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REVIEW

- 1255** Coronavirus disease-2019 and the intestinal tract: An overview

Alberca GGF, Solis-Castro RL, Solis-Castro ME, Alberca RW

- 1267** Metabolic complications of hepatitis C virus infection

Chaudhari R, Fouda S, Sainu A, Pappachan JM

MINIREVIEWS

- 1283** Artificial intelligence for early detection of pancreatic adenocarcinoma: The future is promising

Mendoza Ladd A, Diehl DL

- 1296** COVID-19 and comorbidities of hepatic diseases in a global perspective

Ahmad A, Ishtiaq SM, Khan JA, Aslam R, Ali S, Arshad MI

ORIGINAL ARTICLE

Retrospective Cohort Study

- 1311** Non-responsive celiac disease in children on a gluten free diet

Veeraraghavan G, Therrien A, Degroote M, McKeown A, Mitchell PD, Silvester JA, Leffler DA, Leichtner AM, Kelly CP, Weir DC

Retrospective Study

- 1321** Endoscopic diagnosis for colorectal sessile serrated lesions

Nishizawa T, Yoshida S, Toyoshima A, Yamada T, Sakaguchi Y, Irako T, Ebinuma H, Kanai T, Koike K, Toyoshima O

- 1330** Factors influencing the short-term and long-term survival of hepatocellular carcinoma patients with portal vein tumor thrombosis who underwent chemoembolization

Chen KL, Gao J

SCIENTOMETRICS

- 1341** Global research trends in the microbiome related to irritable bowel syndrome: A bibliometric and visualized study

Zyoud SH, Smale S, Waring WS, Sweileh W, Al-Jabi SW

CASE REPORT

- 1354** Transperineal core-needle biopsy of a rectal subepithelial lesion guided by endorectal ultrasound after contrast-enhanced ultrasound: A case report

Zhang Q, Zhao JY, Zhuang H, Lu CY, Yao J, Luo Y, Yu YY

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Coronavirus disease–2019 and the intestinal tract: An overview

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Abstract

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection can progress to a severe respiratory and systemic disease named coronavirus disease–2019 (COVID-19). The most common symptoms are fever and respiratory discomfort. Nevertheless, gastrointestinal infections have been reported, with symptoms such as diarrhea, nausea, vomiting, abdominal pain, and lack of appetite. Importantly, SARS-CoV-2 can remain positive in fecal samples after nasopharyngeal clearance. After gastrointestinal SARS-CoV-2 infection and other viral gastrointestinal infections, some patients may develop alterations in the gastrointestinal microbiota. In addition, some COVID-19 patients may receive antibiotics, which may also disturb gastrointestinal homeostasis. In summary, the gastrointestinal system, gut microbiome, and gut-lung axis may represent an important role in the development, severity, and treatment of COVID-19. Therefore, in this review, we explore the current pieces of evidence of COVID-19 gastrointestinal manifestations, possible implications, and interventions.

Key Words: COVID-19; SARS-CoV-2; Gastrointestinal; Microbiota; Antibiotics

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Core Tip: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection can progress to a severe respiratory and systemic disease named coronavirus disease-2019 (COVID-19). Nevertheless, SARS-CoV-2 can also generate a gastrointestinal infection. In this review, we explore the impact of COVID-19 on the gastrointestinal system, gut microbiome, and the gut-lung axis and the severity and possible implications and interventions in COVID-19 patients.

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INTRODUCTION

The coronavirus disease-2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Coronaviruses (CoVs) are a family of single-stranded ribonucleic acid (RNA) viruses; currently six subtypes of CoVs can infect humans. Two CoVs, the Middle East respiratory syndrome coronavirus and severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1), are the etiologic agents of the previous epidemics and have caused over 2000 deaths worldwide^[1,2].

COVID-19 can cause a systemic and respiratory infection that can lead to death^[3]. Since November 2019, SARS-CoV-2 has infected over 80 million people and killed over 1.5 million people worldwide, being declared a pandemic by the World Health Organization^[4]. Several comorbidities have been postulated as risk factors for severe COVID-19, such as high age^[5], smoking, chronic obstructive pulmonary disease^[6], obesity^[7], pregnancy^[8], and co-infections^[9].

SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) to invade the host's cells. ACE2 and TMPRSS2 are expressed in many different organs in the human body, such as the lungs, heart, liver, kidney, and brain, intestine luminal cells, colonic epithelial cells, and small intestinal enterocytes^[10-13]. In addition, SARS-CoV-2 infection has been described in multiple organs, including the lungs, pharynx, heart, liver, brain, kidneys, and gastrointestinal tract^[14,15].

COVID-19 AND THE GASTROINTESTINAL TRACT

Gastrointestinal infections have been reported^[16] (Table 1), with a lower frequency in comparison with the previous SARS-CoV-1 infection^[17]. Nevertheless, SARS-CoV-2 can remain positive in fecal samples after nasopharyngeal clearance and may remain infective^[18].

The most frequent gastrointestinal symptoms in COVID-19 are diarrhea, nausea, abdominal pain, and lack of appetite^[19]. After a viral gastrointestinal infection, some patients may develop alterations on the gastrointestinal microbiota such as an increase of Proteobacteria and a simultaneous reduction of Bacteroidetes^[20]. A recent report by Zuo *et al*^[21] identified alterations in the intestinal microbiota of hospitalized patients with COVID-19, with a reduction in beneficial commensals bacteria and an increase in opportunistic pathogens^[21]. In addition, Gupta *et al*^[18] verified a reduction in the community richness and microbial diversity in COVID-19 patients with and without diarrhea. The intestinal tissue and feces may also be acting as a reservoir; recent reports have identified that even after negative nasopharyngeal and oropharyngeal swabs test for SARS-CoV-2 RNA, patients could still possess SARS-CoV-2 RNA in the stool samples^[16,22]. Another report identified that the duration of COVID-19 symptoms was prolonged in patients with diarrhea and that the stool samples from patients with diarrhea were more frequently positive for virus RNA^[23].

Although is not clear the mechanisms responsible for the development of diarrhea in COVID-19, the current hypothesis is that the direct viral infection on the intestinal tissue and local immune response to the virus may be involved. In fact, the detection

Table 1 Manuscripts describing patients with severe acute respiratory syndrome coronavirus-2 ribonucleic acid detection in rectal swabs or fecal samples

COVID-19 respiratory manifestations	COVID-19 gastrointestinal clinical manifestations	Percentage of patients with gastrointestinal clinical manifestations	Rectal swabs or fecal samples positive for SARS-CoV-2	Ref.
Yes	Yes	65.38%	53.42%	[16]
Yes	Yes	60%	50%	[122]
Yes	Yes	80%	90%	[123]
Yes	Yes	11%	22%	[124]
Yes	Yes	33%	80%	[125]
Yes	Yes	No data	39%	[126]
Yes (89 only respiratory/69 respiratory and gastrointestinal)	Yes (48 only gastrointestinal/69 respiratory and gastrointestinal)	56%	54% of a cohort of 22 individuals	[127]
Yes	Yes	No data	29%	[128]
Yes	Yes	31%	55%	[24]
Yes	Yes	No data	83%	[129]
Yes	Yes	No data	25%	[130]

COVID-19: Coronavirus disease-2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2.

of SARS-CoV-2 RNA in stool COVID-19 patients may indicate the possibility of fecal-oral transmission^[24].

In addition to the SARS-CoV-2 impact on the gut immune response, bacterial co-infections and secondary infection could also occur in COVID-19 patients, implicating the necessary usage of antibiotics^[25]. Nevertheless, even in the absence of bacterial co-infections in COVID-19 patients some reports highlighted that the usage of antibiotics is a common clinical practice in COVID-19 patients^[25,26], which could also disrupt the gastrointestinal microbiome. Bacterial communities are present in numerous body sites such as the gut, the respiratory system, and skin; therefore, the unnecessary usage of antibiotics may predispose COVID-19 patients to opportunistic infections inside and outside of the gastrointestinal environment.

