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Review

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What Do Influenza and COVID-19 Represent for Patients With Inflammatory Bowel Disease?

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Abstract

Background: Inflammatory bowel diseases (IBD) are a group of immune and inflammatory diseases; and patients seem to be more vulnerable to influenza and coronavirus disease 2019 (COVID-19). These conditions are characterized by the augmented release of inflammatory cytokines that have been suggested as potential triggers for the acute respiratory distress syndrome, which may favor severe and even fatal outcomes. For these reasons, this review aims to evaluate what influenza and COVID-19 may represent for patients with IBD.

Methods: The search was performed in MEDLINE/PubMed, EMBASE, and Cochrane databases. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed to build the review.

Results: The conventional therapies used by IBD patients may also interfere in the outcomes of influenza and COVID-19. Immune-suppressors agents are associated with a higher risk of infections due to the inhibition of intracellular signals necessary to the host act against pathogens. On the other hand, drugs related to the suppression of the production of cytokines in IBD could bring benefits to reduce mucosal inflammation, and for preventing pneumonia. Moreover, coronaviruses can bind to the target cells through angiotensin-converting enzyme 2 (ACE-2) receptor that is expressed in epithelial cells of the lung and largely the colon and the terminal ileum suggesting that human intestinal tract could be an alternative route for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Conclusions: Once the cytokine storm observed in influenza and COVID-19 is similar to the cytokine pattern observed in IBD patients during the disease flares, the advice is that avoiding the infections is still an optimal option for IBD subjects.

Keywords: Influenza: COVID-19; Ulcerative colitis; Crohn's disease; Inflammatory bowel disease

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Introduction

Inflammatory bowel diseases (IBD) are a group of immune and inflammatory diseases, mainly represented by Crohn's disease (CD) and ulcerative colitis (UC). The pathophysiology of these diseases remains not fully clarified; however, genetic involvement in predisposing individuals is considered. Environmental factors such as diet, smoking, alcohol consumption, and changes in the intestinal microbiome may also be involved [1-3].

There is evidence that influenza is possibly more severe in patients who have IBD and use immunomodulators so that the influenza vaccine is less effective in this group when compared to the general population, although it is strongly recommended [4, 5].

Influenza is a common respiratory illness that can be related to severe illness and death, mainly in patients with chronic inflammatory conditions, and had affected millions of people around the world [6]. Nevertheless, the new line of coronavirus (severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)) is today one of the most worrying pandemics. The method of initial transmission of the virus is possibly related to the consumption and contact with wild animals. Human-human contamination became a source of rapid and worrying dissemination and that international spreading is highlighted, as international travelers became propagators. This fact contributed to coronavirus disease 2019 (COVID-19) becomes a global issue [7, 8].

In addition to respiratory manifestations, patients infected with COVID-19 may present nausea or vomiting, or both, and diarrhea, which denote the involvement of the gastrointestinal tract by this viral infection [9].

Some risk factors were related to COVID-19, such as immunosuppressive therapy, diabetes, hypertension, older age, malnutrition, and pregnancy. Many of these treatments are related to

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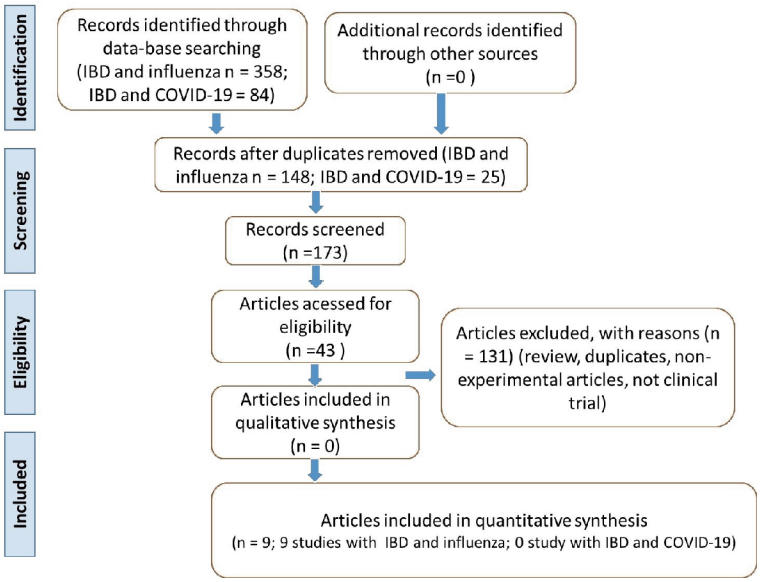

