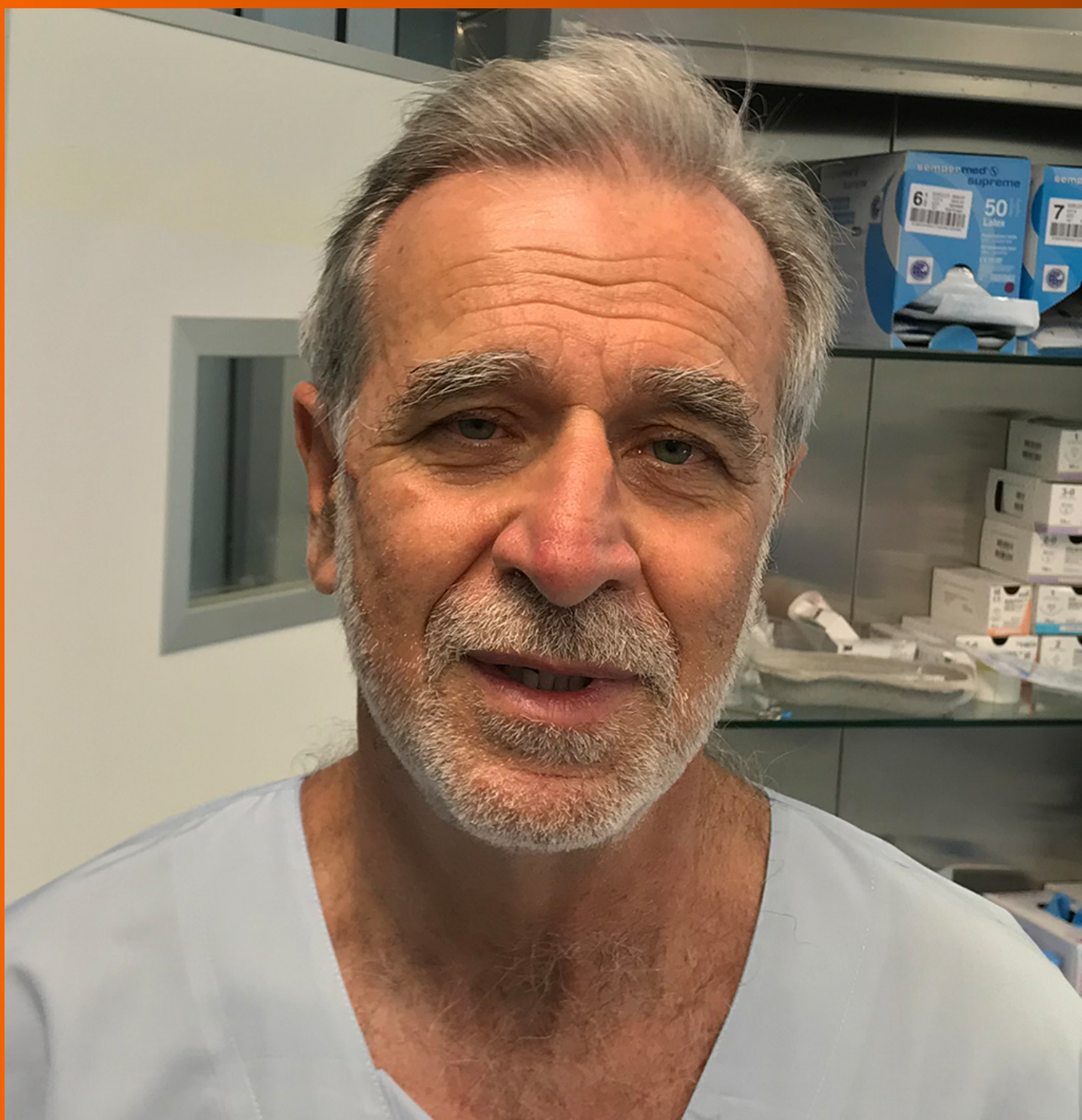


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Therapeutic implications of SARS-CoV-2 dysregulation of the gut-brain-lung axis

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Abstract

The emergence and rapid spread of novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused over 180 million confirmed cases resulting in over 4 million deaths worldwide with no clear end in sight for the coronavirus disease 19 (COVID-19) pandemic. Most SARS-CoV-2 exposed individuals experience mild to moderate symptoms, including fever, cough, fatigue, and loss of smell and taste. However, many individuals develop pneumonia, acute respiratory distress syndrome, septic shock, and multiorgan dysfunction. In addition to these primarily respiratory symptoms, SARS-CoV-2

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can also infiltrate the central nervous system, which may damage the blood-brain barrier and the neuron's synapses. Resultant inflammation and neurodegeneration in the brain stem can further prevent efferent signaling to cranial nerves, leading to the loss of anti-inflammatory signaling and normal respiratory and gastrointestinal functions. Additionally, SARS-CoV-2 can infect enterocytes resulting in gut damage followed by microbial dysbiosis and translocation of bacteria and their byproducts across the damaged epithelial barrier. As a result, this exacerbates pro-inflammatory responses both locally and systemically, resulting in impaired clinical outcomes. Recent evidence has highlighted the complex interactions that mutually modulate respiratory, neurological, and gastrointestinal function. In this review, we discuss the ways SARS-CoV-2 potentially disrupts the gut-brain-lung axis. We further highlight targeting specific responses to SARS-CoV-2 for the development of novel, urgently needed therapeutic interventions. Finally, we propose a prospective related to the individuals from Low- and Middle-Income countries. Here, the underlying propensity for heightened gut damage/microbial translocation is likely to result in worse clinical outcomes during this COVID-19 pandemic.

Key Words: SARS-CoV-2; Gut; Microbiome; Lungs; Brain; Therapeutics

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Core Tip: Severe acute respiratory syndrome coronavirus 2 has spread rapidly, infecting and killing millions worldwide. In addition to respiratory symptoms, coronavirus disease 19 (COVID-19) is associated with enterocyte infection leading to intestinal inflammation, gut barrier damage, and microbial dysbiosis exacerbating the systemic inflammatory response. Viral infiltration to the central nervous system from cranial nerve innervation of the lungs and gut can also cause neuroinflammation and degeneration, which further dysregulates gut and lungs. This review summarizes recent findings on COVID-19 pathogenesis in the gut-brain-lung axis and offers therapeutic interventions to improve clinical outcomes.

