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Review Article

Intestinal permeability changes with bacterial translocation as key events modulating systemic host immune response to SARS-CoV-2: A working hypothesis

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ABSTRACT

The microbiota-gut-liver-lung axis plays a bidirectional role in the pathophysiology of a number of infectious diseases. During the course of severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and 2 (SARS-CoV-2) infection, this pathway is unbalanced due to intestinal involvement and systemic inflammatory response. Moreover, there is convincing preliminary evidence linking microbiota-gut-liver axis perturbations, proinflammatory status, and endothelial damage in noncommunicable preventable diseases with coronavirus disease 2019 (Covid-19) severity. Intestinal damage due to SARS-CoV-2 infection, systemic inflammation-induced dysfunction, and IL-6-mediated diffuse vascular damage may increase intestinal permeability and precipitate bacterial translocation. The systemic release of damage- and pathogen-associated molecular patterns (e.g. lipopolysaccharides) and consequent immune-activation may in turn auto-fuel vicious cycles of systemic inflammation and tissue damage. Thus, intestinal bacterial translocation may play an additive/synergistic role in the cytokine release syndrome in Covid-19. This review provides evidence on gut-liver axis involvement in Covid-19 as well as insights into the hypothesis that intestinal endotheliitis and permeability changes with bacterial translocation are key pathophysiologic events modulating systemic inflammatory response. Moreover, it presents an overview of readily applicable measures for the modulation of the gut-liver axis and microbiota in clinical practice.
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1. Introduction

The outbreak of coronavirus disease 2019 (Covid-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly diffused worldwide and is now considered a pandemic by the World Health Organization [1]. SARS-CoV-2 is a positive-sense single-stranded RNA virus and a member of the Betacoronavirus genus. Coronaviruses bind to their target cells through the angiotensin 2-converting enzyme (ACE2), a monocarboxypeptidase that cleaves numerous peptides within the renin-angiotensin system and other substrates [1]. The cell entry of coronavirus depends on the binding of viral spike (S) proteins to cellular receptors and on S protein priming by host cell proteases [1]. ACE2 is expressed constitutively by the epithelial cells of the lung, intestine, kidneys, and blood vessels and is present in the terminal ileum and colon in concentrations that are amongst the highest in the body [2]. Intestinal involvement and intestinal cell infection were previously demonstrated in the severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) epidemic [3]. A considerable number of SARS-CoV-1 patients experienced gastrointestinal symptoms [4,5]. While SARS-CoV-1 can infect the lungs and intestine, tissue response in these two organs differs. Small pathology findings can be observed in the intestine with optical microscopy, both in biopsies taken during the initial stages [4] and in autopsy samples [6]. However, electron-microscopy [4] and immunohistochemistry [3,6] studies have revealed the presence of SARS-CoV-1 in surface enterocytes and in small vessels in the intestine. Therefore, although changes in the intestine are usually milder than those seen in the lungs, an increase in intestinal permeability to lipopolysaccharides (LPSs) and the translocation of intestinal bacteria are likely to occur. The liver is also a target of coronaviruses.

