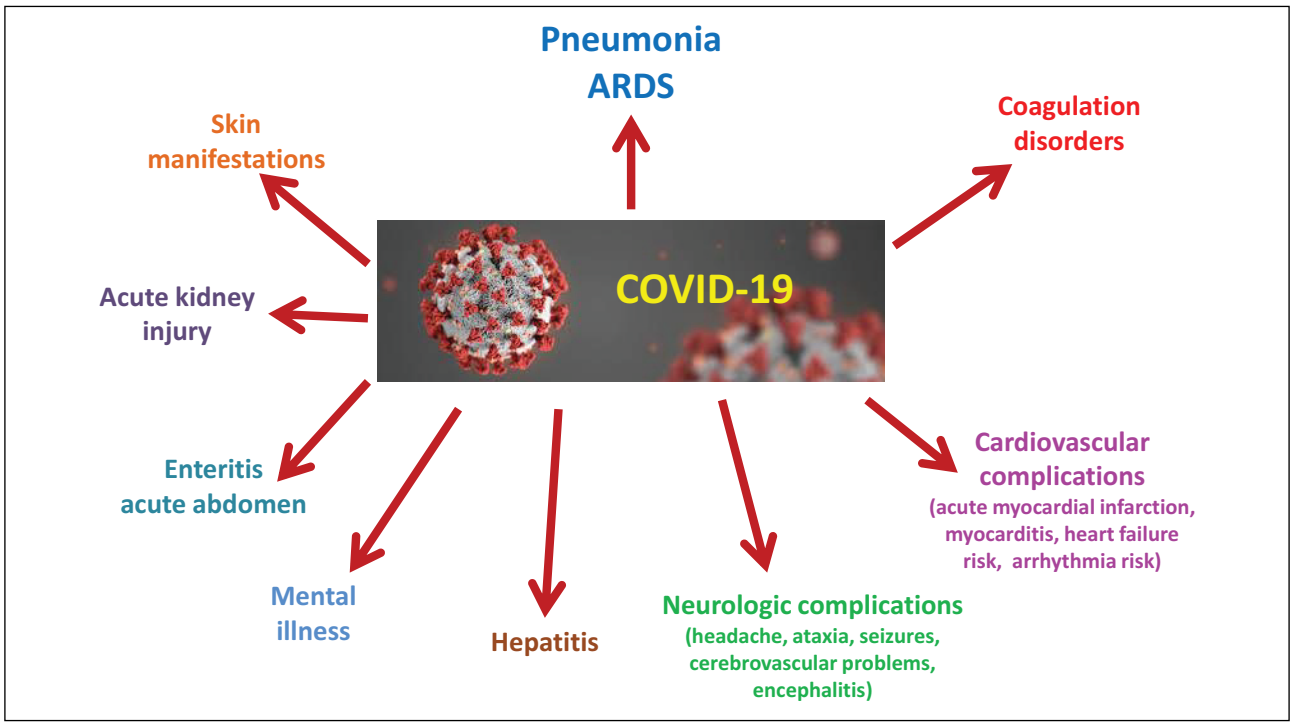

Fig. 3. Different clinical complications of SARS-CoV2 infection.

Freedberg *et al.* revealed that the use of famotidine was associated with a reduced risk for death or intubation. Interestingly, the proton pump inhibitors that are also powerful gastric suppressants did not show such beneficial effects (26). The explanation for these phenomena is the fact that famotidine, as histamine-2 receptor antagonist, inhibits an essential step for the viral replication due to the inhibition of 3-chymotrypsin-like protease (3CLpro) (27).

SARS-CoV2 AND GASTROENTEROLOGICAL MANIFESTATIONS

SARS-CoV2 outbreak exerts a very relevant impact on gastroenterology. Many patients with SARS-CoV2 infection exhibit GI and hepatobiliary manifestations. In different studies, the prevalence of GI manifestations ranges between 11.3% and 79.1% (*Fig. 4* and *5*). The most common symptoms include anorexia, nausea, vomiting, diarrhea, and abdominal pain (28, 29). Interestingly, the time from onset of GI symptoms to hospital presentation is delayed compared to respiratory symptoms (9 versus 7.3 days). As a consequence, such patients can be relocated mistakenly to the gastroenterological instead of the infectious ward (30).

One of the most common symptoms is diarrhea that may be present between 2 – 50% of cases as shown in previous studies. There is increasing evidence that the intestine may present another important target for SARS-CoV2 infection (31). The invasion of the virus through the GI-tract is possible due to the high expression of ACE2 in the intestinal mucosa that may be used by the virus as entrance gate for the invasion (32). Recently, Lamers *et al.* demonstrated in human small intestinal organoids (hSIOs) that enterocytes were readily infected by SARS-CoV2 virus. This was proved by transmission electron microscopy and RNA expression analysis (33). Moreover, Xiao *et al.* demonstrated the immunofluorescent staining for ACE2 and viral nucleocapsid in the gastric, duodenal and rectum mucosa (34). These observations indicate that the fecal-oral transmission could represent an additional route for the viral spread.