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INTRODUCTION

Starting from late 2019 and through 2020, a novel coronavirus, the causative agent of coronavirus disease 19 (COVID-19), initiated one of the deadliest global pandemics warranting extensive panic for the underprepared global health system[1-4]. The pandemic has claimed countless lives (approximately 4 million deaths worldwide of 188 million confirmed cases as of July 15, 2021) and presented unprecedented socio-economic losses[5-8]. The primary mode of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission is airborne, with infectious droplets gaining access into the host respiratory tract. Subsequently, standard clinical indicators comprise fever, cough, fatigue, chills, nausea, headache, dyspnea. Additionally, the loss of taste or smell often ensues[9,10]. Coronavirus infections primarily target the upper respiratory tract, but they also manifest in other regions such as the gastrointestinal tract (GIT). Within the GIT, additional symptoms such as lack of appetite, vomiting, abdominal pain, and diarrhea have been observed in some individuals[11, 12].

SARS-CoV-2 has been shown to infect GIT cells such as human gut enterocytes[13]. SARS-CoV-2 RNA has also been detected in gastrointestinal glandular epithelial cells [14-17]. During infection, compromised gastrointestinal symptom involvement has worse clinical outcomes and takes longer to recover than those with only respiratory

symptoms[18-20]. Subsequently, patients who test positive for viral RNA in feces have poor viral clearance and prolonged delays for infection resolution[21]. SARS-CoV-2 tropism in the lungs and GIT is supported by abundant cellular viral entry receptors such as the angiotensin-converting enzyme-2 (ACE2). ACE2 exists in abundance on the epithelia of the lungs and small intestine (ileum)[22,23]. ACE2 catalyzes the conversion of angiotensin II into angiotensin 1-7; it is crucial for maintaining gut balance through regulation of amino acid homeostasis, innate immunity, the balance of the intestinal microbiome, and by limiting diarrhea[24,25].

The gut is the largest immune organ and is a crucial interconnecting hub, which synchronously orchestrates multiple physiological, cellular, and organ functions[26]. The gut maintains an anti-inflammatory state that supports the growth of trillions of commensal bacteria, which modulate the function of other organs like the brain, heart, kidney, lungs, and liver while favoring its core functions like digestion, absorption of nutrients, and excretion of waste matter[27-30]. This inter-compartmentalized crosstalk infers the need to develop effective gut-specific therapeutics that could limit systemic pathology during diverse viral infections such as human immunodeficiency virus (HIV), SARS-CoV-2, and other related respiratory viruses.

IMMUNE ARCHITECTURE OF A HEALTHY GUT

The gut is one of the most complex immune organs containing a wide variety of immune cells, including myeloid cells, conventional T cells, innate lymphoid cells (e.g., natural killer cells and specialized intraepithelial lymphocyte populations), and epithelial cells[31]. Homeostasis in a healthy gut is mainly fostered through the sustenance of an anti-inflammatory environment crucial for maintaining tolerance to oral antigens, commensal microflora, and bridging an intact mucosal barrier[32,33]. Commensal microflora competes with pathobionts (potentially pathogenic bacteria which are benign during homeostasis) for nutrients within the gut microenvironment, secrete toxins that favor their predominance, and release metabolites that shape gut immunity by providing appropriate anti-inflammatory signals to other immune cells such as macrophages[31,34].

Critical genera of the microbiome also ferment dietary fiber into short-chain fatty acids that support gut immune responses by sustaining the balance of T regulatory (T reg) cells and activated T cells[35]. The released short-chain fatty acids such as butyrate facilitate CD103+ dendritic cell production of retinoic acid, which in turn aid in the generation of FoxP3+ T reg cells and sampling of an antigen across the gut lumen. Increased frequencies of CD4+ regulatory T cells maintain a basal anti-inflammatory state of the gut. Released acetate also improves the integrity of gut epithelial cells[36,37]. Additionally, lamina propria macrophages are highly phagocytic and engulf any foreign microorganisms that may have breached the intact gut mucosal barrier[38]. The gut epithelial cells secrete anti-inflammatory cytokines such as interleukin 10 (IL-10) and transforming growth factor- β (TGF- β), which promote increased frequencies of T regs that are crucial for immunological suppression and induction of mucosal tolerance[39-41].

SARS-COV-2 INFECTION IN THE GUT

During gut infection, SARS-CoV-2 uses its spike (S) proteins on the virus's surface to directly bind to the ACE2 receptor that is highly expressed on target intestinal epithelial cells (enterocytes and goblet cells). A transmembrane serine protease (TMPRSS2) acts synergistically and cleaves the S protein into S1 and S2 subunits, facilitating the host cell's viral entry[15]. Like other viruses such as rotavirus, norovirus, and enteroviruses, the interferon-stimulated genes are activated, resulting in the reinstatement of an antiviral state and restricted SARS-CoV-2 replication[42-44]. Simultaneously, pro-inflammatory cytokines like IL-6, IL-1, and tumor necrosis factor- α (TNF- α) are also released[44]. Severe enterocyte apoptosis follows as soon as the virus overcomes the interferon-mediated antiviral state[16]. The tremendous loss of intestinal epithelial cells diminishes the gut barrier's integrity and gravely impacts the absorption of nutrients, secretion of mucus, and production of antimicrobial peptides[45]. The elevated secretion of pro-inflammatory cytokines also simultaneously activates macrophages towards pro-inflammatory states, which involves the increased surface expression and later shedding of markers such as CD14 and CD163 that are critical for detecting microorganisms and limiting inflammation[16].

A recent unpublished study that comprehensively investigated changes in gut dynamics during SARS-CoV-2 infection shows that there were increases in permeability of gut tight junctions as estimated using zonulin, microbial translocation, lipid-binding protein, and myeloid activation using soluble CD14[46]. Gut barrier damage, microbial translocation, and myeloid cell activation worsened as the disease transitioned into more severe states. All this was heralded when a two-fold increment in tight junction permeability was observed in individuals who died *vs* COVID-19 survivors. Unsurprisingly, alterations in gut homeostasis positively correlated with elevated IL-6, thus confirming increased inflammation as a conduit for loss of gut barrier integrity[46]. Lastly, progressive increments of disrupted citrulline metabolism accompanying the severity of SARS-CoV-2 indicate ongoing microbial dysbiosis and impaired intestinal function[47].

GUT INFLAMMATION AND SARS-COV-2

An optimal balance between T regs and inflammatory T helper 17 (Th17) cells is maintained within a healthy gut. As inflammation occurs, this balance is tipped as pro-inflammatory bacteria are favored over commensals[37]. These pro-inflammatory bacteria induce the secretion of cytokines like IL-6 and IL-17 that select for increased frequencies of Th17 pro-inflammatory CD4+ T cells and susceptibility to inflammatory conditions such as inflammatory bowel disease (IBD)[37].