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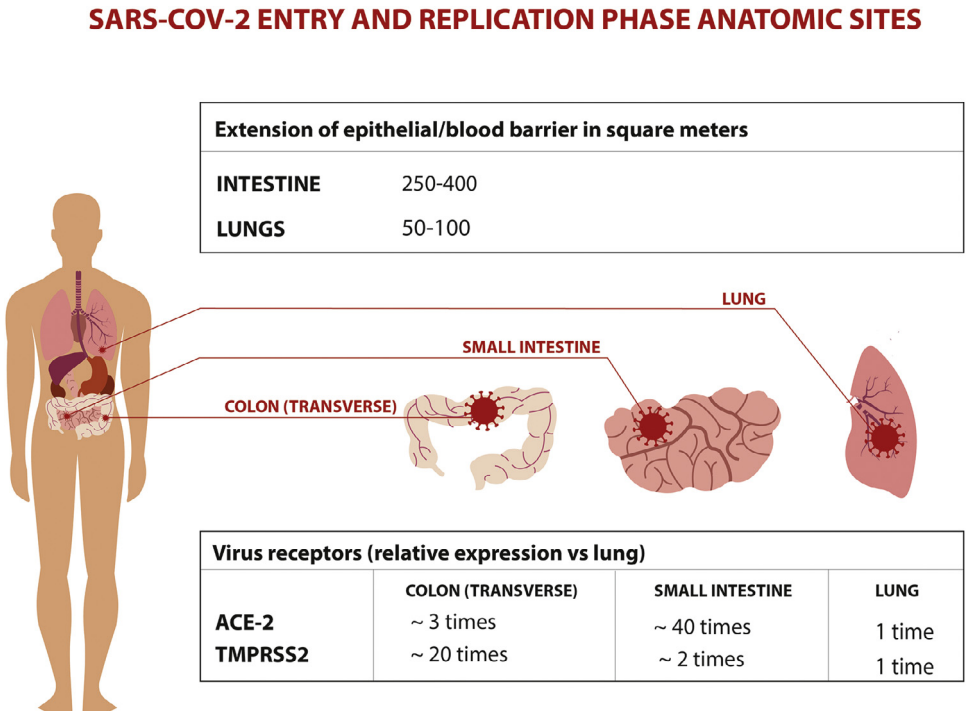

Fig. 1. SARS-CoV-2 entry and replication phase anatomical sites. The expression of ACE2 in the small intestine and colon, respectively, is ~40x and ~3x higher with respect to the lungs, whereas TMPRSS2 expression in the small intestine and colon is respectively ~2x and ~20x higher with respect to the lungs. The extension of the epithelial/blood barrier is 50–100 m^2s in the lungs and 250–400 m^2s in the intestine. Abbreviations: ACE2, Angiotensin-converting enzyme 2; TMPRSS2, Transmembrane serine protease 2.

Viral nucleic acids of SARS-CoV-1 have been found in liver tissue, and percutaneous liver biopsies of SARS-CoV-1 have shown conspicuous atypical features of liver injury, including acidophilic bodies, hepatocyte ballooning, and lobular activities without fibrin deposition or fibrosis [7]. The present review will discuss different pathophysiological mechanisms through which the gastrointestinal tract may contribute to SARS-CoV-2 infection progression.

2. SARS-CoV-1 and SARS-CoV-2 and the gastrointestinal tract

Covid-19 presents with fever and typical respiratory symptoms, but also with gastrointestinal symptoms and liver damage [8-11]. As previously demonstrated in SARS-CoV-1, gastrointestinal manifestations are significant extrapulmonary complaints in Covid-19 patients [8-11]. In particular, diarrhoea is frequent [8-10], while nausea and vomiting have been associated with lung involvement [11]. The potential role of the gut in SARS-CoV-2 infection has been demonstrated in adult and paediatric subjects [12-15]. In particular, the faecal excretion of SARS-CoV-2 has been observed in more than half of infected subjects [13,15], and this excretion is prolonged [14,15] and persists for nearly 5 weeks, even after patient respiratory samples test negative for SARS-CoV-2 RNA [15]. Conversely, although SARS-CoV-2 is detectable in stools, there is no clear evidence regarding the ability of faecal virus excretions to induce infection and thus facilitate faecal-oral transmission. SARS-CoV-2 uses the SARS-CoV receptor ACE2 for entry and the transmembrane serine protease 2 (TMPRSS2) for S protein priming. Interestingly, the evaluation of ACE2 and TMPRSS2 expression according to anatomical sites and cell types revealed that ACE2 expression in the small intestine and colon is respectively ~40x and ~3x higher with respect to the lungs, whereas TMPRSS2 expression in the small intestine and colon is respectively ~2x and ~20x higher with respect to the lungs [16] (Fig. 1). Since vascular involvement may determine the systemic consequences of the infection on different districts, it is important to keep in mind that the extension of the epithelial/blood barrier is 50–100 m^2 in the lungs and 250–400 m^2 in the intestine [17] (Fig. 1).

