Inflammatory effect on the gastrointestinal system associated with COVID-19

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Conflict-of-interest statement: All authors indicated no potential conflicts of interest in publishing this manuscript.

Open-Access: This article is an

Core Tip: Coronavirus disease-2019 (COVID-19) affects not only the respiratory systems but also gastrointestinal (GI) system and function of others organs. Until now, the mechanism of infection that severe acute respiratory syndrome, coronavirus 2 uses is not fully known. GI symptoms are rare but had great relevance in the severity of disease. We summarize the main known mechanisms that are associated with intestinal
INTRODUCTION

Coronaviruses are a family of viruses that cause illnesses such as the common cold, severe acute respiratory syndrome, coronavirus 2 (SARS-CoV-2), and Middle East respiratory syndrome (MERS)[1]. SARS-CoV-2 is the etiologic agent of coronavirus disease 2019 (COVID-19), designated as a pandemic by the World Health Organization on March 11, 2020. Up to January 1st, 2021, COVID-19 has caused globally over 85 million cases[2]. The impact that COVID-19 has had worldwide on health and the economy has been devastating since the number of deaths continues, partly because neither we fully understand the disease nor its transmission. Moreover, there are increasing long-term complications and sequelae after COVID-19 in some people[3,4].

The respiratory tract is the main entry route reported, and the transmission mechanism is via large droplets containing a high enough viral load. The virus is not motile by itself and depends on its rotational diffusivity to align its proteins (organized in hollow spikes called "peplomers") to its targets during the infection process[5]. Infected people in most cases do not develop symptoms (asymptomatic) or have mild symptoms such as fever, dry cough, fatigue, sore throat and/or headache, conjunctivitis, nausea, vomiting, skin rashes, and dysgeusia; which appear 2-14 d after being exposed to the virus[6]. It has been reported that the survival time of SARS-CoV-2 in aerosol form is 4 h, as the virus becomes inactive at 60°C. Propagation of the droplets in the air depends on the ventilation systems of the area where an infected person is spreading the virus while breathing without using personal protection equipment[7].

Additionally, gastrointestinal (GI) symptoms such as diarrhea, nausea, and vomiting have been reported[8], yet this seems to affect only about 1%-3.8% of the studied patients[9]. Nevertheless, the exact molecular mechanism with which SARS-CoV-2 produces GI damage is still unknown. Therefore, this review aims to describe the effect that SARS-CoV-2 produces in the GI tract.

MECHANISM ASSOCIATED WITH COVID-19 INFECTION IN THE GI SYSTEM

SARS-CoV-2 clinical manifestations include GI effects; however, there is insufficient research on the mechanisms that allow digestive colonization by a respiratory virus. With over 80% resemblance between SARS and SARS-CoV-2[8], several studies have shown tropism for the GI tract, as SARS-CoV-2 RNA was detected in stool specimens from COVID-19 patients with diarrhea, suggesting that it can be transmitted by the fecal-oral route[10].

The viral nucleocapsid protein of SARS-CoV-2 has been found in the GI lumen in the esophagus, stomach, duodenum, and the rectal glandular epithelial cells, suggesting this receptor as the entry point of the SARS-CoV-2 virus in the intestinal tract[10-12]. Also, the expression of angiotensin-converting enzyme 2 (ACE2) protein on glandular cells of gastric, duodenal, rectal epithelia (abundantly expression), and esophageal mucosa (less expression) was demonstrated, supporting the entry of SARS-CoV-2 into the host cells by immunofluorescent technique[13].

ACE2 is a receptor member of the angiotensin-converting enzyme (ACE) family of dipeptidyl-carboxypeptidase and is highly homologous to ACE1, which plays an important role in SARS-CoV-2 infection, through a high-affinity attachment to ACE2
receptors in human cells[11]. The primary function of ACE2 is the conversion of angiotensin (Ang) 1 to Ang 1-9 and Ang 2 into Ang 1-7. ACE receptors participate in cell proliferation and hypertrophy, inflammatory response, blood pressure, and fluid balance. Specifically, ACE2 has an important role in regulating cardiovascular, renal, and reproductive functions[10]. Besides its high expression in type II alveolar cells (AT2) in the lungs, the GI tract also expresses ACE2 receptor, particularly in the esophageal epithelium, glandular gastric mucosa, enterocytes, and colonocytes. ACE2 is present in the cytoplasm of the epithelial cells of the stomach and intestine and the cilia of glandular epithelial cells[10-12].

Recent studies have shown that SARS-CoV-2 may cause digestive symptoms by direct viral invasion of target cells and by inflammatory injury. The viral infection process involves a series of steps: (1) A direct cytopathic effect; (2) Downregulation of ACE2 expression with an increase of metalloproteinase action; and (3) Dysregulation of the immune system, with over secretion of proinflammatory cytokines[14]. Plasmatic and lymphocytic infiltration with interstitial edema[10]. Figure 1 includes more details about this process.

In general, all coronaviruses encode a surface glycoprotein and spike protein that binds to host cell receptors ACE2 and allows virus entry. The spike (S) protein of SARS-CoV-2 has a high affinity for human ACE2, which is the main entrance into the cell[12]. Furin is an enzyme that can be found on the small bowel, acting as a serine-protease that can divide the viral S-protein into two fragments: S1 and S2, allowing them to interact with ACE2. The separation of the S-spike into S1 and S2 is essential for the attachment of the virion to both the ACE receptor and the cell membrane[15]. S-protein proteases, such as cathepsins, expose the fusion domain to the endosome by acid-dependent proteolytic cleavage. Successful entry also requires a cellular serine protease, transmembrane protease serine 2 (TMPRSS2)[16]. TMPRSS2 cleaves the S protein of SARS-CoV-2 on the cell membrane, a process that is critical for the fusion of the viral and cell membranes. Importantly, both ACE2 and TMPRSS2 become highly expressed in the ileum and colon[16-18]. Hoffmann et al[19] demonstrated that inhibition of the TMPRSS (the serine protease responsible for splitting the S-spike) blocks the infection of cells by SARS-CoV-2.