COVID-19 AND ENDOSCOPY

SARS-CoV2 outbreak has a dramatic influence on the daily practice of GI endoscopy. Patients scheduled for an endoscopic procedure need to be stratified individually according to risk of COVID-19 (low, intermediate and high risk). Low risk patients undergoing the endoscopic procedure show no symptoms of COVID-19 (cough, fever, shortness of breath), no contact to SARS-CoV2 positive person(s) and no stay in high-risk areas for COVID-19 within the last 14 days. Patients at intermediate risk may show symptoms (cough), but no medical history for contact with SARS-CoV2 positive persons or stay in a high-risk area. Patients with no symptoms, but medical history of contact with a SARS-CoV2 positive person or stay in a high-risk area are also at intermediate risk. Finally, high-risk patients include patients with at least one typical COVID-19 symptom (cough, breathlessness, fever) and contact to SARS-CoV2 positive person(s) or a stay in a high-risk area within the last 14 days and of course positive PCR test for SARS-CoV2. All patients entering the endoscopy unit should wear a surgical mask. Endoscopy staff should reduce exposure hazards by keeping distance from the patient and using gloves, face masks (in case of high risk patients FFP2 or FFP3 masks), face shields and gowns (35).

Endoscopy that is considered to be an aerosol generating procedure (AGP) has as main goal to maximally reduce the infection's risk for patients and health care provider (HCP) (36). Therefore, the indications for the endoscopy during the SARS-CoV2 pandemic may be stratified in three groups including: 1)

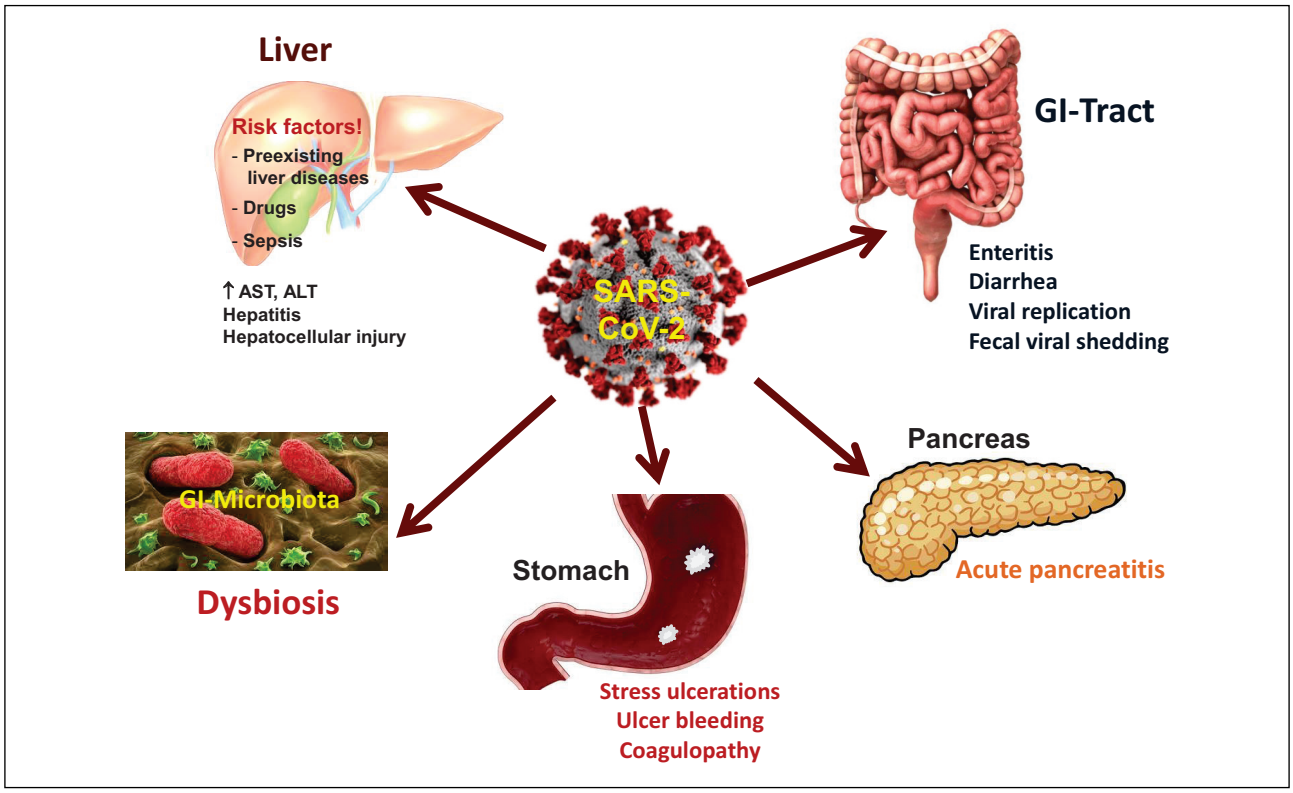

Fig. 4. Possible targets of SARS-CoV2 infection in the gastrointestinal tract, liver and pancreas.

emergency endoscopy 2) urgent endoscopy and 3) elective endoscopic investigations. The indications for emergency endoscopy include upper and lower GI bleeding, acute cholangitis, biliary acute pancreatitis, bolus obstruction, palliation of biliary and luminal obstruction. Emergency endoscopy should be performed in the first 24 hours according to published recommendations.