Besides what can be inferred by data on the expression of ACE2 and TMPRSS2 [13-18,19], direct infection of intestinal cells by SARS-CoV-2 has been demonstrated through the intestinal organoid technique [20]. Since inflammation seems to upregulate ACE2 expression [17], it is important to understand whether patients with inflammatory bowel disease (IBD) are more susceptible to Covid-19 and the cytokine release syndrome (CRS) associated with lung injury and fatal outcome [21]. While the risk of SARS-CoV-2 infection in IBD patients depends on several universal risk factors, including social distancing [22], older age and comorbidities have been associated with a negative outcome in IBD, whereas IBD treatments have not, highlighting that acute IBD flare prevention and inflammation reduction may avoid severe Covid-19 [23].

3. Leaky gut and bacterial translocation promote cytokine release syndrome

SARS-CoV-1 and SARS-CoV-2 infections are characterized by intense systemic symptoms triggered by an exuberant host immune response [25,26]. However, sepsis is not evident in most cases [5-8]. Excessive systemic inflammatory responses with or without the pulmonary counterpart (acute respiratory distress syndrome/ARDS) that are characterized by high levels of a wide range of proinflammatory cytokines and chemokines have been associated with severe morbidity and mortality in a wide variety of viral diseases [25]. Similar features have been reported during the course of acute lung injury caused by respiratory syncytial virus, influenza A virus, and SARS-CoV-1 [25,26]. The reason for this unbalanced inflammatory response in some viral infections is not well understood and is probably multifactorial [25]. Although the role of bacterial LPS has not been demonstrated in human SARS-CoV-1 and SARS-CoV-2, the cellular receptor for degradation products of the intestinal bacterial flora (pathogen-associated