An increased expression of SARS-CoV-2 receptors during other inflammatory conditions has been suggested to affect disease pathogenesis. During IBD and Crohn's disease (CD), epithelial ACE2 expression is elevated in the colon and rectum while diminished in the ileum[48]. As anticipated, gut dysbiosis occurs as pathobionts outcompete commensal bacteria, and macrophage populations transition towards inflammatory states where they secrete increased amounts of pro-inflammatory cytokines such as TNF- α , IL-6, and IL-12[49,50]. The resultant inflammatory damage leads to the destruction of tight junctions within the gut barrier. This later leads to leakage of microbial contents into the systemic circulation. Microbial translocation then ensues and later fuels chronic immune activation[49].

Several studies have investigated the co-occurrence of IBD and COVID-19-related illnesses[51-53]. Here, we discuss the possibility of leveraging IBD therapeutics for treating COVID-19-related symptoms. Current IBD treatments can be divided into two broad categories: (1) Non-biologic; and (2) Biologic therapeutics. Examples of non-biologic therapeutics include small molecules corticosteroids, thiopurines, and 5-aminosalicylates. Each of these therapeutics non-specifically targets multiple inflammatory processes.

On the other hand, biologic therapies target specific inflammatory mediators in the gut to modulate their ability to induce signal transduction[41]. Current biologics used to treat IBD include the monoclonal antibodies infliximab, ustekinumab, and vedolizumab. Infliximab and ustekinumab target pro-inflammatory cytokines TNF- α and IL-12/IL-23, respectively. Since these cytokines are not specific to intestinal inflammation, antibodies that inhibit their action can act throughout the periphery. More specific therapies target IBD like vedolizumab function by blocking the gut homing receptor $\alpha 4\beta 7$ integrin, thereby blocking inflammatory lymphocyte trafficking resulting in reduced inflammation[41,54,55]. Similarly, the biologic natalizumab, an anti- $\alpha 4$ integrin antibody, is also used to treat Crohn's disease, albeit less frequently due to an increased risk of progressive multifocal leukoencephalopathy (Table 1)[56].

Several studies have suggested that IBD non-biologic therapies may worsen clinical outcomes during COVID-19[57-59]. For example, 5-aminosalicylate and its prodrug form sulfasalazine have increased the risk of SARS-CoV-2 infection and increased the risk of hospitalization and mortality[57-59]. Other immunomodulators include thiopurines, calcineurin inhibitors, and methotrexate. When grouped in meta-analyses, these immunomodulators were also associated with an increased risk of infection, hospitalization, and mortality during SARS-CoV-2 infection[57-59]. The data for corticosteroids is more complicated[57-59]. Owing to their nature as non-selective hormone analogs, corticosteroids target gut inflammation non-specifically, resulting in a dampening of the inflammatory response beyond the intestines. This dampened immune response can therefore inhibit the clearance of replicating virus and prolong the duration of infection. Corticosteroids may further negatively impact clinical outcomes by increasing the pro-thrombotic response to SARS-CoV-2, exacerbating already frequent clotting in intrinsically vascular disease. Several case studies have linked this hypercoagulable state in COVID-19 to worsening in the gut, including

Table 1 Comprehensive list of available gut-based and vagus nerve therapies that could be leveraged to limit the severity of coronavirus disease 19 infection

Therapy	Target	Impact	Clinical outcome
Infliximab[57,58]	TNF- α	Reduced pro-inflammatory response induction and leukocyte migration	Reduced infection rate, symptoms, hospital rate, and mortality
Ustekinumab[57]	IL-12/IL-23	Blocks T cell activation	Possible improved outcome (pooled with other biologics)
Vedolizumab[54,57]	$\alpha 4\beta 7$ integrin	Reduced leukocyte trafficking to gut and associated inflammation	Possible improved outcome (pooled with other biologics)
Corticosteroids[57,58,63]	Glucocorticoid and mineralocorticoid receptors	Reduced inflammatory response	Better or worse clinical outcomes, depending on the timing
Microbiome[176]	Butyrate production	Improved gut barrier integrity and decreased microbial translocation	Reduced inflammatory response
Vitamin D[70,72,74]	Th17 cells	Reduced gut and systemic inflammation	Reduced infection risk and enhanced clinical outcomes
Nicotine and related agonists [142,152,153]	$\alpha 7$ nAChR	Reduced Inflammatory Response	Reduced infection rate
Vagus nerve stimulation[151]	$\alpha 7$ nAChR	Increased acetylcholine release	Reduced inflammation

TNF- α : Tumor necrosis factor- α ; IL: Interleukin; Th17: T helper; nAChR: Nicotinic acetylcholine receptor.

ischemic colitis, potentially aggravating an already disrupted gut homeostasis[60,61]. Therefore, it is unsurprising that studies to determine the impact of IBD therapy on COVID-19 have not been pursued. Nonetheless, corticosteroids for IBD are typically administered long-term and precede SARS-CoV-2 infection. Corticosteroids, particularly dexamethasone, reduce mortality in hospitalized SARS-CoV-2 patients receiving oxygen and reduce intensive care unit hospitalization length when given at moderate doses over a short period (6 mg for up to 10 d)[20,62]. In this context, dexamethasone is typically given after the body has begun clearing the virus but before the worst symptoms of COVID-19 due to cytokine storm arise[63]. The difference in infection rate and clinical outcomes for patients receiving treatment before infection suggests that timing is critical for optimizing corticosteroid use.

In addition to modulating immune responses directly, non-biologic medications may influence COVID-19 pathogenesis in other ways. For instance, people receiving non-biologic medications such as corticosteroids, thiopurines, and 5-aminosalicylates have reduced ACE2 and TMPRSS2 expression on enterocytes in the inflamed colon rectum, but not the ileum[48]. This suggests that despite the adverse clinical outcomes with these medications, they may reduce productive gut epithelial infections in people living with IBD. However, these drugs did not cause changes to receptor expression in the uninfamed gut[48]. In contrast, some biologics used to treat IBD have been mostly, though not exclusively, linked to improved clinical outcomes during SARS-CoV-2 infection, offering novel therapeutic interventions. Early studies have shown that the patients administered biologics did not have an increased risk of COVID-19, despite being considered immunocompromised[64,65]. Individual case studies demonstrate that targeting TNF- α with infliximab promises to improve pulmonary symptoms related to COVID-19[66]. Further, an early study grouping multiple biologic therapies showed that clinical outcomes for individuals taking these biologics were five times less likely to be diagnosed with a SARS-CoV-2 infection[67]. However, this analysis was limited due to the small sample size and inability to separate the specific therapies.