GUT MICROBIOTA

The microbiota is influenced by environmental factors, food, drugs, and infections^[27]. Each microbiota possesses unique characteristics^[28,29], differing its composition according to the site in the human body. Many factors influence the microbiome composition such as local pH, temperature, and nutrients^[30]. Microorganisms can be found in nearly every niche of the human body^[31], but the gastrointestinal tract is the largest interface between the host and microorganisms in the human body. There are approximately 10^{13} - 10^{14} microorganisms in the gastrointestinal tract, with greater genomic content than in the human genome^[32].

Microbes and humans have a symbiotic relationship. Commensal microbes are crucial for human health, regulating many physiological functions, degradation of substances, production of metabolites, and immune response^[33]. Microorganisms can activate and stimulate the differentiation of T helper cells (Th) 1, Th2, Th17, and T regulatory cells (Treg), which in consequence can regulate the immune response^[34,35]. A low-diversity in the intestinal microbiota can increase the susceptibility to local^[36] and pulmonary disorders^[37].

The microbiome's environment is in constant regulation, modulated by external microorganisms and other non-bacterial compounds, for example, food in the intestinal microbiota and viruses. An abrupt change in the microbiota can generate an imbalance in the commensal bacteria and/or increase opportunistic microbes, increasing the susceptibility to diseases^[38,39].

The microbiota is essential for the development of the human immune system and can influence both local and non-local immune responses, such as the gut-lung axis^[40].

It is well established that alterations in the gut microbiota can modulate the development of respiratory disease^[41].

In patients with gut dysbiosis such as patients with an established intestinal inflammatory disease or obese patients, the intestinal microbiota may be a secondary risk factor for the development of severe COVID-19^[7]. Besides, patients with COVID-19 may develop a dysbiosis in the gastrointestinal microbiota^[21] and a reduction in short-chain fatty acid-producing bacteria^[42].

GUT MICROBIOTA DYSBIOSIS

Disruption of the gut microbiota can trigger inflammatory events that are associated with metabolic dysfunction, obesity, cancer, and neurological disorders^[43,44]. The proliferation or reduction in certain microorganisms can increase the stimulation of innate immune receptors, like nucleotide-binding oligomerization domain-like receptors and Toll-like receptors^[45]. The stimulation of this receptor triggers several pro-inflammatory signals and the production of cytokine and chemokine, which modulate the adaptive immune system, influencing both local and systemic immune response^[43,44].

The activation of Toll-like receptors on immune cells by the microbiota can generate a low-grade systemic inflammation in the host that is associated with a change in metabolic and immunological responses^[46]. Alterations in the microbiome are related to the development of diseases such as obesity, inflammatory bowel disease, and cancer^[47]. Therefore, SARS-CoV-2 gastrointestinal infections and alteration of gut homeostasis may be implicated in the development of disease and impact immune response to oral vaccines and medicines and the pathogen immune response^[48,49].

NUTRITIONAL INTERVENTION

Several reports have highlighted the potential role of nutrients in the modulation of the immune response to SARS-CoV-2 or a direct anti-viral and/or anti-SARS-CoV-2 properties^[50-53]. During this pandemic, nutritional aspects such as obesity^[7,54], malnutrition^[55], and micronutrient deficiency^[56,57] have been postulated as risk factors for severe COVID-19. Nevertheless, the composition of the human microbiota is influenced by many factors, including dietary components^[41]. Some bacteria can ferment nondigestible carbohydrates (prebiotics), like soluble fibers, to produce short-chain fatty acids (SCFAs). SCFAs can stimulate the growth and/or activity of commensal bacteria and are associated with health benefits. SCFAs can induce the regulation of the intestinal barrier, reduce oxidative stress, control diarrhea, and modulate intestinal motility and also induce a local and systemic anti-inflammatory effect^[58,59].

High-fiber diets can induce the proliferation of beneficial commensal microbes, such as *Lactobacillus* spp. and *Bifidobacterium* spp. in the gastrointestinal tract^[60]. In fact, high-fiber diets may increase immunoglobulin A production and modulate the secretion of interferon-gamma and interleukin (IL)-10^[61-63], which could aid in the control of gastrointestinal infections.