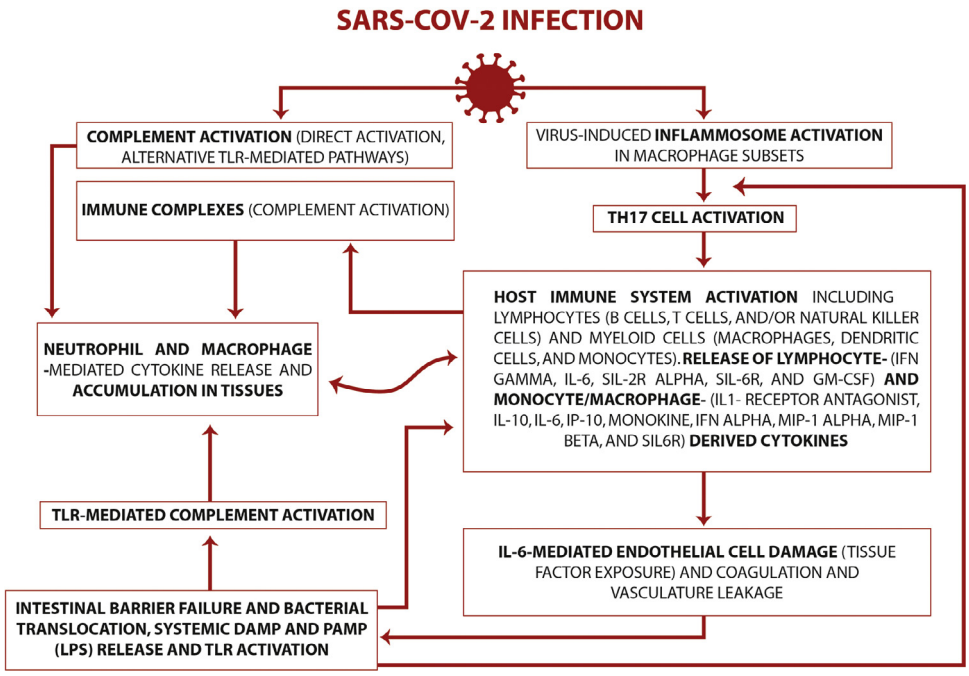

Fig. 2. Host response to SARS-CoV-2 infection and proposed interplay with intestinal barrier permeability and bacterial translocation. SARS-CoV-2 infection and replication culminate in the activation of innate and adaptive immunity, and complement, with systemic and local effects, e.g. cytokine release syndrome. In addition, IL-6-mediated endothelial cell damage [tissue factor exposure], coagulation, and vasculature leakage induce further tissue damage and perpetuate systemic inflammation. This complex systemic and local pathologic condition may induce intestinal damage and increase the intestinal permeability precipitating intestinal barrier failure and bacterial translocation, which in turn auto-fuel vicious cycles of systemic inflammation and tissue damage. Abbreviations: IL, interleukin; SIL-2R, soluble IL-2 receptor; SIL-6R, soluble IL-6 receptor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IP, interferon gamma-inducible protein; MIP, macrophage inflammatory protein; TLR, tool-like receptor; Th17, T helper 17 cell; DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; LPS, lipopolysaccharide.

molecular pattern molecules, in particular LPS), i.e. the toll-like receptor 4 (TLR4), has already been confirmed to induce harmful inflammatory responses during acute viral infections [25]. Furthermore, the peculiar phenotype of Covid-19 inflammatory-cytokine response points toward the activation of T helper 17 lymphocytes, a particular subset of T helper lymphocytes characterized by a high production of interleukin (IL)-17 and other proinflammatory cytokines. This is the same systemic inflammatory response observed in intestinal bacterial translocation [26]. Cross-talk between the lungs and intestinal barrier has been described, which may be relevant in the pathogenesis of ARDS and sepsis [27]. In ARDS and critically ill patients with sepsis, bacterial translocation is widely documented and can be viewed as an advanced event that precipitates lung disease and rapidly worsens systemic inflammation [27]. In other words, intestinal barrier dysfunction can be considered part of multiorgan failure, and contributes to further lung damage and systemic inflammation in ARDS and sepsis [27]. In SARS-CoV-2 infection, bacterial translocation may be an early event related to intestinal damage due to tissue infection, systemic inflammation-induced dysfunction, and IL-6-mediated diffuse vascular damage. A reconciliatory working hypothesis is presented in Fig. 2. SARS-CoV-2 infection and replication culminate in the activation of innate [28] and adaptive immunity [29] and complement [30], with systemic and local effects, e.g. the release of lymphocyte-derived (interferon gamma, IL-6, soluble IL-2 receptor alpha, soluble IL-6 receptor, and granulocyte-macrophage colony-stimulating factor) and monocyte/macrophage (IL-1 receptor antagonist, IL-10, IL-6, interferon gamma-inducible protein-10, monokine, IFN alpha, macrophage inflammatory protein-1 (MIP-1) alpha, MIP-1 beta, and soluble IL-6 receptor) cytokines and neutrophil and macrophage accumulation in tissues [31]. In addition, IL-6-mediated endothelial cell damage (tissue factor exposure), coagulation [32], and vasculature leakage induce further tissue damage and perpetuate systemic inflammation, e.g. CRS [33]. This complex systemic and local pathologic condition may induce intestinal damage and increase the intestinal permeability precipitating intestinal barrier failure and bacterial translocation, with the systemic release of damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs), e.g. LPSs and consequential TLR activation, which in turn auto-fuel vicious cycles of systemic inflammation and tissue damage (Fig. 2). Intestinal bacterial translocation may play an additive/synergistic role in the CRS underlying the unfavourable evolution of Covid-19 [12-27]. Cross talk between LPSs and IL-6 that determines heartburn and systemic inflammatory response independent of prostaglandins has been previously described [34]. Liver cells express ACE2 [35], particularly cholangiocytes, which have easily been experimentally infected by SARS-CoV-2 [36]. The liver injury demonstrated in SARS-CoV-2 and the negative clinical significance of liver test alterations [10] suggest a reduced clearance capacity of the liver filter as compared to bacterial degradation products and other toxins (PAMPs and DAMPs) during SARS-CoV-2.