After viral entry, RNA translates, and viral proteins become synthesized to form new virions released in the GI tract[13]. Thus, leading the CD4+ T cells to reach the small intestine, causing diarrhea and immune damage[12]. ACE2 participates in regulating intestinal inflammation and diarrhea by being a key enzyme in the renin-angiotensin system. It has been shown that loss of ACE2 leads to Ang 2 accumulation. Moreover, the plasma of COVID-19 patients with severe disease presents higher levels of interleukin (IL)-7, IL-10, granulocyte colony-stimulating factor, and recombinant human interferon-induced protein-10, monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-IA (MIP1A), and tumor necrosis factor alpha (TNF-α)[18]. The local inflammation could debilitate the epithelial barrier, and these inflammatory changes can be part of cell damage induced by viral replication and spreading[20]. This inflammation process disturbs the gut microbiota promoting the polarization of Th17 in the small intestine, promoting the recruitment of other immune cells such as neutrophils, and inducing intestinal immune damage, diarrhea, and other GI symptoms. Also, intestinal damage and gut microbiota alteration can affect the gut-liver axis by contamination of the liver with host and microbial metabolites through the portal vein[12].

A study by Xiao et al[13] showed that among 73 hospitalized patients, 53.42% tested positive for SARS-CoV-2 in the stool. The duration of positive stool results ranged from 1 to 12 d, and 23.29% of patients continued to have positive results in stool after being negative in respiratory samples and presenting positive staining for ACE2 receptor and viral nucleocapsid protein in stomach, duodenum, and rectum biopsies. Raising the question if COVID-19 can be transmitted by the fecal-oral route or transmitted by aerosols generated by toilet fumes has been shown with SARS-CoV-2[21,22]. A study conducted by Zhang et al[23] showed that 39.6% of 140 confirmed COVID-19 patients presented GI symptoms among the most common clinical manifestations[23]. Another study reported that 10.1% of 138 confirmed COVID-19 patients, presented diarrhea and nausea[24], furthermore, a recent report showed that 11.4% of 651 patients showed GI symptoms associated with a more severe presentation of the disease[25]. Nonetheless, patients with SARS and MERS have reported more GI symptoms than COVID-19 patients[26]. There has been a high concern in how COVID-19 can affect the body with pre-existing diseases, inflammatory bowel diseases (IBD), such as Crohn disease and ulcerative colitis.
Figure 1 Mechanisms of severe acute respiratory syndrome-coronavirus-2 gastrointestinal infection. The same receptors mediate infections of the gastrointestinal system as in the respiratory system. This situation could begin at the intestinal tract by enterocyte invasion, which possesses angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 receptors recognized by severe acute respiratory syndrome-coronavirus-2. Once in cells, the virus can induce cell death-mediated dysregulation of the immune system by downregulation of ACE2 receptor expression and a direct cytopathic effect. All three mechanisms induce immune dysregulation and increase the inflammation mechanism. Some risk factors that accelerate immune inflammation are obesity, diabetes mellitus, high blood pressure, asthma, cardiovascular disease, and advanced age. Moreover, the virus could enter the liver by the portal vein and induce hepatic failure. ACE2: Angiotensin-converting enzyme 2; TMPRSS2: Transmembrane protease serine 2; DM: Diabetes mellitus; HPB: High blood pressure; CVD: Cardiovascular disease.

A study showed that immunosuppressors modulate the cytokine inflammatory response, thus preventing a more severe manifestation of COVID-19[27]. Also, GI symptoms derived from drug side effects of antibacterials (macrolides, fluoroquinolones, or cephalosporin) and antivirals (chloroquine phosphate, lopinavir, and remdesivir) administered during illness[12].

COVID-19 patients with preexisting comorbidities such as hypertension, asthma, diabetes, cardiovascular problems, and old age, have a higher susceptibility to inflammation. Recent studies have shown that the severity of the clinical course of COVID-19 is related to inflammation and higher levels of proinflammatory cytokines[14]. Studies show that SARS-CoV-2 rapidly activates T cells and induces the release of several inflammatory cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin 1 (IL-1), IL-6, monocyte chemoattractant protein-1, and interferon-gamma (IFN-γ). GM-CSF activates CD14+ cells, CD16+ cells, and monocytes, increasing inflammatory cytokine levels, stepping up the inflammatory cascade. This intense immune response causes tissue damage[28]. T cells from peripheral blood in COVID-19 infection present high cytotoxic activity with more cytotoxic granules, granulysin, and perforin, which shows that activated T cells could speed up systemic inflammation[29]. Also, ACE2 expressing cells release proinflammatory cytokines such as MCP-1, tumor growth factor (TGF-1), TNF-α, IL-1, and IL-6[12].

Recently, COVID-19 intestinal pathogenesis mechanisms have been proposed since SARS-CoV-2 also might interfere with tryptophan absorption. Tryptophan stimulates the mTOR pathway for the production of antimicrobial peptides that maintain gut microbiota homeostasis. This process requires intestinal ACE2 to regulate the expression of neutral amino acid transporters. Tryptophan is absorbed by factors of
the B0AT1/ACE2 transport pathway on the lumen surface of intestinal epithelial cells. When there is not enough niacin or tryptophan intake, there is a high risk of developing pellagra, which eventually develops into colitis. As SARS-CoV-2 infection competes for available ACE2 receptors, it causes tryptophan deficiency and lower production of antimicrobial peptides[16]. COVID-19 murine models showed a deficiency of ACE2 receptors in the colon, which increase susceptibility to inflammation and colitis development due to decreased antimicrobial peptides and the alteration of gut microbiota, finalizing with diarrhea[12,29]. However, this mechanism needs to be proven in humans.

COVID-19 RELATED DAMAGE TO INTESTINAL MICROBIOTA

The human gut microbiota comprises 10^{14} resident microorganisms which include bacteria, archae, viruses, and fungi and has a key role in health through its protective function by regulating various host physiological functions, including dietary digestion, and imparting protective immunity against pathogens[30]. The defense mechanism of microbiota induces alpha-defensin, secretory IgA, and some other AMPs (antimicrobial peptides)[31], affecting innate lymphoid cells, but mainly they affect the innate and adaptive immune system by influencing epithelial or macrophage cell receptors, such as toll-like receptors (TLRs) or NOD-like receptors (NLRs). TLRs are involved in normal mucosal immune system development of the intestine, decreasing inflammatory responses and promoting immunological tolerance to the normal microbiota components. NLRs participate in the adjustment of the IL-18 level, the immune response, dysbiosis, and intestinal hyperplasia[32].

Healthy gut microbiota, primarily dominated by Bifidobacterium spp., Faecalibacterium spp., Ruminococcus spp., and Prevotella spp. Whom’s alterations in the balance between gut microbiota and the immune system, sometimes collectively called “gut dysbiosis” are associated with infections, inflammations, allergies, colorectal cancer, and autoimmune disease[30]. Studies have suggested that “gut-dysbiosis” might contribute to GI symptoms by SARS-CoV-2 infection, i.e., Bacteroides dorei, Bacteroides thetaiaotaomicron, Bacteroides massiliensis, and Bacteroides ovatus, can downregulate the expression of ACE2 during the hospitalization of COVID-19 patients[33].