Prebiotics may alter the microbiota composition by a mechanism called cross-feeding, when the product of a prebiotic's fermentation by a microorganism in the microbiota can be used as a substrate by another microorganism^[64-66]. Another mechanism that prebiotics can alter the microbiota is through pH alterations. The fermentation products are predominantly acids, which may cause a decrease in the intestinal pH, restraining the growth of acid-sensitive bacteria, such as *Bacteroides* spp., and promoting butyrate-producing bacteria^[67].

SCFAs are divided into acetate, propionate, and butyrate. All SCFAs have potential anti-inflammatory effects with the reduction of prostaglandin E2 and inflammatory cytokines^[68]. Acetate can curb the activation of the NLR family pyrin domain containing 3 inflammasome^[69]; propionate can inhibit histone deacetylase and reduce lipopolysaccharide-induced inflammation^[70]. Butyrate has been associated with anti-cancer properties and reduces pulmonary inflammation^[71,72].

Overall, research has demonstrated a potential anti-inflammatory role for SCFAs in both local (intestinal) and non-local inflammation *via* direct anti-inflammatory effects or modulation of the microbiota^[71,73,74].

SCFAs can induce the release of anti-inflammatory cytokines such as IL-10^[75,76], promoting the regulation of Th cells and inflammatory diseases^[77], including

inflammatory bowel disease^[78].

Another intervention for the modulation of the gastrointestinal microbiome is *via* the consumption of probiotics. Probiotics are bacteria that can be ingested and provide a beneficial interaction to the host^[79]. Several studies have investigated the effects of probiotics on the gut microbiota^[80], with conflicting results involving their ability to graft on the commensal microbiota^[81-84]. However, probiotics can produce metabolites that can modify and influence the commensal microbiota, intestinal barrier, and immune system^[85,86].

Probiotics can also aid in the prevention or treatment of bacterial^[87] and viral infections^[88]. The administration of probiotics increases the survival of mice infected with the influenza virus^[87]. Besides the influenza virus, studies have demonstrated beneficial protection against respiratory syncytial virus infection^[89].

The health benefit of probiotics in respiratory viral infections is due to the modulation of cytokine production and oxidative stress^[90]; therefore, they may possibly be an adjuvant treatment for the aberrant release of pro-inflammatory cytokines, chemokines, and oxidative stress during severe COVID-19^[91].

The most used probiotics are *Lactobacillus*, *Bifidobacterium*, and *Enterococcus*^[92]. Although there is extensive research demonstrating their health benefits, currently there is a gap in knowledge involving the ideal dosage and comparison among strains of probiotics^[93].

DISCUSSION

COVID-19 is a potentially deadly disease, which can infect intestinal cells^[13]. SARS-CoV-2 gastrointestinal infections^[16] can generate diarrhea, pain, and vomiting^[19]. To date, few reports have investigated the possible consequences of gastrointestinal infection by SARS-CoV-2; nevertheless, viral infections can alter the gastrointestinal microbiota^[20]. A report by Xu *et al*^[94] identified a reduction in *Lactobacillus* and *Bifidobacterium* in fecal samples from COVID-19 patients^[94]. Also, the microbiome of COVID-19 patients can be disturbed by the necessary or unnecessary use of antibiotics^[34].

Yeoh *et al*^[95] identified that the alteration on the gastrointestinal microbiome in COVID-19 patients was independent of medications. The alterations on the gut microbiome included a reduction in *Faecalibacterium prausnitzii*, *Eubacterium rectale*, and *bifidobacteria* for up to 30 d after SARS-CoV-2 clearance^[95].

The microbiota dysbiosis in COVID-19 may be involved in the inflammatory response and may be a persistent problem after COVID-19 resolution, indicating a possible role for nutritional interventions to curb the inflammatory response and reestablish the gastrointestinal homeostasis of COVID-19 patients.

Dietary and nutritional intervention can modulate the immune response, increasing or dampening the anti-viral response^[59-62]. Western-style diets (low fiber content) can increase *Bacteroidetes* and reduce *Firmicutes*^[96] and are linked to the development of obesity^[97], a risk factor for severe COVID-19^[7]. Although reports have identified an increase in SCFAs in fecal samples from obese individuals^[96], SCFAs have been associated with control of appetite^[98] and increase energy expenditure^[99].