One of the most common causes for emergency endoscopy is GI bleeding. In such cases the endoscopy may provide very effective therapy and allow the risk stratification for re-bleeding. Normally this procedure should be performed within 24 hours of presentation. However, even in such cases one should weigh the pros and cons of the patients' benefit and endoscopist's risk. In some cases, the conservative therapy with blood transfusion and proton pump inhibitors and frequent monitoring of vital and GI symptoms may be justified in order to prevent the infection of the endoscopic staff. In a recent small study by Cavaliere *et al.* (37), all six patients with GI bleeding responded to this conservative management and none of these patients needed endoscopic procedure during their COVID-19 disease.

The indications for urgent endoscopy include the acute flare of inflammatory bowel disease (IBD), staging before surgery, suspected malignancy in the GI-tract, drainage of infected pancreatic pseudocyst. These procedures should not be postponed during the pandemic outbreak. The elective procedures, including endoscopic biliary drainage using plastic or metal stents, screening colonoscopy, diagnostic gastroscopy, enteroscopy, or endoscopic ultrasound, may be postponed during the pandemic for 4 – 6 weeks. Of course, every case should be discussed with the patient and the final decision should be performed after weighing the benefits and risks for the patient. For screening of the colon, a video capsule endoscopy or computed tomography colonoscopy may be performed (38, 39).

The workflows in the endoscopy have changed since the pandemic outbreak. The most important change is the safety for both, patients and endoscopic staff. The use of protective equipment of the staff and risk stratification was effective, as shown in recent studies. The studies, performed in "Corona hot spots", demonstrated that the risk of infection among the endoscopic team and patients is quite low due to preventive measures (40). To further increase the safety of endoscopy, the best future solution, if possible, would be to test every elective patient for SARS-CoV2 infection upfront the endoscopic procedure in order to minimize the infection risks. Testing before endoscopy remains an interesting preventive strategy, however, it is associated with higher health care costs (41).

The COVID-19 pandemic led not only to the significant reduction of GI procedures, but in addition, exerted an adverse effect on GI endoscopy training. During the outbreak, the unexperienced endoscopy trainees have been almost completely excluded from the training. Since the substantial part of the endoscopy procedures are screening colonoscopies and other surveillance procedures, it is important to perform these investigations as early as possible after the regression of the pandemic. Otherwise, the delaying of these procedures may be associated with an increased rate of advanced undetected cancers after the end of the pandemic (42).

Finally, the endoscopic unit may be faced with unusual cases such as the recently published 41-year old patient who presented in the emergency department after intentional ingestion of 10 ml ethanol-containing hand disinfectant for fear of being infected with SARS-CoV2, leading to the corrosive injury in upper GI-tract (43).