A more recent meta-analysis, again grouping different biologics (anti-TNF- α , ustekinumab, and vedolizumab), demonstrated that their use was associated with a risk ratio of hospitalization 0.34 [95% confidence interval (CI) 0.19-0.61], need for intensive care unit 0.49 (95%CI 0.33-0.72), and mortality 0.22 (95%CI 0.13-0.38), suggesting a substantial improvement in clinical outcome[57]. However, one concern is that because people treated with biologics have such muted symptomology, they may serve as silent carriers of SARS-CoV-2[68]. In addition to reducing symptoms, infliximab has also been shown to reduce the expression of ACE2 in the colon, potentially limiting the productive infection of the gut[48]. Because of these findings, a continued study of these monoclonal antibodies is warranted. Luckily, several clinical trials are currently underway, including anti-TNF- α therapies infliximab and

adalimumab.

In addition to prescription therapeutics, other recommendations for IBD can also be applied to SARS-CoV-2 infection. COVID-19 pathogenesis has been characterized primarily by dysregulation of the systemic pro-inflammatory response of Th17 cells, particularly during the cytokine storm. This includes decreases in CD4⁺ T cells expressing Th17 markers CCR6 and CD161, increasing senescence and exhaustion markers CD57 and PD-1[69]. The total number of IL-17A-producing CD4⁺ and CD8⁺ T cells was significantly increased despite these findings. These studies suggest that targeting IL-17 may improve clinical outcomes for COVID-19 patients[69].

Further, early during the pandemic, low circulating vitamin D became a known risk factor for SARS-CoV-2 infection, and severe pathogenesis, including associations with significantly higher pro-inflammatory cytokines, including IL-6[70,71] was noted. For this reason, vitamin D supplementation has been recommended for high-risk individuals[70]. Oral vitamin D supplements are absorbed by the small intestine, where they may modulate local Th17 cells, including reduced production of IL-17[72]. In clinical practice, vitamin D is frequently recommended for patients prescribed corticosteroids to manage their IBD symptoms to prevent bone density loss[73]. It is also recommended to reduce or protect against IBD onset of symptoms, in part by suppressing IL-17 production[72]. Further, vitamin D has been linked to increased expression of tight epithelial junctions and blocking apoptosis in the intestine, strengthening gut integrity and preventing bacterial translocation[74,75]. However, whether dampened COVID-19 pathogenesis is linked to inhibition of pro-inflammatory Th17 cells or by a different mechanism remains unknown.

One final concern regarding SARS-CoV-2 during IBD has been the safety and efficacy of vaccination with current therapeutics, many of which are immunosuppressive because so far, phase III clinical trials have excluded patients with IBD[76,77]. Previous studies have found IBD patients treated with anti-TNF- α therapies have a muted response when administered other vaccines (pneumococcal, influenza), leading to further questioning of efficacy[76,78,79]. Despite these concerns, the benefits of vaccination outweigh many of the risks of SARS-CoV-2 infection, and vaccination is likely beneficial for most patients with IBD, even if receiving immunosuppressive therapies[76,80,81]. However, future studies are needed to determine efficacy for this population.

SARS-COV-2 INFECTION RESULTS IN MICROBIAL DYSBIOSIS IN THE GUT

SARS-CoV-2-related microbial dysbiosis manifests the enrichment of pathobionts such as *Ruminococcus gnavus*, *Ruminococcus torques*, and *Bacteroides dorei* (*B. dorei*) *Bacteroides vulgatus*. These bacteria have also been implicated in IBD and ulcerative colitis pathogenesis, further strengthening their role in gut dysfunction[82,83]. SARS-CoV-2 dysbiosis was also accompanied by loss of crucial bacteria that have been previously implicated in the lowering of inflammation, such as *Bifidobacterium adolescentis*, *Faecalibacterium prausnitzii* (*F. prausnitzii*), *Collinsella aerofaciens*, and *Eubacterium rectale* (*E. rectale*)[84] (Figure 1). Another study highlighted that *Clostridium hathewayi* (*C. hathewayi*), *Clostridium ramosum* (*C. ramosum*), and *Coprobaecillus* were linked to COVID-19 severity[85]. Unsurprisingly, these microbial signatures (*C. hathewayi*, *C. ramosum*, and *Coprobaecillus*) have also been associated with pathogenic/inflammatory gut conditions such as diarrhea, colitis, IBD, and overall inflammation[86-88]. This situation's gravitas is further supported by observations made in a separate study that showed that the inflammatory species, *Proteobacteria*, was reported in the guts of COVID-19 patients[89].

Alternatively, several anti-inflammatory bacteria, including *F. prausnitzii*, *B. dorei*, *Bacteroides thetaiotaomicron*, *Bacteroides massiliensis*, and *Bacteroides ovatus* were linked to improved clinical outcomes in SARS-CoV-2 patients. Remarkably, *Bacteroides* were reported to down-regulate ACE2 expression in the gut[85]. The fecal microbiome has also been determined to be dysbiotic for periods as long as 30 d after clearance of SARS-CoV-2 infection, further contributing to the extensive list of health complications reported in COVID long haulers who never wholly recover and recuperate to a healthy state[84,90]. To this effect, it was noted that microbiomes of recovered patients were enriched in *Bifidobacterium dentium* and *Lactobacillus ruminis* species and reduced *E. rectale*, *Ruminococcus bromii*, *F. prausnitzii*, and *Bifidobacterium longum*[84]. Therapeutics involving antibiotics to stabilize the gut microbiome by eliminating SARS-CoV-2 associated pathobionts revealed that these regimens did not affect the

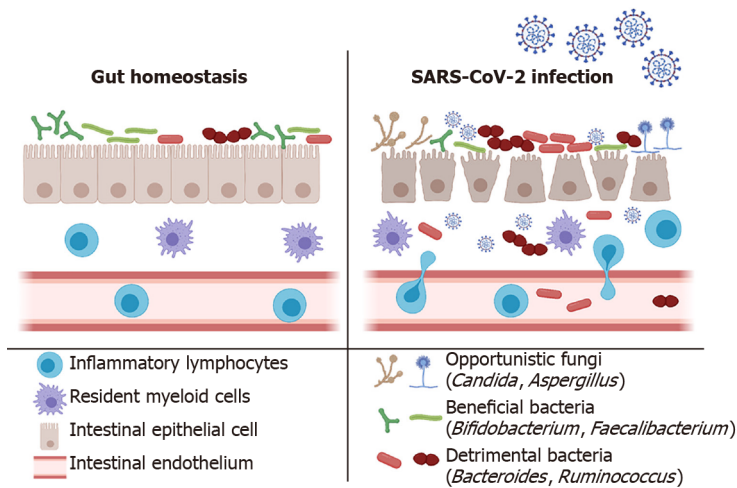


Figure 1 Severe acute respiratory syndrome coronavirus 2 infection induces microbial dysbiosis and intestinal inflammation. Severe acute respiratory syndrome coronavirus 2 infections of intestinal epithelial cells result in a pro-inflammatory immune response leading to infiltration of inflammatory lymphocytes and disrupting the gut barrier. This disruption to homeostasis allows overgrowth of detrimental bacteria resulting in dysbiosis, and the impaired gut barrier facilitates the translocation of bacteria exacerbating the inflammatory response. Additionally, opportunistic fungal infections have been found in some patients, further contributing to the dysfunction. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