Microbial dysbiosis with decreased levels of Lactobacillus and Bifidobacterium and the abundance of Clostridium hathewayi, Clostridium ramosum, and Coprobacillus positively correlated with the severity of the disease[33]. A study in a Chinese population reported that intestinal infection by SARS-CoV-2 can induce the production of proinflammatory factors such as IL-18. IL-18 is a proinflammatory cytokine produced by multiple enteric cells, including intestinal epithelial cells, immune cells, and the enteric nervous system, is shown increased in the serum of COVID-19 patients. IL-18 levels seem to correlate with an abundance of Peptostreptococcus, Fusobacterium, and Citrobacter, indicating changes in gut microbiota[34].

Obesity presents changes in microbiota, dysregulation of cytokine profiles, and higher levels of ACE2 in adipocytes[35]. As the opposite, an adequate fiber intake and whole grains diet improves intestinal microbiome composition, reduces intestinal inflammation markers like CRP, IL-6, and TNF-α[36]. Besides the colon and intestines, the liver is another organ the SARS-CoV-2 could affect[29].

LIVER INJURY IN COVID-19 PATIENTS

The few reports regarding liver damage by COVID-19 come from autopsies carried out in different hospital centers. The incidence of liver damage in patients with COVID-19 ranges from 14% to 53%[37]. Patients with elevated liver function tests were more likely to have a moderate-high degree fever, and these elevations were significantly more prevalent in male patients (68.67% vs 38.36%). It is important to mention that it is difficult to define how COVID-19 generates liver damage since patients at the time of hospitalization usually have chronic diseases such as non-alcoholic hepatic steatosis, which increases the progression of the disease, hepatitis C such as those reported by Schmitt[20,38]. Among the biochemical indicators, there have been reports of elevated aminotransferases approximately on the tenth day of hospitalization[39].

Patient biopsies reveal the presence of hepatocyte mitosis with acidophilic bodies, moderate inflammation, and balloon degeneration. In the SARS virus epidemic in 2003, a study reported the elevation of aminotransferases in a range of 300-400, and prominent mitoses, which refers to what researchers have published in various studies.
from these pandemics. The authors assumed that the prominent mitosis was likely due to a hyperproliferative state and cell cycle arrest[40].

Some researchers hypothesized that the direct action of the virus on liver cells causes centrilobular, perportal necrosis without significant inflammation compatible with acute liver damage. Also, the authors report that development of cholestasis and a great reactive biliary proliferation as consequences of the virus are to be expected. They further consider the possibility that the virus enters the liver through the portal vein[38]. The definitive mechanism by which liver injury occurs in COVID-19 patients remains unclear. There are multiple theories of the pathophysiology of the viral infection that could explain this phenomenon: (1) ACE2-mediated direct viral infection of hepatocytes; (2) Critically-ill status and immune-mediated injury; or (3) Drug hepatotoxicity[11] (Figure 2).

Liver damage by COVID-19 can be clarified thanks to the severe inflammatory response and cytotoxicity of the active replication with ACE2 receptors expressed in the liver, especially in cholangiocytes and epithelial cells of the bile duct, which is why the liver is also considered a target organ for SARS-CoV2 infection[41].

Fiel et al[42] found this elevation associated with pharmacological treatment with lopinavir/ritonavir. However, a review demonstrated that aminotransferases are only significantly elevated in severe COVID-19 cases. Drug toxicity has served as one mechanism for COVID-19-associated liver injury, damage that is secondary and does not make them susceptible to viral infection. However, little is known about the incidence of hepatotoxicity of various drugs used in COVID-19. Understandably, efforts are currently made regarding this concern. These efforts will prove important in developing a reasonable intervention and reducing the harmful effects of drug-induced hepatotoxicity for patients[28].

SARS-COV-2 AND THE PANCREAS

Expressed in the pancreas is the angiotensin converting enzyme 2 specifically in the exocrine glands, and islets[43] therefore, it is susceptible to SARS-CoV-2 infection. In a cohort of 121 patients with COVID-19 in China, 10% had increased lipase levels but only 4% showed pancreas enlargement or dilatation in computerized tomography (CT) scans[44].

In another cohort of 71 patients in the United States, 12% had increased lipase levels but only 3% exceeded three times the upper normal limit. None of the patients had normal pancreas images in CT scans[45]. In a cohort of 83 patients with COVID-19 in the United States, 16.8% had increased lipase levels (three times the upper limit). Researchers have associated high lipase levels with admission to the intensive care unit and intubation after a multivariable-adjusted model[46]. In a retrospective pooled analysis, the pooled prevalence of hyperlipasemia was 12% and the pooled odds ratio for severe COVID-19 was 3.143[47]. The ACE2 receptor is also highly expressed in pancreatic islet cells[43]; therefore, SARS-CoV-2 infection can theoretically cause islet damage resulting in acute diabetes, which associates to patients with pancreatic injury and high blood sugar. Mechanisms by which pancreatic injury could occur include the direct cytopathic effects of SARS-CoV-2 or indirect systemic inflammatory and immune-mediated cell responses, resulting in organ damage or secondary enzyme abnormalities. Antipyretics, which most of the patients in this study took before admission, could also cause drug-related pancreatic injury[48]. However, more information to understand the role of pancreatic injury in patients with COVID-19 is needed.

TREATMENTS OF GI SYMPTOMS

At the current stage of the COVID-19 pandemic, several vaccines are in their last stages of authorization for emergency use[49,50]. While full distribution will continue as a challenge, hopes of major population immunity are coming close. Yet, until we have a more resistant population, respiratory complications will continue as the major symptom reported during a COVID-19 infection. Interestingly, other lesser-known indicators that manifest, such as those of the GI which include vomiting, nausea, and diarrhea[12,51]. Many studies have shown that vomiting and nausea can be present in upwards of 30% and 15% of patients[12]. Interestingly enough, in a pediatric setting, one reported case showed patients with no-respiratory affliction who were all COVID-19 positive; all presented GI alterations. Several showed gastroenteritis, another
Before severe acute respiratory syndrome-coronavirus-2 infection, there are risk factors considered that could be poor prognostic factors, such as chronic diseases, the use of drugs that affect the liver and the inflammation process. The virus can infect the liver through the portal vein. There are three proposed mechanisms of liver damage: inflammation induced by cytokine storm and activation of hepatic immunity, angiotensin-converting enzyme 2-mediated direct viral infection of hepatocytes, epithelial cells, and cholangiocytes, and drug hepatotoxicity mediated by some antivirals employed for coronavirus disease-2019 (COVID-19) treatment. The three mechanisms culminate in altered coagulation, hepatic ischemia, and elevation of aminotransferases and bilirubin levels. Following this, the incidence of liver damage derived from COVID-19 is up to 53%, which could develop cholestasis and reach high mortality risk. ACE2: Angiotensin-converting enzyme 2.