Figure 1. Flow diagram showing the study selection (PRISMA guidelines). IBD: inflammatory bowel disease; COVID-19: coronavirus disease 2019; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

increased risks of infections. For these reasons, patients with UC and CD should be considered a possible risk group [7, 10].

Furthermore, it is known that the virus requires the angiotensin-converting enzyme 2 (ACE-2) receptor to perform its entry into the cell. The ACE-2 receptor is found in large quantities in alveolar cells of the lungs, but the small intestine is also known to express this receptor. A study showed the presence of the virus and ACE-2 receptor in the biopsy taken in the stomach, duodenum, and rectum of a patient infected with SARS-CoV-2. Beyond that, *in vitro* studies have linked the increase in the expression of ACE-2 through a pro-inflammatory secretory pattern, since interferon-gamma (IFN-γ) can induce ACE-2, whose promoter region contains several cytokine responsive transcription factor binding sites [10-12].

For these reasons, this review aims to evaluate what influenza and COVID-19 may represent for patients with IBD.

Methods

Focused question

This review was performed to answer the focused question: "Are IBD patients more vulnerable to influenza or COVID-19?"

Language

Only studies in English were selected.

Databases

This review has included studies available in MEDLINE/PubMed (National Library of Medicine, National Institutes of Health), EMBASE, and Cochrane databases. The descriptors used were Influenza and Inflammatory Bowel Disease or Ulcerative Colitis or Crohn's Disease and COVID-19 and Inflammatory Bowel Disease or Ulcerative Colitis or Crohn's Disease. The authors of this review have followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Data extraction and selection of the studies

The inclusion criteria were studies performed in humans, including randomized clinical trials (RCTs). The exclusion criteria were reviews, studies not in English, editorials, and poster presentations.

The search for this review was performed by two independent reviewers (SMB and JNM) for the identification of studies based on the titles and abstracts of the studies. Full-text articles were evaluated to support the decision-making process if necessary. A third person (RAG) resolved disagreements between these reviewers.

The three reviewers independently performed the extraction of the characteristics of the included studies and outcomes. The PRISMA flowchart was used to expose the inclusion/exclusion retrieved records.

The Population, Intervention, Comparison, and Outcomes (PICO) were used to perform the review process.

Results

The flow diagram (Fig. 1) shows the selection of the articles, as well as the inclusion and exclusion criteria. After identifying the articles, only nine studies were selected to build this