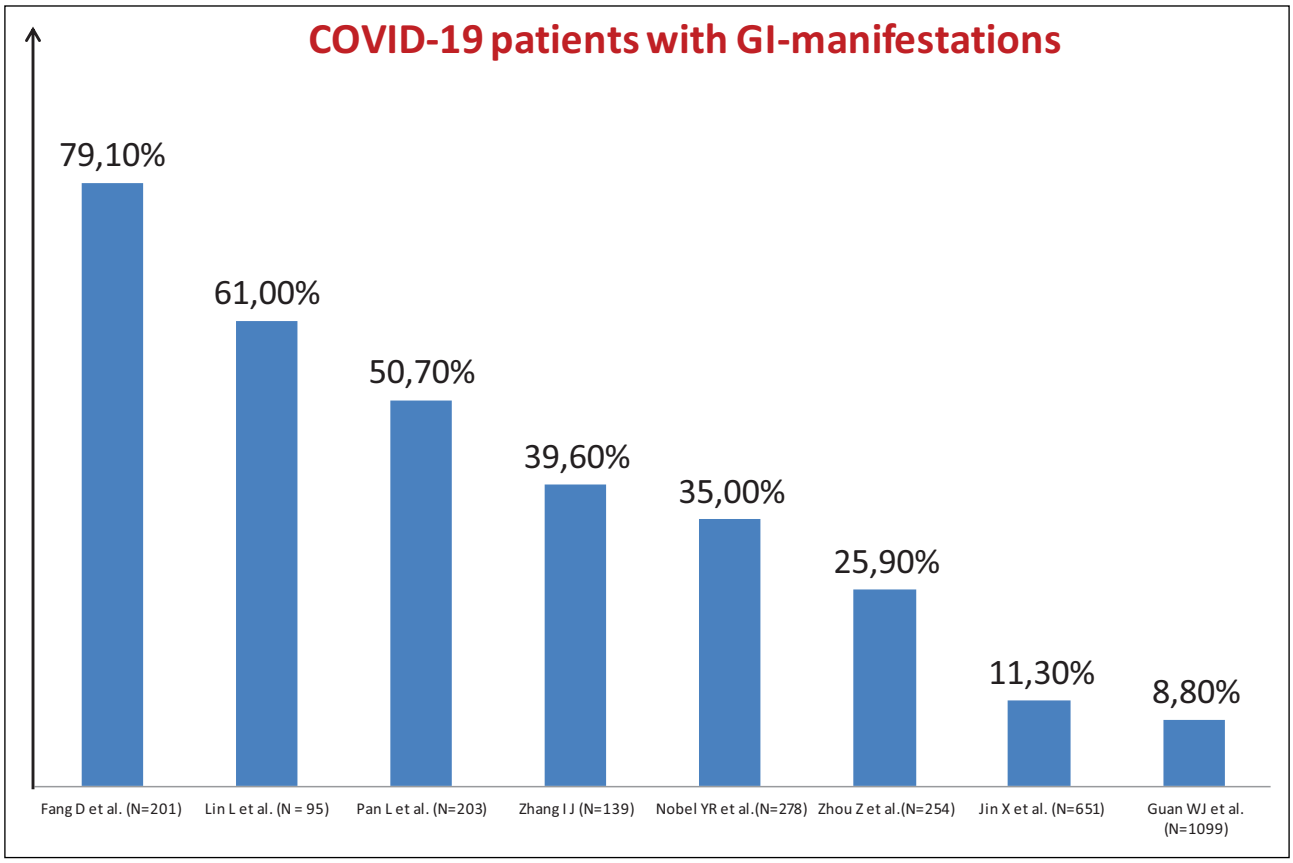

Fig. 5. Frequency of GI complications in different clinical studies.

SARS-CoV2 AND INFLAMMATORY BOWEL DISEASES

Inflammatory bowel diseases (Crohn's disease, ulcerative colitis) are chronic inflammatory and idiopathic diseases affecting the GI-tract. The pathogenesis of inflammatory bowel diseases (IBD) is multifactorial, including genetic factors, life style factors, nutrition, gut microbiota and psychological distress (44, 45).

SARS-CoV2 outbreak was associated with a psychological distress caused by social distancing, lockdown, and difficult access to health care. The increased exposure to stress and increased stress vulnerability may lead in IBD patients to the

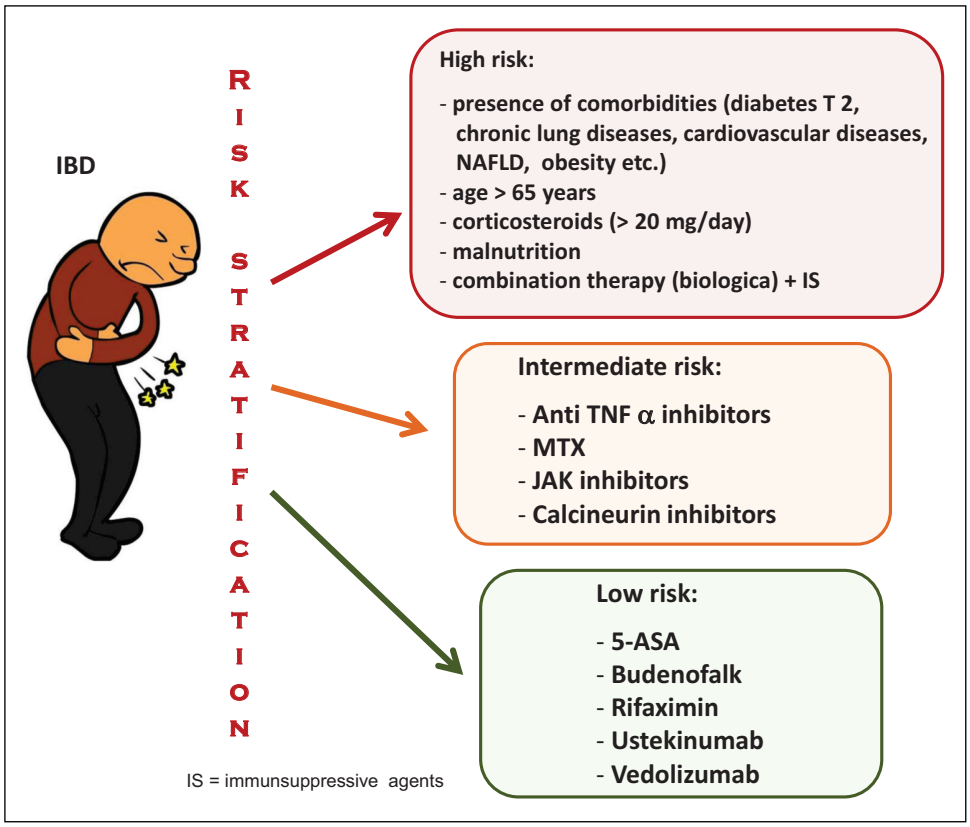

Fig. 6. Risk stratification for COVID-19 in patients with inflammatory bowel disease in dependence of anti-inflammatory therapy.