As more data becomes available, GI manifestations such as loss of appetite seem to be direct signs of COVID-19. Counter to the GI manifestations brought about by COVID-19, several drugs used to combat the effects of the virus have secondary side effects. Drugs like remdesivir, hydroxychloroquine, favipiravir, ivermectin, and azithromycin can induce side effects such as vomiting, nausea, elevated liver enzymes, weight loss, abdominal pain, and others [53]. The Table 1 display wide information.

In addition, COVID-19 patients can present a hyper-inflammatory state, with systemic response and cytokine storm mediated by IL-6, IL-8, and TNF-α, which can induce platelet activation and thrombosis, also presenting endothelial dysfunction due to direct virus damage and inflammation [54]. Heparin is used in COVID-19 patients as prophylactic therapy to prevent thrombosis. However, heparin-induced-thrombocytopenia (HIT) after administering low doses may not be enough to counteract the hypercoagulable state, leading to coagulation problems in these patients [55]. Heparin treatment, by a direct interaction between heparin and platelets, induces platelet clumping or sequestration. This event occurs within the first 48-72 h after starting treatment and generates mild and transient thrombocytopenia [56]. In some cases, thrombosis could be associated with HIT after heparin cessation [57].

In the GI system, the intestinal microbiota plays a crucial role in the correct balance and maintenance. If unbalanced component processing becomes inefficient, direct damage to the intestinal mucosa results in more accessible routes for viral infection [12, 58]. Studies have confirmed that probiotics can assist in this treatment; both bifidobacterium and lactic acid can help induce antibody production [12]. It is important to mention that patients with severe GI symptoms require a nutritional risk assessment, as it becomes a predictor of outcome both in the long term and the short term [59].

COVID-19 individuals presenting irritable bowel disease are of particular interest since this condition warrants the use of immunosuppressants and steroids. Interestingly, vedolizumab and ustekinumab do not increase the risk of COVID-19, hence patients can continue its use safely. Yet, thiopurines, anti-tumor necrosis factor (anti-TNF) agents, and JAK inhibitors may continue to present a risk. In mild cases, 5-ASA and budesonide use are reasonable [53]. We should take special consideration to outweigh the benefit against the risk for each case. Also, unless emergent, patients should defer all surgical procedures until pandemic conditions rescind [60]. We should
| Pharmacological intervention | Mechanism of action                                                                 | Adverse effects                                                                 | Ref.       |
|------------------------------|------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|------------|
| Hydroxychloroquine           | Elevated endosomal pH; Disruption of lysosome-endosome fusion. Inhibition of cell-virus fusion when interacting with N-terminal domain of the SARS-CoV-2 peak | QT segment prolongation; Gastrointestinal Adverse Effects                         | [62-64]    |
| Chloroquine                  | Inhibits RNA-dependent polymerases, decreases endosomal iron release required for DNA replication, and inhibits glycosylation of viral envelope glycoproteins | Gastrointestinal adverse effects; visual and extrapyramidal disturbances; Arrhythmogenic cardiotoxicity | [65-67]    |
| Remdesivir                   | Transcription Inhibitor                                                             | Caution in patients with severe renal impairment [estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73] or severe liver disease | [68]       |
| Lopinavir/Ritonavir          | Lopinavir binds to the viral protease and prevents the cleavage of the Gag-Pol polyprotein, resulting in the production of non-infectious immature viral particles. Ritonavir increases the plasma concentration of lopinavir by inhibiting the metabolism of cytochrome P450 3A (CYP3A) | Gastrointestinal adverse effects                                                 | [64, 65, 68-72] |
| Ribavirin                    | Interferes with RNA polymerase and viral protein synthesis                           | Hemolytic anemia; Leukopenia; Teratogenic                                         | [68]       |
| Interferon                   | Degradation of viral RNA; Alteration of RNA transcription; Inhibition of protein synthesis and apoptosis | Worsening psychiatric conditions, cytopenia, and uncontrolled seizures           | [68]       |
| Corticosteroids, dexametason  | Inhibitor of the inflammatory process                                              | Impair the immune response; Bacterial pneumonia risk; Hyperglycemia; Osteoporosis; Hypertension | [68-70]    |
| Azithromycin                 | Bacteriostatic antibiotics; Anti-inflammatory effects Immunomodulatory effects      | QTc with the risk of arrhythmias                                                  | [71, 73]   |
| Heparin                      | Antiplatelet                                                                        | Risk GI symptoms; Bleeding; Heparin-induced thrombocytopenia                      | [74]       |
| Favipiravir                  | Competitive inhibitor of RNA-dependent RNA polymerase                               | GI adverse effects; liver injury                                                  | [75, 76]   |

SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2; GI: Gastrointestinal.

consider patients with Crohn's disease for colectomy with end ileostomy. An important aspect to take into consideration is comorbidities, such as diabetes and hypertension, which are exacerbators of damage in COVID-19. As expected, comorbidities become paramount in symptom management, because of the high risk they represent [60, 61].

**CONCLUSION**

By now, we know that GI symptoms in COVID-19 disease such as diarrhea are related to gut microbiota alterations that alter profile cytokines, either by SARS-CoV-2 ACE2 alterations or as a secondary effect of antibiotic and antiviral drugs employed in treatment. However, additional research is needed for the hepatic and pancreatic manifestations that aggravates the patient’s situation, and a deeper understanding of the sequelae after symptoms of the disease. Until now, the knowledge that we have mainly involves the host; however, we must not ignore the pathogenicity of the virus and the recent variants that are currently circulating since these could in the future serve to explain in greater detail the mechanisms involved in the intestinal damage or with the presentation of GI symptoms that can accompany COVID-19 respiratory disease.