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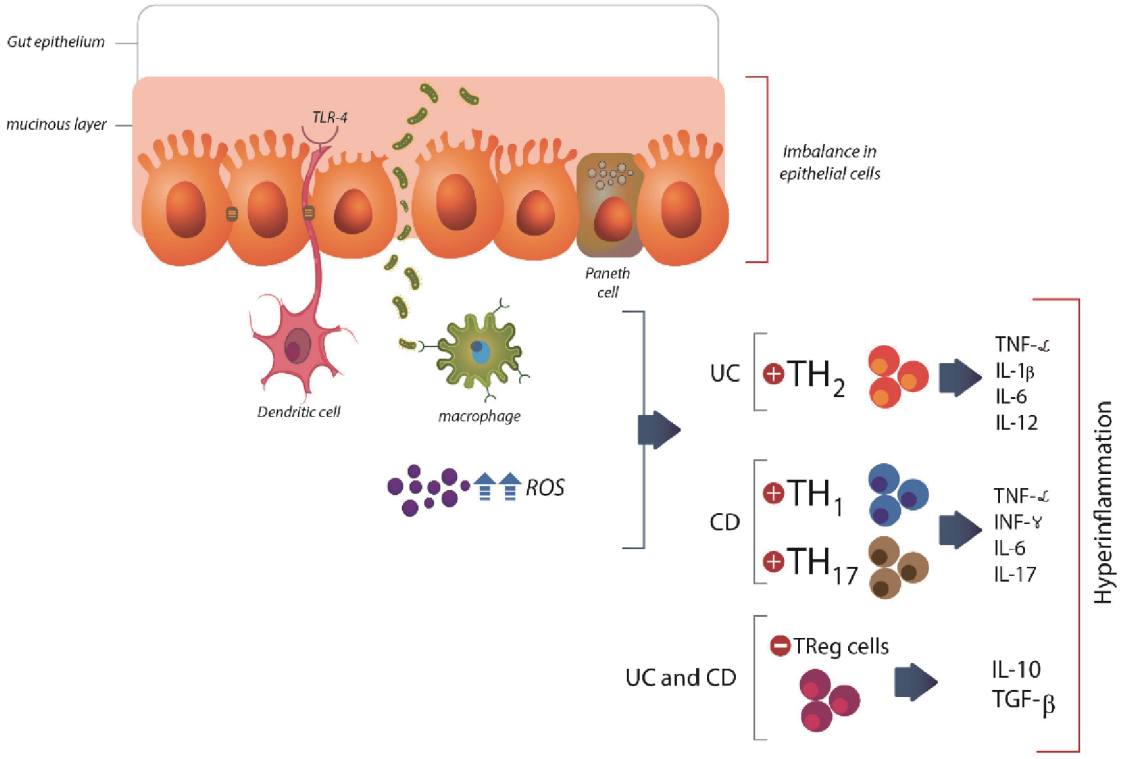

Figure 2. Pathophysiologic aspects of inflammatory bowel disease. The imbalance in the mucinous layer and epithelial cells leads to increased permeability to pathogens and activation of inflammatory pathways. In UC, the response is mediated by TH2, and in DC is mediated by TH1 and TH17 resulting in the synthesis of inflammatory cytokines (TNF-α, IFN-γ, IL-6, IL-17, IL-23). This scenario is also represented by a reduction in the activity of Treg cells and reduction of IL-10 and TGF-β. DC: dendritic cell; TNF-α: tumor necrosis factor-α; IFN-γ: interferon gamma; IL: interleukin; TGF-β: transforming growth factor-β; NFκβ: nuclear factor kappa β; TH: T helper cell; UC: ulcerative colitis; CD: Crohn's disease; ROS: reactive oxygen species.

review. Altogether, 1,548 IBD patients were enrolled in the selected studies, 961 with CD, 493 with UC, 10 with indeterminate colitis, and seven with Behcet's disease, age 6 - 75 years old. Two studies did not report the type of IBD of the patients enrolled.

Discussion

IBD in a nutshell

The prevalence of both UC and CD are augmenting sharply over the end of the 20th century, and beginning of the 21st century, and can be considered as the most prevalent gastrointestinal disorders in industrialized countries [13, 14].