4. Endotheliitis as an effector of gastrointestinal tract damage

Covid-19 patients are at a high risk of both venous and arterial thromboembolism [37]. Thrombocytopenia and increased D-dimer levels are common and associated with worse clinical outcomes in Covid-19 patients [38]. Indeed, the majority of Covid-19 patients who die present disseminated intravascular coagulation [39]. However, further investigations are needed to determine whether these marked prothrombotic changes are specific for this viral agent or secondary to the cytokine storm. Viruses can stimulate systemic inflammatory response and cause an imbalance between procoagulant and anticoagulant mechanisms. Platelets themselves are acti-

vated upon antigen recognition and interact with white blood cells to form clots to facilitate the removal of pathogens [38]. SARS-CoV-1 was reported to be associated with specific autoptic changes including proliferation, swelling, and apoptosis of endothelial cells, in addition to oedema, infiltrates of inflammatory cells, and necrosis of small vessel walls in the lungs, heart, brain, kidneys, liver, and gastrointestinal tract [40]. Strikingly similar histological pictures have recently been reported in Covid-19 patients with diffuse severe endotheliitis of the submucosal vessels in the small bowel [41]. In a way, this kind of endothelial injury is similar to that commonly reported in intestinal transplant-associated thrombotic microangiopathy, which is observed after hematopoietic stem cell transplant [42]. Indeed, in these cases ischaemic enterocolitis presents with abdominal pain and gastrointestinal bleeding. A similar picture can also be seen in type II/III cryoglobulinemic vasculitis, a well-known extrahepatic feature of chronic hepatitis C and other viral infections [43] due to immune complex deposition along medium and small vessel walls, or of antiphospholipid syndrome. Of note, Covid-19 cases with multiorgan ischaemic damage due to antiphospholipid syndrome presenting with fever, diarrhoea, and respiratory symptoms have been reported [44]. For this reason, it may be speculated that SARS-CoV-2-associated diarrhoea and enterocolitis is due to a plethora of mechanisms leading to microischemic damage of the GI tract, rather than to direct viral damage of enterocytes resulting in malabsorption [45]. Unfortunately, data from endoscopic or autoptic reports on the pattern of Covid-19 damage to the GI tract are limited. One of the few initial reports on endoscopic findings in patients with Covid-19 highlighted segmental haemorrhagic colitis in the absence of virocytes [46].

One study found that bowel wall abnormalities were highly frequent findings in Covid-19 patients (13/42 or 31% of CT scans) and were associated with intensive care unit (ICU) admission (OR 15.5) [24]. Pathology correlates demonstrated ischaemic enteritis with patchy necrosis and fibrin thrombi in the arterioles of operated patients. Interestingly, in the same study 54% of Covid-19 patients who underwent abdominal ultrasound had a dilated sludge-filled gallbladder suggestive of cholestasis, a finding that may reflect the reduction in bile flow and biliary stasis observed in intestinal function failure [24]

Whether ischaemic damage in the gastrointestinal tract is more relevant than direct viral damage is an intriguing question. Recently, Effenberger et al. [47] investigated faecal calprotectin (FC) levels in 40 patients with Covid-19 stratified according to the presence of active diarrhoea, ceased diarrhoea, or no experience of diarrhoea. They found increased FC levels in Covid-19 patients with ceased or ongoing diarrhoea as compared with Covid-19 patients without diarrhoea. Notably, while FC levels correlated with circulating IL-6 levels, there was no correlation between FC levels and faecal SARS-CoV-2 RNA. These findings also suggest that intestinal damage is not directly caused by the virus.

5. Pre-existing increased intestinal permeability may contribute to negative COVID-19 outcomes in patients with noncommunicable chronic diseases