recovery of the microbiome. Therefore, these findings negate this approach as a possible future gut microbial rejuvenation strategy[84]. In contrast, previous studies have shown that probiotics improve immune responses to other respiratory tract viral infections such as Influenza and Rhinoviruses[91,92]. Also, in patients with severe COVID-19 disease who cannot ingest probiotics, the use of butyrate enemas could act as adjunctive therapy for repairing intestinal epithelial cell wall damage, lowering chronic immune activation promoting gut-brain axis function[93].

Analysis of the fungal mycobiome using deep shotgun metagenomic sequencing revealed significant proportions of opportunistic fungal pathogens such as *Candida albicans*, *Candida auris*, and *Aspergillus flavus* were enriched in the gut microbiota of COVID-19 hospitalized patients[94]. Similarly, separate studies have detected *Aspergillus* in respiratory tract secretions and tracheal aspirates of patients with COVID-19[95,96]. Unsurprisingly, in patients with *Aspergillus* in their fecal microbiomes, the cough was noted as one of the significant symptoms that emphasized intricate systemic distortion of the gut-lung axis[97]. In such cases, antifungal medications should be considered.

THE SARS-COV-2 INFECTION AFFECTS THE HOMEOSTASIS OF THE GUT-LUNG AXIS

The gut-lung axis has been proposed to be a bi-directional conduit by which each organ can modulate the function and inflammatory state. This includes the production of metabolites such as short-chain fatty acids (SCFAs) by the gut microbiome, lymphocyte trafficking from the lungs or the gut into the periphery where they redirect systemic immune responses, and indirect neuronal innervation *via* the central nervous system (CNS) and cranial nerves bridging each organ[98,99]. The bi-directionality of the gut-lung axis, while capable of promoting beneficial communication, as noted, also represents an avenue for disruption in immune regulation. Changes in the composition and function of the gastrointestinal flora operate to effect change in the respiratory tract through the mucosal immune system, while reciprocally, disturbances to the respiratory tract flora consequently affect the digestive tract through immune regulation[100]. Infection from SARS-CoV-2 causes effector CD4⁺ T cells to reach the small intestine by accessing the C-C chemokine receptor type 9 (CCR9) *via* the gut-lung axis resulting in intestinal immune damage and diarrhea[101]. A study related to the influenza virus demonstrated that lung-derived CCR9+CD4⁺ T cell levels were increased following viral infection[102]. Ye *et al* [101] summarized that the small intestinal epithelium can express CCL25, which actively recruits CCR9+CD4⁺ T cells to the small intestine, resulting in intestinal immune damage and polarization of Th17 cells in conjunction with overproduction of

IL-17A. This, in turn, leads to neutrophil recruitment, thus establishing diarrhea onset and other gastrointestinal symptoms during SARS-CoV-2 infection. Generally, COVID-19 patients presenting with gastrointestinal symptoms (> 20% of cases) are more likely to be complicated by acute respiratory distress syndrome (ARDS) and are more prone to fatigue, headache, and cough[101]. Another pathway that may be involved in the severity of ARDS during SARS-CoV-2 infection is the C5a-C5aR1 axis. Proportionate to the severity of ARDS, soluble levels of C5a were found to be increased, and C5aR1 receptors were reported with high expression levels in the blood and pulmonary myeloid cells; furthermore, in C5aR1 knock-in mice, acute lung injury was prevented by the introduction of anti-C5aR1 therapeutic monoclonal antibodies suggesting that this axis could be used to limit lung inflammation[89]. Given that ACE2 is highly expressed in the gastrointestinal tract, specifically intestinal epithelial cells, the esophagus, and the lungs, this may make it a target organ for SARS-CoV-2 infection[103]. Therefore, probiotics offer a favorable potential treatment addressing the gastrointestinal symptoms in COVID-19 by operating to sustain the healthy balance of the gut microecology and protect the respiratory tract from bacterial infections[100]. ACE2, while present across different tissue types, is most prominent in the lungs, which highlights the importance of understanding the network involved to combat the hypersensitivity of the receptor in this tissue, which may lead to worse respiratory illness.

Another branch that extends from the lung-gut axis includes the lung-brain conduit, which proposes to connect severe neurological dysfunction and injury with associated lung injury. In general, CoV-induced inflammation and oxidative stress may represent a crucial mechanism for the onset of neurological symptoms. SARS-CoV-2, in particular, has been shown to have the neuroinvasive potential[104]. The vagus nerve innervates the lung's distal airway, and upon stimulation, nerve endings release acetylcholine (ACh), which functions to regulate lung infection[105] (Figure 2). ACh secreted from neuronal and non-neuronal sources acts to decrease inflammation, and using an Influenza A model, a previous study showed that viral infection caused an influx of cholinergic lymphocytes while inhibiting ACh synthesis resulted in extended pulmonary inflammation, increased inflammatory macrophage activation, and delayed tissue repair (Reviewed in[106]).

Similarly, it was demonstrated that a deficiency to the $\alpha 7$ nicotinic ACh receptor (nAChR) acts to worsen lung infection, inflammation, and injury while increasing circulatory levels of pro-inflammatory cytokines. Additionally, $\alpha 7$ nAChR activation by GTS-21, which enhances the phagocytic ability of hyperoxic macrophages, is a prominent method for improving bacterial clearance and reducing lung injury[107], suggesting an involvement of lung-gut-brain connection. During infection, viruses may breach the CNS by various routes, including the vasculature, olfactory and trigeminal nerves, or the lymphatic system. However, the direct mechanism that SARS-CoV-2 utilizes is unknown[108]. One hypothesis is that SARS-CoV-2 enters the CNS by breaching the olfactory route, thereby circumventing the blood-brain barrier (BBB). More than 80% of COVID-19 patients presented with gustatory and olfactory impairments lending support to this access point[104].