In addition, very low fiber-diets can lower mucus production on the intestine and increase the susceptibility to gastrointestinal infections^[39]. Importantly, a change in diet can modify the microbiota composition^[100]. The microbial communities are in constant change and are also affected seasonally by food consumption^[101]. In fact, a reduction in the consumption of fiber can change the microbiota in as little as 1 d, reducing SCFAs production^[102].

In opposition, high fiber-diets increase *Firmicutes* and *Actinobacteria* on the gut microbiota^[103] and increase the production of SCFAs, which can aid in the reduction of pulmonary inflammation, *via* the gut-lung axis^[41,104,105] and promote a local and systemic anti-inflammatory response *via* IL-10 production and Treg cells^[75,76,106]. The ingestion of probiotics may stabilize or alter the gastrointestinal microbiome, especially after a perturbation of the microbiota such as post usage of antibiotics or gastrointestinal infections^[107].

Probiotic treatments with *Bacillus subtilis* and *Enterococcus faecalis* have been demonstrated to reduce ventilator-associated pneumonia^[108]. Treatment with *Lactobacillus rhamnosus* can reduce ventilator-associated pneumonia and *Clostridium difficile*-associated diarrhea in mechanically ventilated patients^[109], making it a possible addition to the treatment of patients with severe COVID-19 in intensive care units with assisted mechanical ventilation. Treatment with *Lactobacillus* may be of particular

importance, because respiratory infections may cause a reduction in *Lactobacillus*, and an increase in *Enterobacteriaceae* and intestinal IL-17 inflammation^[110].

Targeting IL-17 has been postulated as a treatment for COVID-19^[111] because of the increase in IL-17 in severe COVID-19 patients compared to moderate COVID-19 patients^[111]. IL-17 and IL-17-producing T helper cells (Th17), type three innate lymphoid cells, invariant natural killer cells, and $\gamma\delta$ T cells are involved in the immune response of COVID-19^[112]. IL-17 receptor is expressed on the surface of many different cells such as neutrophils, eosinophils, epithelial cells, keratinocytes, and fibroblasts^[112]. In addition, IL-17 can directly influence the expression of ACE2, SARS-CoV-2 entry's receptor^[113].

The usage of IL-17 blockade, such as monoclonal antibodies against IL-17A and/or IL-17 receptor A, may represent a possible therapeutic option for COVID-19^[112]. Nevertheless, IL-17 is an important cytokine in the immune response against *Streptococcus pneumoniae* and *Pseudomonas aeruginosa*, common pathogens in respiratory and intestinal tract infections^[112,114]. Secondary bacterial infections can occur in the respiratory system following SARS-CoV-2 infection, especially in patients with invasive mechanical ventilation^[34]. IL-17 is especially important for intestinal homeostasis^[115]. Therefore, treatment with anti-IL-17 should consider the possible risk for an increase in susceptibility for bacterial infections both respiratory and intestinal.

COVID-19 patients may also develop a cytokine storm syndrome, which may induce multi-organ failure and lead to death or long-term consequences^[91]. In this context, probiotics or prebiotics treatment have been previously demonstrated anti-inflammatory effects in respiratory infections *via* the increase in SCFAs^[71,73,74,88,116].

SCFAs production and health benefit can be increased by the ingestion of highly fermentable fiber diets^[117], probiotics^[73], oral administration of drugs like tributyrin (a prodrug of butyrate)^[118], or SCFAs directly^[119-121].

In this context, the intake of prebiotics and/or probiotics can represent a significant prophylactic intervention and/or recovery of COVID-19 patients.

CONCLUSION

The SARS-CoV-2 infection on the gastrointestinal tract and the long-term consequences of COVID-19 in gastrointestinal homeostasis still needs further investigations. It is clear that SARS-CoV-2 can infect the gastrointestinal tract and impact the intestinal immune response and the gut microbiome. Currently, there is no specific treatment for COVID-19, but investigations on the impact of nutritional intervention *via* modulation of the immune response or *via* microbiota are being investigated and may represent a significant prophylactic intervention and/or recovery of COVID.

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