The host response to SARS-CoV-2 is certainly attributable to the biological characteristics of the virus. However, pre-existing conditions that may affect host response can exacerbate the CRS and lead to negative outcomes (severe ARDS, ICU admission, organ failure, and death). Pre-existing endothelial dysfunction is a common denominator amongst people who have an increased risk of a severe form of Covid-19 [48]. Indeed, hypertension, diabetes, obesity, cardiovascular disease, cancer, chronic kidney disease, chronic liver disease, Alzheimer's disease, advanced age, and male sex increase the risk of a moderate or severe Covid-19 outcome [49]. In each of these conditions, endothelial dysfunction may be present. Intriguingly, endothelial dysfunction and leaky gut coexist in preventable noncommunicable chronic diseases [48,50]. Indeed, increased intestinal permeability has been described in many gastrointestinal, liver, and systemic inflammatory and autoimmune diseases [50]. Increased intestinal permeability has been reported in 10.5–42.9% of ulcerative colitis patients, 36% of Crohn's disease patients, 34% of systemic sclerosis patients, 30% of patients with type 1 diabetes, 25% of patients with primary biliary cholangitis, 65% of patients with chronic liver disease and type 2 diabetes, 35% of patients with liver cirrhosis, 31% of patients with non-alcoholic fatty liver disease, and 36% of autistic patients. These conditions, particularly metabolic and liver diseases, were found to be highly prevalent amongst hospitalised Covid-19 patients at the highest risk of negative outcomes [51-56]. Interestingly, one of the first reports concerning the Covid-19 epidemic in the US described a population of 24 hospitalised and severely ill overweight/obese (median BMI 33.2+/−7.2) subjects with type II diabetes (58%) and obstructive sleep apnoea (21%) and reported a 50% mortality rate [51]. According to a meta-analysis of 18 studies [10], almost 40% of Covid-19 patients had one or more comorbidities, with hypertension, cardiovascular disease, and type II diabetes mellitus being the most frequent [10]. Furthermore, noncommunicable preventable diseases, such as metabolic syndrome, seem to have an unfavourable prognostic role [9]. A negative prognostic role has also been attributed to systemic inflammation markers such as white blood count and c-reactive protein levels [8,11], gastrointestinal symptoms such as nausea and vomiting [11], and liver test abnormalities [9]. Patients with severe Covid-19 had higher rates of gastrointestinal symptoms and liver injury as compared to those with non-severe disease [52]. Although histomorphological studies are lacking, liver test abnormalities, including transaminase and gamma-glutamyl transferase elevation, were recorded in about 30% of Covid-19 patients [8-10], while the presence of cardiovascular or metabolic comorbidities was present in about 40% of patients, thus suggesting a high prevalence of non-alcoholic fatty liver disease in patients with a severe Covid-19 phenotype [8-10,53,54]. In a large series of 5700 hospitalised patients from New York-area hospitals [55], older patients, men, and those with pre-existing conditions were highly prevalent, similar to what has been reported in China [55]. Lighter and colleagues found that patients under 60 with a BMI over 35 were at least twice as likely to be admitted to the ICU and were 3x more likely to die than patients with lower BMI [56]. The aforementioned intestinal permeability changes associated with metabolic disorders may account for the clinical severity of these middle-aged patients [7-14,18]. Furthermore, the different prevalence of metabolic syndrome, which is higher in Western countries, may contribute to the higher infection fatality ratio [IFR] attributed to the United Kingdom [57] as compared to China [58].

A pre-existing increase in intestinal permeability, dysbiosis, and low-grade latent systemic inflammation may help trigger and fuel the inflammatory-cytokine storm in Covid-19 through the systemic release of DAMPs and PAMPs (LPS) and TLR activation, which in turn maintains a vicious cycle of systemic inflammation and tissue damage (Fig. 2).

6. Implications: Gut-liver axis and microbiota modulation as potential therapeutic targets against COVID-19

Based on the aforementioned hypothesis, the gut-liver axis should be investigated as a possible therapeutic target in Covid-19 patients. Simple indications such as avoiding alcohol and the non-clinically justified intake of drugs with potential negative effects on the intestinal mucosa and/or microbiota, such as NSAIDs, antibiotics, proton-pump inhibitors, and drugs and supplements