**ACKNOWLEDGEMENTS**

Special thanks to Sergio Lozano for reviewing this manuscript.
REFERENCES

1 National Institutes of Health. Coronaviruses. [cited 13 November 2020] Available from: https://www.niaid.nih.gov/diseases-conditions/coronaviruses

2 World Health Organization. WHO Coronavirus disease. [cited 13 November 2020] Available from: https://www.who.int

3 Yang C, Wang J. Transmission rates and environmental reservoirs for COVID-19 - a modeling study. J Biol Dyn 2021; 15: 86-108 [PMID: 33402047 DOI: 10.1080/17513758.2020.1869444]

4 Center for Disease Control and Prevention. Late sequela of COVID-19. [cited 13 November 2020] Available from: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/Late-sequae.html

5 Dbouk T, Drikakis D. On coughing and airborne droplet transmission to humans. Phys Fluids (1994) 2020; 32: 053310 [PMID: 32574229 DOI: 10.1063/5.0011960]

6 Luttrell S, Baj J, Karakula-Juchnowicz H, Teresiński G, Buszewicz G, Ciesielka M, Sitarz E, Forma A, Karakula K, Flieger W, Portincasa P, Maciejewski R. COVID-19: Specific and Non-Specific Clinical Manifestations and Symptoms: The Current State of Knowledge. J Clin Med 2020; 9 [PMID: 32516940 DOI: 10.3390/jcm9061753]

7 Nazari A, Jafari M, Rezaei N, Taghizadeh-Hesary F. Jet fans in the underground car parking areas and virus transmission. Phys Fluids (1994) 2021; 33: 013603 [PMID: 33746483 DOI: 10.1063/5.0033557]

8 Cheung KS, Hung IFN, Chan PPy, Lung KC, Tso E, Liu R, Ng YY, Chu MY, Chung TWH, Tam AR, Yip CCY, Leung KH, Fung AY, Zhang RR, Lin Y, Cheng HM, Zhang AJX, To KKW, Chan KH, Yuen KY, Leung WK. Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples From a Hong Kong Cohort: Systematic Review and Meta-analysis. Gastroenterology 2020; 159: 81-95 [PMID: 32251668 DOI: 10.1053.j.gastro.2020.03.065]

9 Almeida JFM, Chethier EZ. COVID-19 and the gastrointestinal tract: what do we already know? Einstein (Sao Paulo) 2020; 18: eRW5909 [PMID: 33206816 DOI: 10.31744/einstein_journal/2020RW5909]

10 Galanopoulos M, Gkeros F, Doukatas A, Karianakis G, Pontas C, Tsoukalas N, Viazis N, Liatsos C, Mantzaris GJ. COVID-19 pandemic: Pathophysiology and manifestations from the gastrointestinal tract. World J Gastroenterol 2020; 26: 4579-4588 [PMID: 32884218 DOI: 10.3748/wjg.v26.i31.4579]

11 Wong SH, Lui RN, Sung JJ. Covid-19 and the digestive system. J Gastroenterol Hepatol 2020; 35: 744-748 [PMID: 32215956 DOI: 10.1111/jgh.15047]

12 Ye Q, Wang B, Zhang T, Xu J, Shang S. The mechanism and treatment of gastrointestinal symptoms in patients with COVID-19. Am J Physiol Gastrointest Liver Physiol 2020; 319: G245-G252 [PMID: 32639848 DOI: 10.1152/ajpgi.00148.2020]

13 Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for Gastrointestinal Infection of SARS-CoV-2. Gastroenterology 2020; 158: 1831-1833.e3 [PMID: 32147753 DOI: 10.1053/j.gastro.2020.02.055]

14 Edler P, Lodýga M, Dobrowolska A, Rydzewska G, Kamchie-Milz J. Addressing multiple gastroenterological aspects of coronavirus disease 2019. Pol Arch Intern Med 2020; 130: 420-430 [PMID: 32356641 DOI: 10.20452/pamw.15332]

15 Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS [PMID: 32253371 DOI: 10.1080/17513758.2020.1869444]

16 Edler P, Lodýga M, Dobrowolska A, Rydzewska G, Kamchie-Milz J. Addressing multiple gastroenterological aspects of coronavirus disease 2019. Pol Arch Intern Med 2020; 130: 420-430 [PMID: 32356641 DOI: 10.20452/pamw.15332]

17 Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS [PMID: 32253371 DOI: 10.1080/17513758.2020.1869444]

18 Edler P, Lodýga M, Dobrowolska A, Rydzewska G, Kamchie-Milz J. Addressing multiple gastroenterological aspects of coronavirus disease 2019. Pol Arch Intern Med 2020; 130: 420-430 [PMID: 32356641 DOI: 10.20452/pamw.15332]

19 Edler P, Lodýga M, Dobrowolska A, Rydzewska G, Kamchie-Milz J. Addressing multiple gastroenterological aspects of coronavirus disease 2019. Pol Arch Intern Med 2020; 130: 420-430 [PMID: 32356641 DOI: 10.20452/pamw.15332]

20 Edler P, Lodýga M, Dobrowolska A, Rydzewska G, Kamchie-Milz J. Addressing multiple gastroenterological aspects of coronavirus disease 2019. Pol Arch Intern Med 2020; 130: 420-430 [PMID: 32356641 DOI: 10.20452/pamw.15332]

21 Edler P, Lodýga M, Dobrowolska A, Rydzewska G, Kamchie-Milz J. Addressing multiple gastroenterological aspects of coronavirus disease 2019. Pol Arch Intern Med 2020; 130: 420-430 [PMID: 32356641 DOI: 10.20452/pamw.15332]

22 Edler P, Lodýga M, Dobrowolska A, Rydzewska G, Kamchie-Milz J. Addressing multiple gastroenterological aspects of coronavirus disease 2019. Pol Arch Intern Med 2020; 130: 420-430 [PMID: 32356641 DOI: 10.20452/pamw.15332]

23 Edler P, Lodýga M, Dobrowolska A, Rydzewska G, Kamchie-Milz J. Addressing multiple gastroenterological aspects of coronavirus disease 2019. Pol Arch Intern Med 2020; 130: 420-430 [PMID: 32356641 DOI: 10.20452/pamw.15332]

24 Edler P, Lodýga M, Dobrowolska A, Rydzewska G, Kamchie-Milz J. Addressing multiple gastroenterological aspects of coronavirus disease 2019. Pol Arch Intern Med 2020; 130: 420-430 [PMID: 32356641 DOI: 10.20452/pamw.15332]

25 Edler P, Lodýga M, Dobrowolska A, Rydzewska G, Kamchie-Milz J. Addressing multiple gastroenterological aspects of coronavirus disease 2019. Pol Arch Intern Med 2020; 130: 420-430 [PMID: 32356641 DOI: 10.20452/pamw.15332]

26 Edler P, Lodýga M, Dobrowolska A, Rydzewska G, Kamchie-Milz J. Addressing multiple gastroenterological aspects of coronavirus disease 2019. Pol Arch Intern Med 2020; 130: 420-430 [PMID: 32356641 DOI: 10.20452/pamw.15332]

27 Edler P, Lodýga M, Dobrowolska A, Rydzewska G, Kamchie-Milz J. Addressing multiple gastroenterological aspects of coronavirus disease 2019. Pol Arch Intern Med 2020; 130: 420-430 [PMID: 32356641 DOI: 10.20452/pamw.15332]

28 Edler P, Lodýga M, Dobrowolska A, Rydzewska G, Kamchie-Milz J. Addressing multiple gastroenterological aspects of coronavirus disease 2019. Pol Arch Intern Med 2020; 130: 420-430 [PMID: 32356641 DOI: 10.20452/pamw.15332]
Pancreatic Damage After SARS-CoV-2 Infection.