Furthermore, in a cohort of 214 COVID-19 patients, 36.4% developed neurologic symptoms ranging from acute cerebrovascular diseases, consciousness impairment, and skeletal muscle symptoms[109]. As reviewed by Nuzzo and Picone, another study used a cellular model to demonstrate that respiratory syncytial virus infection propagates reactive oxygen species (ROS) production transitively, creating oxidative stress that supports the idea that lung inflammation may be a determinant of systemic oxidative stress[104]. The brain, a primary tissue for metabolizing oxygen, is particularly vulnerable to ROS, and SARS-CoV-2 could generate enough ROS to cause brain injury.

In addition to the host immune system's direct mutual interaction in the gut-brain-lung axis, commensal and pathogenic bacteria in the gut microbiome can also influence COVID-19 pathogenesis. SCFAs such as acetate, butyrate, and propionate, being the most prominent immunomodulatory metabolites, maintain and reinforce intestinal epithelial integrity to decrease inflammation in the gastrointestinal tract and respiratory tract by increasing differentiation and fortifying against tight junction permeability[110]. During SARS-CoV-2 infection, increased permeability was associated with clinical worsening, including multiorgan failure[111]. SCFAs produced by the microbiota influence the inflammatory state of the host's epithelial cells, innate and adaptive immune cells directly or indirectly, and utilize the mesenteric lymphatic system for translocation of intact bacteria, their fragments or metabolites through the intestinal barrier, thereby modulating the lung immune response upon entry to the systemic circulation[112,113]. Additionally, SFCA butyrate suppresses intestinal

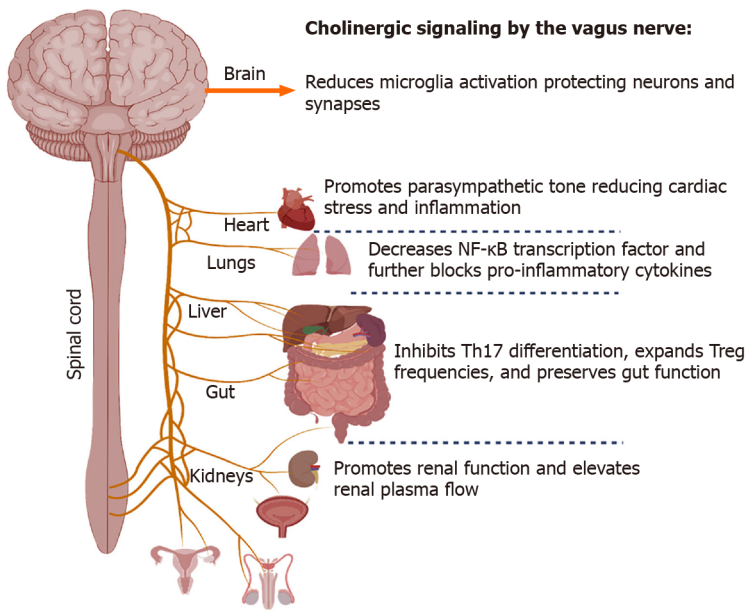


Figure 2 Role of acetylcholine on immune micro-environments in diverse tissues including the brain, heart, lungs, and gut. Cholinergic signaling can be exploited to reduce microglia activation in the central nervous system, lower systemic inflammation, and promote optimal organ function in diseased states such as severe coronavirus disease 19 infection where systemic dysfunction occurs.

inflammation by inhibiting histone deacetylase (HDAC) activity. Inhibition of HDAC enhances the mTOR-S6K pathway required for T cell differentiation and cytokine expression and enhances histone 3 acetylation at Foxp3 Locus to allow transcription to occur and Treg cell differentiation[114,115]. Further, GPR43 activation by butyrate can inhibit NF-κB activity and stimulate anti-inflammatory signaling, including IL-8 and IL-10[116].

Previous work on other respiratory viruses also documents disruptions to the gut microbiota. Interestingly, SARS-CoV-2 has been reported to deplete the levels of short-chain fatty acid-producing bacteria such as *Parabacteriodes merdae*, *Bacteriodes stercoris*, and *Lachnospiraceae bacterium*[117]. Thus, respiratory influenza can indirectly induce intestinal immune injury and alter gut microbiota, resulting in the outgrowth of *Enterobacteriaceae* and reduction of *Lactobacilli* and *Lactococci*[113]. In the influenza-related lung response in mice, intestinal TLR activation is required for NF-κB-dependent pathways for the innate immune response. In this case, disruptions of the microbiota were unrelated to the influenza virus and mediated by Th17 cells[118].

Similarly, other respiratory infections, such as a respiratory syncytial virus (RSV), distort the gut microbiome's balance by depleting *Lachnospiraceae* and *Lactobacillaceae* families while enriching *Bacteroidaceae*[119]. Experimental studies designed to administer high fiber diets favor the enrichment of short-chain fatty acid butyrate-producing bacteria, thus promoting the interferon antiviral state within the lungs of RSV-infected individuals[120]. In turn, depletion of the gut microbiome has been shown to hinder optimal alveolar macrophages' optimal functionality by reducing oxidative respiratory burst capacity and later diminishing their bactericidal effects [121].

IMPACT OF SARS-COV-2 INFECTION ON THE BRAIN-GUT AXIS

The gut microbiome has been shown to directly modulate multiple brain functions such as immune modalities like inflammation and neuroendocrine states like mood, stress, anxiety, and memory functions[122-125]. Within the gut, two plexuses comprise the enteric nervous system (ENS): one at the submucosa and the other associated with the muscularis propria. Together, these two plexuses sense the inflammatory and local microbial milieu. The ENS can regulate many aspects of CNS health and behavior through the production of inflammatory mediators, hormones, and direct neuronal innervation of the vagus nerve from the medulla oblongata[126,127]. The release of short-chain fatty acids by gut commensal bacteria improves the BBB's integrity, reduces inflammation signaling in microglia/astrocytes, and enhances neurogenesis within neurons. Collectively, this promotes reduced aging, better memory, and

improved cognitive development[128].

During gut inflammation, as exemplified with IBD, distorted microbiota populations drive mucosal myeloid cells' activation and subsequent release of pro-inflammatory cytokines that sustain epithelial gut damage. In turn, this activates a cascade of gut pain sensory pathways, dysregulates the enteric nervous system, and simultaneous gut-brain dysfunctions[129-132]. Besides distortion of the lung-gut axis, SARS-CoV-2 dysbiosis of the microbiome could also negatively impact other organs such as the brain. SARS-CoV-2 diminishes crosstalk with the brain by depleting crucial short-chain fatty acid-producing bacteria within the gut microbiome[117] (Figure 3). Furthermore, SARS-CoV-2 has been shown to gain access to the brain by crossing the neural-mucosal interface in olfactory mucosa, where the olfactory mucosal, endothelial, and nervous tissue are closely intertwined[133]. After this, SARS-CoV-2 localizes within the medulla, where respiratory and cardiovascular activities are controlled[133-135]. Thus, this could account for the neurological symptoms such as loss of smell and taste, persistent headaches, confusion, cerebrovascular disease, muscle pain, ataxia, seizures, and dizziness observed in COVID-19 patients[136]. The CNS also supports gut function making the gut-brain axis bi-directional[137,138]. However, the impact of SARS-CoV-2 pathology within the CNS on the direction of gut functions such as peristalsis, modulation of gut immune responses, and directing digestion is yet to be fully comprehended[139].