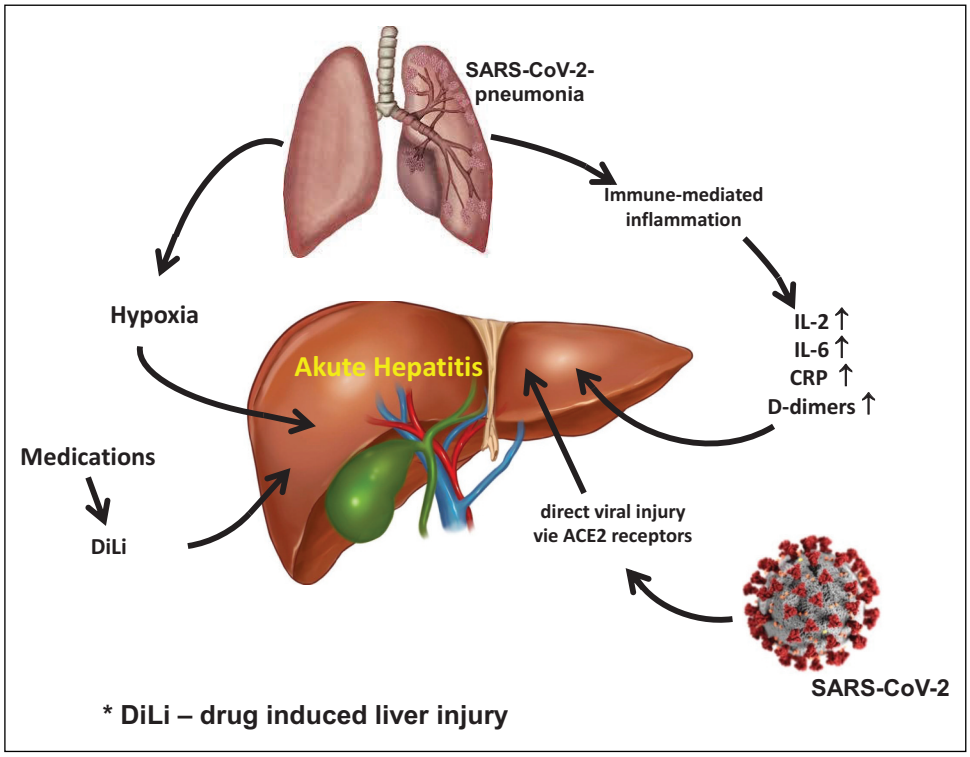

Fig. 7. Different mechanisms of liver injury in patients with SARS-CoV2 infection.

development of an acute flare (46). IBD patients can be caught in a vicious circle in which the growing burden of psychological stress leads to an acute flare that in turn aggravates the anxiety leading to the deterioration of the intestinal inflammation.

Patients with IBD treated with a variety of immunosuppressive therapies, including corticosteroids, biologicals, JAK inhibitors or other immunosuppressive agents, are more susceptible for infections (47, 48). It seems obvious that many patients have the tendency to discontinue their immunosuppressive treatment. This discontinuation is associated with an increased risk of developing an acute flare. For better monitoring the outcomes of COVD-19 in patients with IBD, the international pediatric and adult database Surveillance Epidemiology of Coronavirus Under Research Exclusion (SECURE-IBD) was launched. According to this database (30.3.2020), 164 COVID-19 IBD patients were identified (93 with Crohn's disease and 66 with ulcerative colitis, 2 IBD patients unclassified). 38 patients were hospitalized and the death fatality was 5% (AGA website). These results indicate that patients with IBD do not show a higher mortality rate despite the immunosuppressive therapy. The explanation for this may be the fact that the main role in the development of "cytokine storm" in course of acute respiratory distress syndrome plays the overexpression of tumor necrosis factor alpha (TNF-α). This reinforces the hypothesis that anti-TNF-α therapy could be even beneficial and protect the patients against severe forms of SARS-CoV2. Recently Tursi *et al.* (49) described a case of a 30 year old male with IBD under treatment with mesalazine 3 g/day and adalimumab 40 mg every other week that was admitted to hospital, tested positively for SARS-CoV2. COVID-19 disease manifested as mild interstitial inflammation in the chest CT scan and the patient needed only oxygen support. Interestingly, no aggravation of IBD was observed due to COVID-19 and this patient stayed in the remission and the fecal calprotectin value remained normal. In order to not to endanger the patient, adalimumab therapy was paused during viral infection. This case indicates that biologic therapy in IBD patient does not represent a massive threat in terms of COVID-19 infection.

These results are surprising, because normally patients with IBD, treated with corticosteroids, biologic or immunosuppressive agents, are more susceptible for infections. Compared to other therapeutic regimens, these drugs increase the risk for different viral infections such as herpes simplex virus, varicella zoster virus, cytomegalovirus infection or hepatitis B reactivation. Age represents an important independent risk factor for opportunistic infections in IBD patients (50).

Considering the risk for infections the biologic therapy shows significant differences. Whereas anti TNF-α antibodies and JAK inhibitors like tofacitinib show increased risk for infections, both vedolizumab and ustekinumab exhibit a much better safety profile (51).

The Chinese Society of IBD made some recommendations for managing patients with IBD during the COVID-19 pandemic (52). Based on the observation made during the epidemic in Wuhan, the experts recommend continuing current treatment, given that the disease is stable. If a new therapy is started, the therapy with vedolizumab or ustekinumab should be considered as a first line therapy due to their good safety profile. Tofacitinib should not be newly prescribed, because this drug significantly increases the risk for viral infections (especially varicella zoster virus). During the pandemic, only emergency endoscopy should be performed. Elective endoscopy should be postponed. Every patient that needs emergency surgery should be screened for COVID-19. Patients with acute fever should immediately consult their IBD doctor.