IBDs are lifelong conditions characterized by cracks in the epithelial lining (or abnormal mucus production) of some areas of the intestine; and the non-healing (defective repair) of the mucosal damage is of crucial importance. The inflammatory process related to the development of these diseases involves alterations in the permeability of the epithelial cells, microbiome patterns, and imbalanced immune response resulting in the stimulation of Tool-like receptors (TLR), dendritic cells and differentiation of $CD4^+$T-cells into T helper cells (TH1, TH2, TH9, and TH17). The results of this process lead to the release of the pro-inflammatory (interleukin (IL)-1β), IL-4, IL-6, IL-9, IL-17, IL-23, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ. This imbalanced inflammatory process disrupts the bowel homeostasis (Fig. 2). Besides the influx of macrophages and neutrophils and the over-production of inflammatory cytokines, there is also an increment in the production of proteolytic enzymes and free radicals that contribute to inflammation and may lead to ulcerations. The consequences for the patients are diarrhea, abdominal pain, bleeding, weight loss, increased risk to colon cancer, and decreased quality of life [15].

In UC patients, the inflammatory pattern is mediated mainly by TH2 responses and limited to the colon and rectum. In patients with CD, the inflammatory process is mediated by TH1 and TH17 and involves skipped areas from mouth to anus. Phases feature both UC and CD denominated flares in which the patients present rises in the chronic inflammatory pattern, disease severity, and periods of clinical remission [16, 17].

The clinical protocol for IBD includes sulfasalazine, mesalazine, corticosteroids, antibiotics, azathioprine, methotrexate, infliximab, adalimumab, and other anti-TNF. Many of these therapies are associated with increased risk for infections, and can also interfere with the expected results of immunization against the influenza virus (Table 1 [18-26]). For

Table 1. Randomized Clinical Trials Showing the Effects of the Vaccine for Influenza in IBD Patients [23, 49-56]

Reference	Country	Population	Intervention/comparison	Outcomes
[18]	USA	69 IBD patients (40 on anti-TNF monotherapy, 19 on vedolizumab), and 20 healthy controls (HC) (18 - 64 yrs).	Patients were allocated to receive influenza high dose vaccine or standard dose.	IBD patients on anti-TNF monotherapy that received a high-dose influenza vaccine showed significantly increased post-immunization antibody levels compared with the standard vaccine.
[26]	Japan	44 CD and 88 UC (41-42 yrs) with no significant differences in immunosuppressive therapies, disease activity, and endoscopic findings.	Patients and controls received single or double doses of seasonal QIV. 22 subjects received immunomodulatory monotherapy, 16 received anti-TNF-α single-agent therapy; 15 received immunosuppressant and anti-TNF-α agent.	Single-dose of QIV induced sufficient immunogenicity in IBD patients, and the additional vaccination did not show improvements. Immunogenicity was reduced in patients that were receiving infliximab.
[25]	Canada	115 CD, 22 UC and 1 unclassified IBD (9 - 60 yrs) on the maintenance of infliximab therapy.	Patients received 2012/2013 influenza vaccine at the time of infliximab infusion or midway between infusions.	Serologic protection to the influenza vaccine was achieved in 45-80% of IBD patients on maintenance infliximab therapy. The vaccine timing relative to infliximab infusion did not affect the achievement of serologic protection.
[24]	France	172 CD and 83 UC (18 - 64 yrs) who received at least 3 months of treatment (for those with IS or anti-TNF therapy) or without any indication to start IS therapeutics in the following 3 months.	Patients received the trivalent influenza vaccine for years 2009 - 2010 and 2010 - 2011. Hemagglutination inhibition titers were assessed before, 3 weeks, and 6 months after vaccination. Participants were divided into three groups: patients that had no IS, IS without anti-TNF, and anti-TNF with or without IS.	3 weeks after the first vaccination, the rates of seroprotection were 77%, 75% and 66% for A/H1N12007, 77%, 68% and 52% for A/H3N2 and 97%, 96% and 95% for B strain in groups A, B, and C, respectively. Seroconversion rates for A/H1N12007, A/H3N2, and B strain did not differ according to treatment group. After 6 months of vaccination, seroprotection rates were lower in group C compared to group A, and B. Persistence of seroprotection was lower in patients with anti-TNF.
[23]	Japan	38 CD, 33 UC, and 7 Behcet's disease; (≥ 20 yrs) receiving IS therapy, immunomodulators and/or anti-TNF-a agents, and 11 HC.	The participants received the trivalent influenza vaccine and randomized into groups of single vaccination and two vaccination booster.	No significant differences were seen in the immune response between 3 weeks post-vaccination in the single vaccination group and 3 weeks post-second vaccination in the booster vaccination group. A higher pre-vaccination titer was related to enough seroprotection rate after vaccination for the H1N1 strain. The second booster of trivalent influenza vaccination did not improve the immune response.
[22]	Hungary	127 CD and 82 UC patients (> 18 yrs) stable for more than 3 months, with no signs of activity and not requiring any treatment modification.	156 patients received influenza vaccination and 53 patients did not (control group). The influenza vaccine used was: A/California/7/2009 (H1N1), A/Victoria/361/2011 (H3N2), B/Wisconsin/1/2010-like B/Hubei-Wujiagang/158/2009. The whole virion vaccine (Fluval AB) was given to 57, and split virion vaccine (IDFlu9) was given to 99 patients.	Post-immunization titers of both influenza subtypes were significantly increased after split virion vaccines compared to the control group and whole virion vaccine group. The antibody titers of influenza B also increased in the split virion vaccine group treated with anti-TNF-α therapy. The levels of IL-2 decreased after the intervention. Disease relapse was observed in only 10% of the patients and was more common in vaccinated patients.
[21]	Italy	36 CD, 26 UC, and 31 HC (18 - 75 yrs). 47 patients were on anti-TNF-α monotherapy and 15 on anti-TNF-α combined with IS.	All the subjects received the MF59-adjuvanted H1N1 vaccine.	Seroprotective titers in UC and CD patients were comparable to HC. The seroconversion rate was lower than HC in IBD patients both on anti-TNF-α monotherapy or combined with IS. There was a suboptimal response to the vaccine in IBD patients on therapy with anti-TNF-α and IS compared to those on anti-TNF-α monotherapy and HC.