Liu F. 10.1053/j.gastro.2020.03.055

Wang F. 10.1016/j.jcmgh.2020.09.015

Fiel MI. 10.1111/Liv.14730

Nardo AD. 2004; CL. SARS-associated viral hepatitis caused by a novel coronavirus: report of three cases. 1566 [PMID: 123054860 DOI: 10.1168/s40779-020-00279-z]

Jin X, Lian JS, Hu JH, Gao I, Zheng L, Zhang VM, Hao SR, Jia HY, Cai H, Zhang XL, Yu GD, Xu KJ, Wang XY, Gu JQ, Zhang SY, Ye CY, Jin CL, Lu YF, Yu X, Yu XP, Huang JR, Xu KL, Ni Q, Yu CB, Zhu B, Li YT, Liu J, Zhao H, Zhang X, Yu L, Guo YZ, Su JW, Tao JJ, Lang GJ, Wu XX, Wu WR, Qv TT, Xiang DR, Yi P, Shi D, Chen Y, Ren Y, Qiu YQ, Li LJ, Sheng J, Yang Y. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut 2020; 69: 1002-1009 [PMID: 32213556 DOI: 10.1136/gutjnl-2020-320926]

Luo X, Zhou GZ, Zhang Y, Peng LH, Zou LP, Yang YS. Coronavirus and gastrointestinal diseases. Mil Med Res 2020; 7: 49 [PMID: 33054860 DOI: 10.1186/s40779-020-00279-z]

Gou W, Fu Y, Yue L, Chen G, Cai X, Shuai M, Xu F, Yi X, Chen H, Zhu Y, Xiao M, Jiang Z, Miao Z, Xiao C, Shen B, Wu X, Zhao H, Ling W, Wang J, Chen Y, Guo T, Zheng JS. Gut microbiota may underlie the predisposition of healthy individuals to COVID-19. medRxiv 2020; 1-44 [DOI: 10.1101/2020.04.22.2007691]

Zhang Y, Geng X, Tan Y, Li Q, Xu C, Xu J, Hao L, Zeng Z, Luo X, Liu F, Wang H. New understanding of the damage of SARS-CoV-2 infection outside the respiratory system. Biomed Pharmacother 2020; 127: 110195 [PMID: 32361161 DOI: 10.1016/j.biopha.2020.110195]

Ma C, Cong Y, Zhang H. COVID-19 and the Digestive System. Am J Gastroenterol 2020; 115: 1003-1006 [PMID: 32340523 DOI: 10.14309/aig.0000000000000691]

Dhar D, Mohanty A. Gut microbiota and Covid-19: possible link and implications. Virus Res 2020; 286 [PMID: 32818081 DOI: 10.1016/j.virusres.2020.198081]

Muniz LR, Knoops C, Yeretsian G. Intestinal antimicrobial peptides during homeostasis, infection, and disease. Front Immunol 2012; 3: 310 [PMID: 23087688 DOI: 10.3389/fimmu.2012.00310]

Baghbanian T, Nizkad H, Azadbakht J, Izadpanah F, Haddad Kashani H. Dual and mutual interaction between microbiota and viral infections: a possible treat for COVID-19. Microb Cell Fact 2020; 19: 217 [PMID: 33242320 DOI: 10.1186/s12934-020-01483-1]

Zuo T, Zhang F, Lui GCC, Yeoh YK, Li AYL, Zhan H, Wan Y, Chung ACK, Cheung CP, Chen N, Lai CKC, Chen Z, Tao EYK, Fung KSC, Chan V, Ling L, Joynt G, Hui DSC, Chan FKL, Chan PKS, Ng SC. Alterations in Gut Microbiota of Patients With COVID-19 During Time of Hospitalization. Gastroenterology 2020; 159: 944-955. e5 [PMID: 32442562 DOI: 10.1053/j.gastro.2020.03.048]

Tao W, Zhang G, Wang X, Guo M, Zeng W, Xu Z, Liu L, Zhang K, Wang Y, Ma X, Chen Z, Jin T, Weng J, Zhu S. Analysis of the intestinal microbiota in COVID-19 patients and its correlation with the inflammatory factor IL-18 and SARS-CoV-2-specific IgA. medRxiv 2020; 1-9 [DOI: 10.1101/2020.08.12.20173781]

Al Heilay S, Hashim MY, Senok A, Gaudet M, Abou Tayoun A, Hamoudi R, Alsheikh-Ali A, Hamid Q. Regulation of Angiotensin Converting Enzyme 2 in Obesity: Implications for COVID-19. Front Physiol 2020; 11: 555039 [PMID: 33071815 DOI: 10.3389/fphys.2020.555039]

Xu Y, Wan Q, Feng J, Du L, Li K, Zhou Y. Whole grain diet reduces systemic inflammation: A meta-analysis of 9 randomized trials. Medicine (Baltimore) 2018; 97: e12995 [PMID: 30412134 DOI: 10.1097/md.0000000000012995]

Jothisman D, Venugopul R, Abedin MF, Kaliannoorithi I, Rela M. COVID-19 and the liver. J Hepatol 2020; 73: 1231-1240 [PMID: 35235666 DOI: 10.1016/j.jhep.2020.06.006]

Schmit G, Lelotte J, Vanhaeyst J, Horsmans Y, Van Bockstael M, Baldwin P. The Liver in COVID-19-Related Death: Protagonist or Innocent Bystander? Pathobiology 2021; 88: 88-94 [PMID: 33108789 DOI: 10.1159/000512008]

Fan Z, Chen L, Li J, Cheng X, Yang J, Tian C, Zhang Y, Huang S, Liu Z, Cheng J. Clinical Features of COVID-19-Related Liver Functional Abnormality. Clin Gastroenterol Hepatol 2020; 18: 1561-1566 [PMID: 32283325 DOI: 10.1016/j.cgh.2020.04.002[Available]

Chau TN, Lee KC, Yao H, Tsang TY, Chow TC, Yeung YC, Choi KW, Tso YK, Lau T, Lai ST, Lai CL. SARS-associated viral hepatitis caused by a novel coronavirus: report of three cases. Hepatology 2004; 39: 302-310 [PMID: 14767982 DOI: 10.1002/hep.20111]