In every IBD patient, risk stratification for COVID-19 should be performed in ambulatory or hospital setting (*Fig. 6*). Patients with high risk include: patients with comorbidities (especially diabetes, NASH, cardiovascular or lung diseases), patients > 70 years, patients under corticosteroid doses > 20 mg/day, presence of malnutrition, and combination therapy with biological and immunosuppressive agent. Intermediary risk shows patients under biologic therapy with anti-TNF-α therapy, patients receiving MTX, JAK inhibitors or calcineurin-inhibitors. Low risk includes use of 5 aminosalicylates, budesonide, cholestyramine, lorepamide, luminal antibiotics such as rifaximin and biologicals with low risk of infection such as ustekinumab and vedolizumab.

COVID-19 AND LIVER

The infection with SARS-CoV2 may be accompanied by the abnormal levels of aminotransferases in up to 61.1% of cases. This indicates that infection with SARS-CoV2 virus may lead in some patients to liver injury. Generally, the changes in the liver function tests caused by the virus are transitory and the development of severe liver injury is uncommon (53).

The pathomechanism of the liver injury include direct harmful action of the virus *via* ACE-2 receptors expressed on cholangiocytes and hepatocytes, drug-induced liver disease and liver complications due to sepsis (54) (*Fig. 7*).

Huang *et al.* postulated that the incidence of abnormal levels of alanine and aspartate aminotransferase (ALT, AST) and hepatic dysfunction is more frequent in patients with severe diseases, especially in those patients that require therapy in the ICU (5). In fact, the literature has shown discrepant results. Guan *et al.* (7) observed elevated levels of AST more commonly in patients with severe course of COVID-19 as compared to non-severe cases (39.4% versus 18.2%). In contrast, Wu *et al.* (55) demonstrated no significant differences in liver function tests between severe and non-severe cases. An impairment of liver function in patients with COVID-19 depends on different factors like genetics, use of medication leading to drug-induced liver disease (like hydroxychloroquine, toclizumab, remdesvir, antibiotics), overproduction of proinflammatory cytokines (especially "cytokine storm") and the presence of a pre-existing liver disease, especially non-alcoholic fatty liver disease that increases the vulnerability to a viral-induced liver damage. At the moment there is no evidence for the late onset liver function damage due to an SARS-CoV2 infection.

There is increasing evidence that patients with chronic liver diseases (CLD) are at higher risk for severe COVID-19 infections. CLD are characterized by progressive deterioration of liver functions for more than six months. The most common etiologies are alcoholic and metabolic liver disease, autoimmune liver diseases, chronic viral hepatitis, chronic liver diseases with genetic causes and others. The end-stage of these diseases is liver cirrhosis (53).

Among other chronic liver diseases, one of the most prevalent is non-alcoholic fatty liver disease (NAFLD) (recently renamed as metabolic-associated fatty liver disease-MAFLD) (56, 57). MAFLD is commonly associated with diabetes, hypertension and obesity. MAFLD is a highly complexed disease with multiple pathogenic factors and also extrahepatic manifestations. It encompasses different stages such as steatosis, steatohepatitis, fibrosis and end-stage liver cirrhosis (58). Previous publications demonstrated that patients with MAFLD have an increased risk for pneumonia-related mortality (59).

Generally, patients with obesity with high prevalence of MAFLD are risk patients for the development of severe COVID-19. Interestingly, in patients aged less than 60 years, the presence of MAFLD was associated with the more frequent presence of severe COVID-19 accompanied by the "cytokine storm" (60). In