potentially associated with drug-induced liver injury, may prove beneficial in terms of preventive measures. Furthermore, as recommended in other serious acute infections, enteral nutrition should be preserved. Beyond drug stewardship and dietary indications, the gut-liver axis can be targeted through other treatment options including antibiotics, prebiotics, probiotics, symbiotics, postbiotics, and faecal microbiota transplantation [59-60]. These treatment options could involve different therapeutic pathways based on different phases of SARS-CoV-2 infection. First, some probiotics have been shown to act against other viruses (e.g. rotavirus) in vitro and to decrease the duration of the virus in human stool samples [61-62]. Therefore, their administration may reduce the permanence of SARS-CoV-2 in patient faecal samples. This could result in a reduced reservoir for the infection, a reduced risk of transmission through the faecal-oral circuit, and reduced gastrointestinal symptoms. Microbiome therapeutics could also act at the initial phase of the disease before it potentially evolves into a critical clinical picture. Several microbiome modulators are known to beneficially influence the immune system and the release of anti-inflammatory cytokines [63-64], with a potential effect on the development of SARS-CoV-2-related CRS, which is one of the key drivers of worsening Covid-19 clinical severity. Specifically, elevated tissue and serum levels of IL-6 are implicated in the pathogenesis of various inflammatory and autoimmune disorders and CRS. Inflammatory response in SARS-CoV-2 infection is largely characterized by an increase in IL-1 and IL-6 [65]. A combination of Bifidobacterium animalis ssp. lactis and Lactobacillus rhamnosus GG (LGG) daily was able to decrease IL-6 production in 290 children receiving vaccines for Streptococcus pneumoniae and Bordetella pertussis [66]. Moreover, in mice the administration of immunobiotic Lactobacillus plantarum to the respiratory tracts in acute pneumonia virus infection promoted survival in association with diminished levels of IL-6 [67]. In addition, treatment with LGG led to changes associated with decreased IL-6 levels [68]. Moreover, some microbiome modulators, mainly prebiotics and probiotics, helped maintain intestinal barrier integrity through the production of short-chain fatty acids, which have a trophic activity on enterocytes and tight junctions [69]. Finally, microbiome-targeted therapeutics may also play a role in Covid-19 patients already admitted to ICU [70]. In patients admitted to the ICU as a result of traumatic injury, microbiome β-diversity has been associated with different outcomes, including mortality risk, hospital length of stay, ICU length of stay, number of days on the ventilator, hospital-acquired infections, and ARDS [71]. Probiotics have been shown to reduce the risk of ICU-acquired infections in aggregate [72] and several meta-analyses have also found reductions in ICU-acquired pneumonia (OR, 0.59; 95% CI, 0.42–0.79) and ICU length of stay [73]. Notably, in a double-blind randomised controlled trial of 80 children with acute lung injury in a paediatric ICU, Lactobacillus acidophilus was able to decrease serum TNF-α and IL-6 levels and lead to a higher volume to peak tidal expiratory flow and improved mean arterial and pulmonary arterial pressure, with significant differences as compared with placebo [74]. Furthermore, faecal microbiota transplantation was able to increase overall survival and decrease the risk of bloodstream infection in fragile inpatients with C. difficile infection [75]. However, despite these promising results, the use of microbiome modulators should be carefully considered in critically ill patients due to the potential severe adverse events that can occur in this setting [76]. Overall, different strategies aimed at modulating the intestinal microbiota while preserving biodiversity and eubiosis should be taken into consideration from the onset of SARS-CoV-2 infection. Indeed, the attempt to reach or maintain homoeostasis in the gut-liver axis may be seen as a prophylactic strategy favouring a milder course of SARS-CoV-2 infection, while rapidly targeting gut-liver involvement may favour recovery. However, additional randomized controlled trials are warranted. The evidence summarised above also supports the theoretical therapeutic role of gut microbiota and permeability modulators in SARS-CoV-2 infection.

Conclusions

There is convincing preliminary evidence linking microbiota-gut-liver axis perturbations, proinflammatory status, and endothelial damage in noncommunicable preventable diseases with Covid-19 severity. The reduction of the mortality induced by the use of dexamethasone in patients hospitalized with Covid-19, supports furtherly the clinical relevance of the propagation of the systemic inflammation in Covid-19 [77]. Intestinal damage caused by SARS-CoV-2 may further contribute to a disequilibrium and CRS. These mechanisms may account for the clinical severity of Covid-19 observed in patients with certain chronic disorders. While solid clinical data and a proven pathophysiological link between the gut, systemic inflammatory response, and the lungs in the progression of SARS-CoV-2 are necessary, the gut-liver axis and microbiota should be considered likely key players and possible therapeutic targets.

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Declaration of Competing Interest

None

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