Nardo AD, Schneeberger-Gleixner M, Bakai M, Dixon ED, Lax SF, Trauner M. Pathophysiological mechanisms of liver injury in COVID-19. Liver Int 2021; 41: 20-32 [PMID: 33190346 DOI: 10.1111/liv.14730]

Fiel MI, El Jamal SM, Paniz-Mondolfi A, Gordon RE, Reidy J, Bandojice J, Advani R, Kilaru S, Pourmand K, Ward S, Thung SN, Schiano T. Findings of Severe Hepatic Severe Acute Respiratory Syndrome Coronavirus-2 Infection. Cell Mol Gastroenterol Hepatol 2021; 1-8 [DOI: 10.1016/j.jcmgh.2020.09.015]

Wang F, Wang H, Fan J, Zhang Y, Zhao Q. Pancreatic Injury Patterns in Patients With Coronavirus Disease 19 Pneumonia. Gastroenterology 2020; 159: 367-370 [PMID: 32247022 DOI: 10.1053/j.gastro.2020.03.055]

Liu F, Long X, Zhang B, Zhang W, Chen X, Zhang Z. ACE2 Expression in Pancreas May Cause Pancreatic Damage After SARS-CoV-2 Infection. Clin Gastroenterol Hepatol 2020; 18: 2128-2130.
Delgado-Gonzalez P et al. Gastrointestinal system and COVID-19

e2 [PMID: 32334082 DOI: 10.1016/j.cgh.2020.04.040]

McNabb-Baltar J, Jin DX, Grover AS, Redd WD, Zhou JC, Hatthorn KE, McCarty TR, Bazarbashi AN, Shen L, Chan WW. Lipase Elevation in Patients With COVID-19. *Am J Gastroenterol* 2020; 115: 1286-1288 [PMID: 32496339 DOI: 10.14309/ajg.0000000000000732]

Barluss U, Williams B, Dhana K, Adnan D, Khan SR, Mahdavinia M, Bishelsari F. Marked Elevated of Lipase in COVID-19 Disease: A Cohort Study. *Clin Transl Gastroenterol* 2020; 11: e00215 [PMID: 32764201 DOI: 10.14309/ctg.0000000000000215]

Moharesti A, Batt M. An update on the pathophysiology of osteoarthritis. *Ann Phys Rehabil Med* 2016; 59: 333-339 [PMID: 27546496]

Alves AM, Yvanotto EY, Marzinotto MAN, Teixeira ACS, Carrilho FJ. SARS-CoV-2 Leading to acute pancreatitis: an unusual presentation. *Braz J Infect Dis* 2020; 24: 561-564 [PMID: 32961108 DOI: 10.1016/bjid.2020.08.011]

Mahase E. Covid-19: Pfizer and BioNTech submit vaccine for US authorisation. *BMJ* 2020; 371: m4552 [PMID: 33219049 DOI: 10.1136/bmj.m4552]

Callaway E. COVID vaccine excitement builds as Moderna reports third positive result. *Nature* 2020; 587: 337-338 [PMID: 33199901 DOI: 10.1038/d41586-020-02348-7]

Su S, Shen J, Zhu L, Qiu Y, He JS, Tan JY, Iacucci M, Ng SC, Ghosh S, Mao R, Liang J. Involvement of digestive system in COVID-19: manifestations, pathology, management and challenges. *Therap Adv Gastroenterol* 2020; 13: 1756284820934626 [PMID: 32595762 DOI: 10.1177/1756284820934626]

Cai X, Ma Y, Li S, Chen Y, Rong Z, Li W. Clinical Characteristics of 5 COVID-19 Cases With Non-respiratory Symptoms as the First Manifestation in Children. *Front Pediatr* 2020; 8: 258 [PMID: 32574284 DOI: 10.3389/fped.2020.00255]

Dhar J, Samanta J, Kochhar R. Corona Virus Disease-19 pandemic: The gastroenterologists' perspective. *Indian J Gastroenterol* 2020; 39: 220-231 [PMID: 32783168 DOI: 10.1007/s12664-020-01075-2]

Carfora V, Spinelli G, Ricciolino R, Di Mauro M, Migliaccio MG, Motolla FF, Verde N, Coppola N. Vanvitelli COVID-19 group. Anticoagulant treatment in COVID-19: a narrative review. *J Thromb Thrombolysis* 2021; 51: 642-648 [PMID: 32809158 DOI: 10.1007/s11239-020-02242-0]

Porfidia A, Pola R. Venous Thromboembolism and Heparin Use in COVID-19 Patients: Juggling between Pragmatic Choices, Suggestions of Medical Societies and the Lack of Guidelines. *J Thromb Thrombolysis* 2020; 50: 68-71 [PMID: 32367471 DOI: 10.1007/s11239-020-02125-4]

Ahmed M, Majeed A, Powell R. Heparin induced thrombocytopenia: diagnosis and management update. *Postgrad Med J* 2007; 83: 575-582 [PMID: 17823223 DOI: 10.1136/pgmj.2007.059188]

Jang IK, Hursting MJ. When heparins promote thrombosis: review of heparin-induced thrombocytopenia. *Circulation* 2005; 111: 2671-2683 [PMID: 15911718 DOI: 10.1161/CIRCULATIONAHA.104.518563]

Marciani L, Gowland PA, Spiller RC, Manoj P, Moore RJ, Young P, Fillery-Travis AJ. Effect of meal viscosity and nutrients on satiety, intragastric dilution, and emptying assessed by MRI. *Clin Transl Gastroenterol* 2020; 11: 337-338 [PMID: 33727675 DOI: 10.14309/ctg.0000000000000324]

Esposito S, Vincenzi C, Nigg M, Thomans K, Rutishauser J, Aujesky D, Rodondi N, Donzé J, Stanga Z, Mueller B, Schuetz P. Nutritional risk screening (NRS 2002) is a strong and modifiable predictor risk score for short-term and long-term clinical outcomes: secondary analysis of a prospective randomised trial. *Clin Nutr* 2020; 39: 2720-2729 [PMID: 31882232 DOI: 10.1016/j.clnu.2019.11.041]

Baryah ANS, Misra V, Mahajan R, Sood A. Impact of Corona Virus Disease-19 (COVID-19) pandemic on gastrointestinal disorders. *Indian J Gastroenterol* 2020; 39: 214-219 [PMID: 32749642 DOI: 10.1007/s12664-020-01071-6]