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Table 1. Randomized Clinical Trials Showing the Effects of the Vaccine for Influenza in IBD Patients [23, 49-56] - *(continued)*

Reference	Country	Population	Intervention/comparison	Outcomes
[20]	Belgium	407 CD, 159 UC, and 9 indeterminate colitis patients (40.3 yrs) with stable IBD treated with immunomodulators and/or biological therapy.	Patients received influenza H1N1 adjuvanted and non-adjuvanted vaccines. The authors evaluated the risk of the flare of IBD after vaccination and disease activity.	After 4 weeks of intervention, the absence of flare was observed in 377 patients with CD (96.7%) and 151 with UC (95.6%). The risk of IBD flare appears to be not increased after H1N1 vaccination.
[19]	Poland	30 IBD (not specified the type) patients (6 - 18 yrs) with previously diagnosed IBD and 34 HC.	Participants were divided into 3 groups: A, treated with ASA, metronidazole or ciprofloxacin; B, treated with ASA and immunomodulatory; and C, healthy children as control. All the subjects were vaccinated with the split type vaccine with the antigens of influenza strains: A/New Caledonia/20/99 (H1N1), A/California/7/04 (H3N2), and B/Shanghai/361/02.	Anti-HA and anti-NA 1 and 6 months post-vaccination were higher than baseline levels. In group A, the protection rate achieved the highest level for antigens A/H1N1 and B 6 months after vaccination. In group B, the highest protection rate was observed after 6 months. The response rate in group A remained the same 1 and 6 months post-vaccination, while in group B, the highest response rate was noted 6 months after the vaccine.