NICOTINE RECEPTORS, POSSIBLE THERAPEUTIC TARGETS FOR LIMITING SARS-COV-2 DAMAGE IN THE GUT AND BRAIN

Several epidemiological studies from the United States, Europe, and south and east Asia have concluded that tobacco smokers have a lower risk of SARS-CoV-2 infection [140-144]. Additionally, smokers may also have a reduced risk of significant symptoms once infected with SARS-CoV-2, despite typically experiencing increased morbidity and mortality during other respiratory infections[142]. Nicotine is the receptor agonist for nAChRs that contribute to tobacco smoke's addictive and psychoactive properties. In contrast to exogenous nicotine, the endogenous agonist for nAChRs, ACh is produced by neurons and lymphocytes, an essential neuro-immune modulator. The α 7nAChR, in particular, regulates the cholinergic anti-inflammatory response (CAIP) [145]. During acute inflammation, efferent signals from the CNS induce the release of ACh at the enteric nervous system, where they modulate T-cell dynamics, including the induction of Tregs and inhibition of Th17 cells and suppression of local inflammation, including the releases of TNF- α , IL-1 β , and HMGB1[146,147]. One hypothesis for nicotine's inhibitory effects is that exogenous α 7nAChR agonists recapitulate the effects of ACh release by the vagus nerve, thereby reducing cytokine storm risk both locally at the inhalation site (the lungs) and systemically, including in the gut. This mechanism may be a likely reason nicotine improves ulcerative colitis symptoms[146, 148]. The argument for cholinergic modulation is made even more compelling when considering that neither smoking nor nicotine consumption decreases ACE2 or TMPRSS2 and may increase their expression in the lower airways[149,150]. COVID-19 patients should not be encouraged to smoke or consume nicotine. However, alternative methods of modulating the CAIP have been suggested. Vagus nerve stimulation (VNS) delivers electrical impulses to the left vagus nerve *via* a small device implanted below the collar bone currently used to treat treatment-resistant epilepsy and major depressive disorder. However, less-invasive transcutaneous auricular VNS is being developed. Although more extensive clinical studies are ongoing, case studies have indicated possible benefits in reducing plasma IL-6 levels when using these devices[151]. Alternatively, α 7nAChR agonists or acetylcholinesterase inhibitors have been proposed to reduce systemic inflammation[152,153].

A recent report describing ACE2 and TMPRSS2 expression during chronic vagus nerve stimulation showed no changes in either protein or enterocytes[154], although each gene was strongly correlated with CHRNA7 gene expression RNA-seq[154]. Another report separately described how the spike glycoprotein's receptor-binding domain on SARS-CoV-2 possesses significant structural homology with α -bungarotoxin, a neurotoxin produced by kraits that target α 7nAChR, the product of CHRNA7 translation[155]. In their discussion, the authors suggest this homology blocks normal cholinergic signaling by competitive inhibition leading to an excessive pro-inflammatory response that cannot be alleviated by vagal signaling. If that is the case, the co-expression of CHRNA7 and ACE2 with TMPRSS2 would mean that infected gut epithelial cells are producing viral particles that inhibit cholinergic

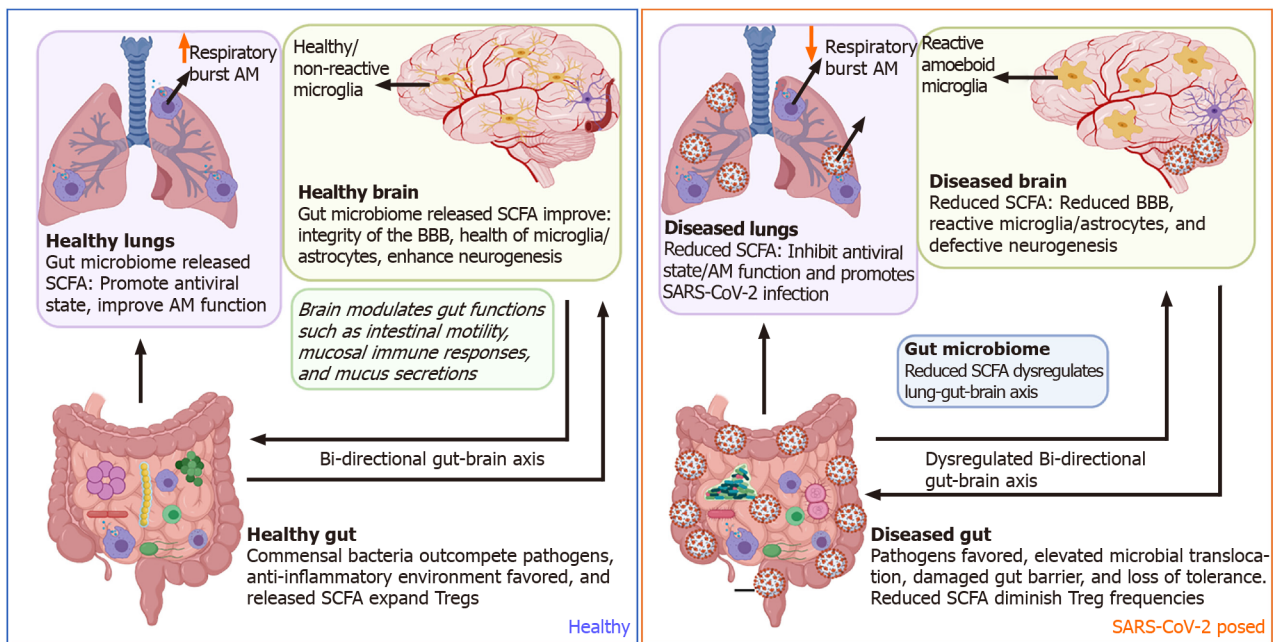


Figure 3 Potential mechanisms by which severe acute respiratory syndrome coronavirus 2 dysregulates the gut-brain axis. Side by side comparisons of the gut-brain-lung axis in a healthy state vs a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exposed state. In a healthy state, commensal bacteria outcompete pathogens within the gut micro-environment leading to a predominantly anti-inflammatory state. Peptides released by commensal gut bacteria support optimal brain and lung function. During SARS-CoV-2 infection, gut microbial dysbiosis dysregulates gut, lung, and brain function. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; BBB: Blood-brain barrier; AM: Alveolar macrophages; SCFA: Short-chain fatty acids; T-reg: T regulatory cells.

signaling on themselves. A loss of cholinergic signaling fails to block HMGB1, allowing increased microbial translocation at the gut barrier exacerbating inflammatory responses[156]. Targeting this interaction on colonocytes may offer considerable protection from pathogenesis, including the cytokine storm. A similar correlation between ACE2 and CHR7 expression has been found on airway epithelial cells, suggesting these cells specifically may be the mechanism by which nicotine modulates infection rates and pathogenesis when endogenous ACh fails[157].