Remzi FH, Panis Y, Spinelli A, Kotze PG, Mantzaris G, Söderholm JD, d’Hoore A, Bemelman WA, Yamamoto T, Pemberton JH, Tietz E, Öresland T, Flesher P. International Organization for the Study of IBD Recommendations for Surgery in Patients With IBD During the Coronavirus Disease 2019 Pandemic. *Dis Colon Rectum* 2020; 63: 870-873 [PMID: 32350506 DOI: 10.1111/dcr.13521]

Hersberger L, Bargetzi L, Bargetzi A, Trbojev D, Fehr R, Baechli V, Geiser M, Deiss M, Bargetzi A, Tribolet P, Fehr R, Baechli V, Geiser M, Deiss M, Gomes F, Nigg M, Thomann K, Brand C, Ruthissera J, Aujesky D, Rodondi N, Donzé J, Stanga Z, Mueller B, Schuetz P. Nutritional risk screening (NRS 2002) is a strong and modifiable predictor risk score for short-term and long-term clinical outcomes: secondary analysis of a prospective randomised trial. *Clin Nutr* 2020; 39: 2720-2729 [PMID: 31882232 DOI: 10.1016/j.clnu.2019.11.041]

Exposito S, Noviello S, Pagliano P. Update on treatment of COVID-19: ongoing studies between promising and disappointing results. *Infecz Med* 2020; 28: 198-211 [PMID: 32335561 DOI: 10.1016/j.ifmed.2020.11.001]

Mao SA, Klonoff DC, Akram J. Efficacy of chloroquine and hydroxychloroquine in the treatment of COVID-19. *Eur Rev Med Pharmacol Sci* 2020; 24: 4539-4547 [PMID: 32373903 DOI: 10.26355/eurrev_202004_21038]

Lofgren SM, Nicol MR, Bangdiwala AS, Postk A, Okafor EC, Skipper CP, Pullen MF, Engen NW, Abassi M, Williams DA, Nascone AA, Axelrod ML, Lother SA, MacKenzie LJ, Drobot G, Marten N, Cheng MP, Zarychanski R, Schwartz IS, Silverman M, Chagla Z, Kelly L, McDonald EG, Lee TC, Hussel KH, Boulware DR, Rajasingham R. Safety of Hydroxychloroquine Among Outpatient Clinical Trial Participants for COVID-19. *Open Forum Infect Dis* 2020; 7: ofaa500 [PMID: 33204764 DOI: 10.1093/ofid/ofaa500]

Becker RC. Covid-19 treatment update: follow the scientific evidence. *J Thromb Thrombolysis* 2020; 59: 43-53 [PMID: 32338320 DOI: 10.1007/s11239-020-02120-9]

Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in
treatment of COVID-19 associated pneumonia in clinical studies. *BioSci Trends* 2020; 14: 72-73

[PMD: 32074550 DOI: 10.5582/BST.2020.01047]

67 Pascarella G, Strumia A, Piliego C, Bruno F, Del Buono R, Costa F, Scarlata S, Agrò FE. COVID-19 diagnosis and management: a comprehensive review. *J Intern Med* 2020; 288: 192-206 [PMID: 3248588 DOI: 10.1111/joim.13091]

68 Song Y, Zhang M, Yin L, Wang K, Zhou Y, Zhou M, Lu Y. COVID-19 treatment: close to a cure? *Int J Antimicrob Agents* 2020; 56: 106080 [PMID: 32634603 DOI: 10.1016/j.ijantimicag.2020.106080]

69 Fatima SA, Asif M, Khan KA, Siddique N, Khan AZ. Comparison of efficacy of dexamethasone and methylprednisolone in moderate to severe covid-19 disease. *Ann Med Surg (Lond)* 2020; 60: 413-416 [PMID: 33200031 DOI: 10.1016/j.amsu.2020.11.027]

70 Mattos-Silva P, Felix NS, Silva PL, Robba C, Battaglini D, Pelosi P, Rocco PRM, Cruz FF. Pros and cons of corticosteroid therapy for COVID-19 patients. *Respir Physiol Neurobiol* 2020; 280: 103492 [PMID: 32659271 DOI: 10.1016/j.resp.2020.103492]

71 Pani A, Lauriola M, Romandini A, Scaglione F. Macrolides and viral infections: focus on azithromycin in COVID-19 pathology. *Int J Antimicrob Agents* 2020; 56: 106053 [PMID: 32534189 DOI: 10.1016/j.ijantimicag.2020.106053]

72 Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Song B, Cai Y, Wei M, Li X, Xia J, Chen N, Xiang J, Yu T, Bai T, Xie X, Zhang L, Li C, Yuan Y, Chen H, Li H, Huang H, Tu S, Gong F, Liu Y, Wei Y, Dong C, Zhou F, Gu X, Xu J, Liu Z, Zhang Y, Shang L, Wang K, Li K, Zhou X, Dong X, Qu Z, Lu S, Hu X, Ruan S, Luo S, Wu J, Peng L, Cheng F, Pan L, Zou J, Jia C, Liu X, Wang S, Wu X, Ge Q, He J, Zhan H, Qu F, Guo L, Huang C, Jaki T, Hayden FG, Horby PW, Zhang D, Wang C. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med* 2020; 382: 1787-1799 [PMID: 32187464 DOI: 10.1056/nejmoa2001282]

73 Sultana J, Cutroneo PM, Crisafulli S, Puglisi G, Caramori G, Trifirò G. Azithromycin in COVID-19 Patients: Pharmacological Mechanism, Clinical Evidence and Prescribing Guidelines. *Drug Saf* 2020; 43: 691-698 [PMID: 32696429 DOI: 10.1007/s40264-020-00976-7]

74 Hippensteel JA, LaRiviere WB, Colbert JF, Langouët-Astrié CJ, Schmidt EP. Heparin as a therapy for COVID-19: current evidence and future possibilities. *Am J Physiol Lung Cell Mol Physiol* 2020; 319: L211-L217 [PMID: 32519894 DOI: 10.1152/ajplung.00199.2020]

75 Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, Liao X, Gu Y, Cai Q, Yang Y, Shen C, Li X, Peng L, Huang D, Zhang J, Zhang S, Wang F, Liu J, Chen L, Chen S, Wang Z, Zhang Z, Cao R, Zhong W, Liu Y, Liu L. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. *Engineering (Beijing)* 2020; 6: 1192-1198 [PMID: 32346491 DOI: 10.1016/j.eng.2020.03.007]

76 Coones EA, Haghbayan H. Favipiravir, an antiviral for COVID-19? *J Antimicrob Chemother* 2020; 75: 2013-2014 [PMID: 32417899 DOI: 10.1093/jac/dkaa171]