Anti-HA: antihemagglutinin; Anti-NA: anti-neuraminidase; ASA: 5-acetylsalicylic acid; CD: Crohn's disease; CDAI: Crohn's disease activity index; HBI: Harvey Bradshaw index; IBD: inflammatory bowel disease; IL-2: interleukin 2; IM: intramuscular; IS: immunosuppressive; QIV: quadrivalent inactivated influenza vaccine; SC: subcutaneously; TNF: tumoral necrosis factor; UC: ulcerative colitis; HC: health control; yrs: years.

these reasons, IBD patients should be considered a possible risk group regarding influenza and COVID-19 [1, 7, 10, 27, 28].

Influenza

Influenza viruses belong to the family orthomyxovirus. The envelope of the virus of influenza A exhibits two main surface glycoproteins named hemagglutinin A and neuraminidase. The first is responsible for membrane fusion, and the second is responsible for the release of the virions. Many health patients and IBD subjects who are infected by the influenza virus may need hospitalization that may include intensive care and sometimes interruption of the immunosuppressive drugs. Moreover, disease flares have been reported after influenza infection [29-31].

Among the subtypes of influenza A, H1N1 and H3N2 seem to mutate during the season and are related to more severe disease when compared with influenza B (B/Victoria and B/Yamagata). IBD patients are at increased risk for severe complications from influenza viruses, and the Advisory Committee on Immunization Practice and gastroenterology practice guidelines recommend annual influenza immunization. Increase in the antibody levels obtained with vaccination may reduce infection processes [18, 32]

Authors have shown that targeting influenza virus glycoprotein hemagglutinin seems to be essential protection against influenza. On the other hand, clinical trials have shown an essential role for T-cells in the achievement of protection. The concentrations of influenza-specific IFN-γ producing $CD4^+$ and $CD8^+$ T-cells are negatively correlated with the development or severity of the condition [33-35].

H1N1 viral infections have been reported worldwide and represent the leading cause of severe acute pneumonia, and acute respiratory distress syndrome (ARDS). For these reasons, H1N1 epidemics may represent a challenge and a severe burn to public health systems [36].

Patients with severe influenza infection present a robust increase in the levels of TNF-α, IL-6, IL-8, IFNs, and monocyte chemoattractant protein-1 (MCP-1), interferon-inducible protein-10 (IP-10), and C-C motif chemokines ligand 5 (CCL-5). This scenario of hyper-inflammation is named cytokine storm and leads patients to an increased risk of morbidity and mortality (Fig. 3) [37, 38].

The estimative is that 3 - 5 million cases of severe illness and about 290,000 to 650,000 deaths per year can result from the influenza infection [31, 39].

COVID-19

The SARS-CoV-2 emerged in Wuhan in December 2019 in a Chinese Province and quickly spread throughout the world, generating a pandemic. In February 2020, the International Committee on Taxonomy of Viruses named the condition as "Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)?, and the World Health Organization (WHO) designated the disease as COVID-19; and more than 20,000 cases were

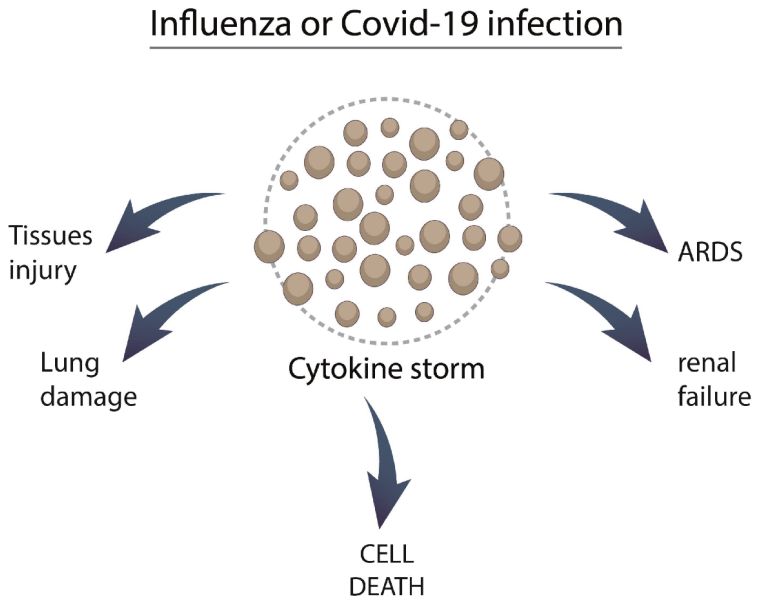

Figure 3. Possible mechanisms involving influenza and COVID-19 with cytokine storm. COVID-19: coronavirus disease 2019; ARDS: acute respiratory distress syndrome.