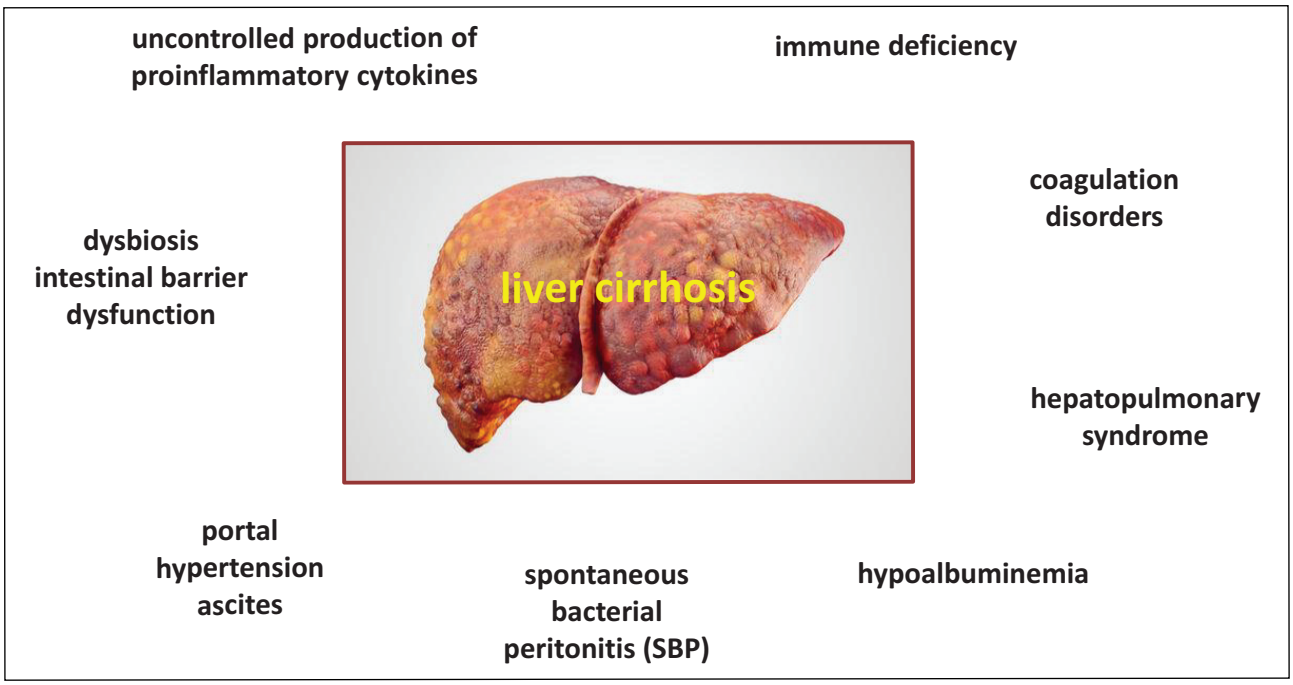

Fig. 8. Different factors and mechanisms responsible for severe course of COVID-19 in patients with liver cirrhosis.

another study, Cai *et al.* assessed 14 patients with SARS-CoV2 infection and preexisting NAFLD. Six of these patients showed a severe disease process (61). Therefore, it is important to identify the prognostic factors for severe COVID-19 in patients with MAFLD. One of the important prognosis factors is the presence of fibrosis in the liver. Just recently, Byrne *et al.* (58) presented that the presence of fibrosis in patients with MAFLD significantly increases the risk of developing a severe form of COVID-19. More studies are needed to better understand the link between MAFLD and higher risk for SARS-CoV2-related mortality.

Patients with autoimmune liver disease are at increased risk of infection due to the use of immunosuppressive therapy, corticoids and altered immune function. Previous studies demonstrated that patients treated with immunosuppressive medication have an increased risk for viral infections. Against these expectations, the experience data gathered in the epicenters of the infection in Wuhan/China or Lombardy/Italy did not show a higher risk for ARDS due to COVID-19 and increased mortality among these patients. The immunosuppressive therapy should not be reduced or stopped to avoid acute flare of disease and unnecessary admission to the hospital. In patients with stable chronic autoimmune disease, the follow-up visit could be postponed until the pandemic is over. Alternatively a web-based or telephone-based consultation can be performed. It is useful to send general information and recommendation to the patients. Acute flares of acute autoimmune hepatitis, especially obstructive jaundice in primary sclerosing cholangitis (PSC), require hospital treatment (53, 62).

Patients with liver cirrhosis are at high risk of developing serious infections including SARS-CoV2-virus with high mortality due to some favorable pathophysiological mechanisms such as cirrhosis-induced immune deficiency, intestinal dysbiosis, genetic predisposition, bacterial translocation, porto-systemic shunting and liver dysfunction (*Fig. 8*). As a consequence, patients with liver cirrhosis may develop acute-on-chronic liver failure accompanied by overwhelming inflammatory response (63). In their recent publication, Singh S *et al.* (64) have found a significantly risk for mortality due to COVID-19 (RR 4.6, 95% CI 2.6 – 8.3, P < 0.0001) among patients with liver cirrhosis as compared to patients without liver disease. Patients with advanced liver cirrhosis and high risk for decompensation should be monitored with a web-based system in order to prevent from unnecessary hospital visits during the pandemic. In addition, patients should be informed about the hygienic measures (washing of hands) and the importance of social distancing. Despite these recommendations, the patients with liver cirrhosis are prone to develop acute decompensation during the pandemic due to the multiple factors, such as irregular medication, lack of regular follow-up visits, decreased endoscopic surveillance, increased natrium intake in junk food and alcohol consumption due to lockdown and social isolation, increased stress, and decreased mobility. Urgent procedures associated with acute liver decompensation such as paracentesis of ascites or treatment of esophageal varices should be organized in hospital on COVID-free wards.

There is an established correlation between the PNPLA3 rs738409 C > G single nucleotide polymorphism (SNP) and hepatic steatosis and fibrosis in hepatitis C virus (HCV) infected patients (65). It has been demonstrated that PNPLA3 rs738409[G] allele is a reliable predictor for steatosis and fibrosis in patients with chronic hepatitis C. The presence of G allele along with severe steatosis and insulin resistance are significant predictors for liver fibrosis progression but whether this exacerbation of disease caused by single nucleotide polymorphism is influenced by COVID-19 infection in HCV patients remains to be studied. For instance, sofosbuvir, the clinically approved anti-HCV drug, has recently been recommended to suppress other families of positive-strand RNA viruses (66) but the promising study with this drug efficacy against COVID-19 is still awaited.

COVID-19 AND PANCREAS

Pancreatic cells highly express angiotensin converting enzyme 2 (ACE2) that SARS-CoV2 requires to entry the cells. This indicates a possible involvement of pancreas in patients

with COVID-19 disease (67). Recent reports indicate that some infected patients may develop acute pancreatitis with elevation of serum amylase and lipase (68). In such cases, typical findings of acute pancreatitis may be observed on abdominal CT. Every physician, especially gastroenterologist should be aware of this complication because patients may present untypical for COVID-19 abdominal pain and elevation of lipase before the respiratory symptoms appear. Due to the growing SARS-CoV2 pandemic, the testing for SARS should be included in the differential diagnosis of patients with acute pancreatitis, especially those patients coming from "hot spots" and having had contact to SARS positive patients.