It should be noted that in addition to a disruption to its anti-inflammatory functions, the vagus nerve may also contribute to the COVID-19 pathology in other ways. During Parkinson's disease, α -synuclein aggregates travel from the gut to the CNS in the vagus nerve *via* retrograde axonal transport[158]. The innervation of both the lungs and gut, where significant viral replication occurs, may allow a similar direct transport to the CNS[159]. This hypothesis is corroborated by the recent reports, which showed that the brain stem has an increased inflammatory response during COVID-19 compared with other brain regions. Where cranial nerves IX and X (glossopharyngeal and vagus nerves) meet, the medulla oblongata, in particular, has a higher viral load than the rest of the CNS[160]. The axonal and synaptic loss at the dorsal motor nucleus and nucleus solitarius near this region may be contributing to the loss of autonomic control of respiratory function, cardiac arrhythmias, and gastrointestinal symptoms like diarrhea and vomiting[161,162]. Complicating the role of nicotine in COVID-19 pathogenesis, its administration can inhibit Th17-driven neuroinflammation, thereby possibly protecting these regions in smokers[163]. A better understanding of this process, if it exists, could contribute significantly to minimizing neuropathogenesis during SARS-CoV-2 infection.

CONCLUSION

SARS-CoV-2 infection in the gut leads to alterations in gut microbiota with depletion of bacterial genera that produce crucial metabolites such as short-chain fatty acids that sustain optimal brain function. Future studies focusing on using probiotics to replenish commensals' dwindling populations as a strategy to reverse gut dysbiosis while maintaining the gut-brain axis during COVID-19 are needed[164]. Furthermore, additional efforts should be applied to the testing strategies currently used to manage inflammatory conditions affecting the gut for their potential in the direction of

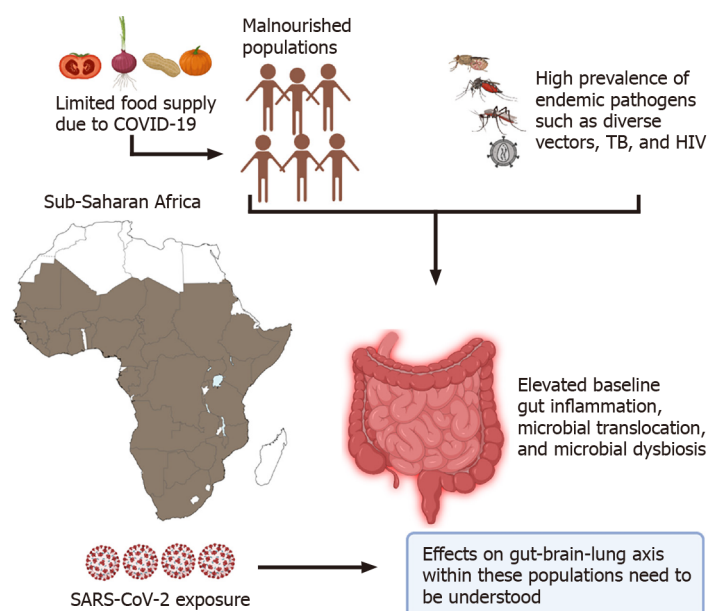


Figure 4 Elevated baseline gut inflammation observed in Sub-Saharan African individuals could lead to severe coronavirus disease 19 associated dysregulation of the gut-brain-lung axis. Continuous exposure to various endemic pathogens such as human immunodeficiency virus, tuberculosis, multiple vectors like tsetse flies, and several mosquitoes, in addition to low diets, set the ground for high levels of gut dysbiosis within the entire community populations. Additional studies focused on evaluating the effects of baseline gut dysbiosis on coronavirus disease 19 infection are highly warranted. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 19, HIV: Human immunodeficiency virus; TB: Tuberculosis.

COVID-19 associated dysbiosis, gut damage, and microbial translocation. Targeting vagal stimulation and diverse nicotinic receptors could offer lower organ inflammation and confer systemic protection across the gut-brain and lung organs.

Lastly, special consideration should be given to populations worldwide where there is a high incidence of coinfections such as HIV and tuberculosis (TB) that target the gut early on in infection, cause dysbiosis and lead to microbial translocation[165-167]. In the world's poorest regions like Sub-Saharan Africa, most individuals are continuously exposed to endemic pathogens like helminths and TB that could lead to elevated baseline levels of gut damage, immune activation, and possible microbial translocation [168-171]. Recently, Bhaskaran *et al*[172] analyzed data from 27480 individuals co-infected with HIV within the United Kingdom. Their data revealed that people living with HIV had a higher risk of COVID-19 death than those without HIV, after adjusting for the age and sex with a hazard ratio (HR) of 290 (95%CI 0.196-0.430; $P < 0.0001$). However, the absence of testing, limited case reporting, and poor health care limits our understanding of the SARS-CoV-2 pandemic on this continent[172].

The sudden lifestyle changes imparted by the pandemic within these populations have tremendously strained their chances of survival. In countries where restrictions or lockdowns are enforced, most individuals from these regions rely on the government to supply free food rations[173]. However, the low quality of this freely distributed food fuels the already highly prevalent risk of malnutrition within these populations[174]. As we have illustrated, limited dietary access within these communities could further aggravate gut dysbiosis leading to severe systemic disorientation during SARS-CoV-2 infection. The complexity of these variables, in addition to limited health service delivery and governmental support[175] could exacerbate gut-brain disruptions within diverse populations in Sub-Saharan Africa (Figure 4).

In these trying times of the COVID-19 pandemic, the connotation of a healthy gut-healthy mind could translate into one's ability to orchestrate a meaningful immune response that could limit SARS-CoV-2 infection and maintain systemic homeostasis and diminish side effects from virus exposure. Leveraging therapies currently being used to improve gut health could be exploited for better disease outcomes during severe disease. Additional studies on the gut-brain axis, particularly from diverse populations across the world, are warranted.

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