COVID-19 AND GUT MICROBIOTA

In recent years, there is an emerging evidence for the presence of the bidirectional cross-talk between gut microbiota and the lungs termed gut microbiota-lung axis. Negative alterations of gut microbiota termed dysbiosis may affect pulmonary immunity. On the other side, lung inflammation can induce changes in the gut microbiota. The mechanisms by which gut microbiota affect the development of lung diseases and *vice versa* remain poorly understood. As possible candidates, the involvement of regulatory T cells, toll like receptors, release of inflammatory mediators and surfactant protein D have been proposed (69).

These observations indicate that therapeutic strategies to improve gut microbiota, including use of prebiotics, probiotics or synbiotics, could have beneficial effects on the GI symptoms in COVID-19 patients. Their use is of importance in case of antibiotic therapy disrupting the gut microbiome (70). SARS-CoV2 invades the GI epithelium *via* ACE2 receptor that is expressed in the whole GI-tract. The role of ACE2 in the GI-tract is not fully understood, but there is evidence that this protein regulates the expression of antimicrobial peptides and maintains the equilibrium of the gut microbiota. Interestingly, the deficiency of ACE2 results in highly increased susceptibility to intestinal inflammation leading to cancer. For instance, the ACE2/MAS receptor pathway might be of great importance in cancer preventions since the production of Ang1-7 is decreased in breast cancer cells *in vitro*, whereas the expression of MAS receptor was increased in these cells (71). This observation suggests that agonists of MAS receptor could be useful in the treatment of various cancers but the efficacy of Ang1-7 in protection against SARS-CoV2 invading gastrointestinal epithelium requires extensive investigations.

Importantly, the transplantation of the altered gut microbiota from ACE2 mutant mice into germ free wild type host was able to transmit the increased propensity for the development of colitis. With other words, ACE2 is a regulator of immunity and gut microbiota ecology (72). This observation indicates that SARS-CoV2 infection could lead to the disruption of gut microbiota (dysbiosis). This is not surprising because previous studies have shown the negative effect of viral infections on gut microbiota. Recently, it has been shown in the murine model that the antibiotic treatment caused a significant increase in mortality of C57Bl6 mice infected with paramyxoviral virus type1 (Sendai virus). In other murine models, the authors showed effects of influenza and respiratory syncytial virus on the development of dysbiosis (73).

The outbreak of COVID-19 is not only a global health problem, but also represents one of the most important stressors. The causes of stress are multifaceted, including fear of infection, social distancing, quarantine, lockdown, financial damage, travel restriction, lack of effective vaccine or treatment *etc.* All these stressors influence mental health and the function of the GI-tract. As shown previously by our group, stress significantly affects the gut microbiota inducing a dysbiosis (74). These effects may be exacerbated by obesity that is recognized as an important risk for severe progression of COVID-19 (75). In addition, advanced age is one of the important risk factors for COVID-19 and increased mortality. It is well established by studies that the aging is also significantly associated with increasing gut dysbiosis (76). Also, differences in the intestinal microbiota were found in relation to age in subjects with and without another GI-tract disorder such as celiac disease (CD) (77). In another study with patients with histamine intolerance, food hypersensitivity, and food allergy, the altered occurrence of Proteobacteria and Bifidobacteriaceae, the reduced alpha-diversity as well as elevated stool zonulin levels have been reported (77). The major message from this study was that dysbiosis and intestinal barrier dysfunction are important features in histamine intolerant patients (78). Thus, it is not excluded that the gut microbiota might be of potential value as a diagnostic biomarker and therapeutic target for COVID-19, but further studies on the validation this hypothesis are definitely needed.

Since the gut microbiota influences the systemic immune and inflammatory response, the therapy with prebiotics or probiotics to improve the gut microbiota diversity could play an important adjuvant role in the prevention of severe progression of COVID-19 (79). Finally, the use of antibiotic and antiviral substances may also negatively affect the equilibrium of gut microbiota (80). The perturbation of the microbiota induced by antibiotic treatment may have further negative effects on the course of the SARS-CoV2-induced disease.

In conclusion:

1) SARS-CoV2 virus invades GI-tract and is associated with a number of GI manifestations, including diarrhea, nausea, the abdominal pain and vomiting.
2) Viral receptor ACE2 is highly expressed in the GI-tract and enables the invasion of the GI epithelium.
3) COVID-19 is associated with the shedding of the virus *via* the GI-tract.
4) Patients with acute diarrhea should be tested for SARS-CoV2 infection.
5) COVID-19 is associated with liver manifestations and pancreatic injury.
6) Patients with preexisting liver diseases, particularly NAFLD and liver cirrhosis, have a higher risk for severe COVID-19 course of these diseases and associated mortality.
7) SARS-CoV2-induced dysbiosis is multifaceted and can be associated with alterations caused by stress, drug therapy, age, and changes in ACE-2 expression.

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