confirmed. On 13 January 2021, there have been 90,335,008 confirmed cases, including 1,954,336 deaths. Unfortunately the numbers are still growing, as well as the number of affected countries [40-42].

COVID-19 belongs to the *Nidovirales* order, coronavirus family, and is characterized by a single-stranded ribonucleic acid (RNA)-enveloped virus. Its genome is aligned with the Bat-CoV and Bat-CoV RaTG13 genome of *Rhinolophus affinis.* Bats, civet cats, and pangolins have been considered intermediates in transmitting the virus to humans (Fig. 4) [43, 44].

COVID-19 presents four major structural proteins: the spike surface glycoprotein, small envelope protein, matrix protein, and nucleocapsid protein. The first protein is capable of binding to the host receptors through the receptor-binding domains of the ACE-2 that is present in several organs such as the respiratory system, gastrointestinal tract, thymus, lymph nodes, bone marrow, kidney, liver, and brain [45, 46].

Patients may infect other people even before the initiation

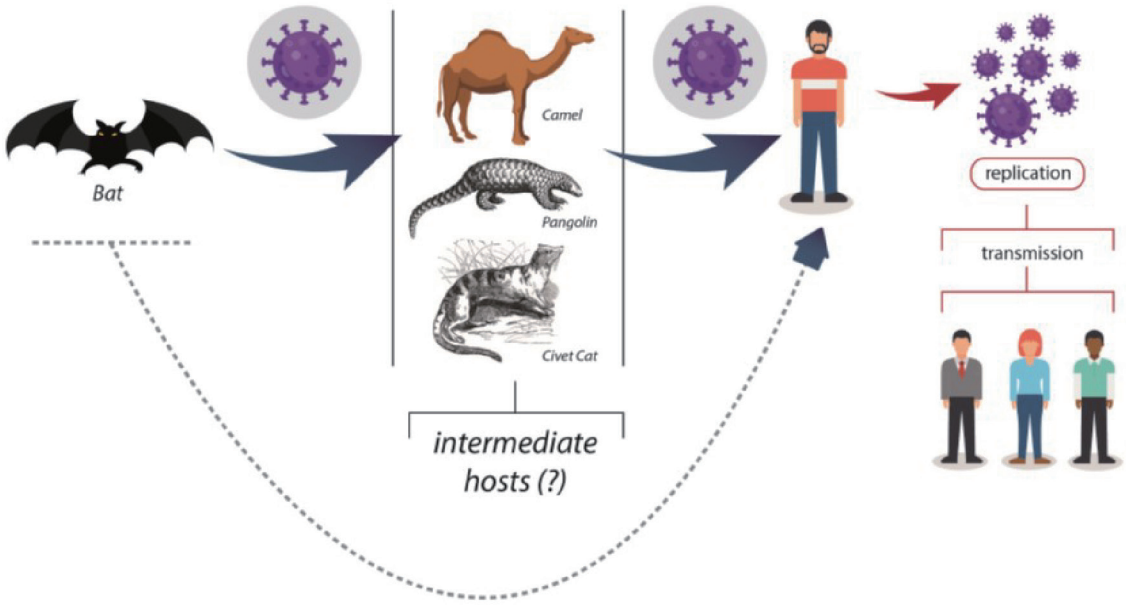

Figure 4. Possible origin and transmission for SARS-CoV-2 infection. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

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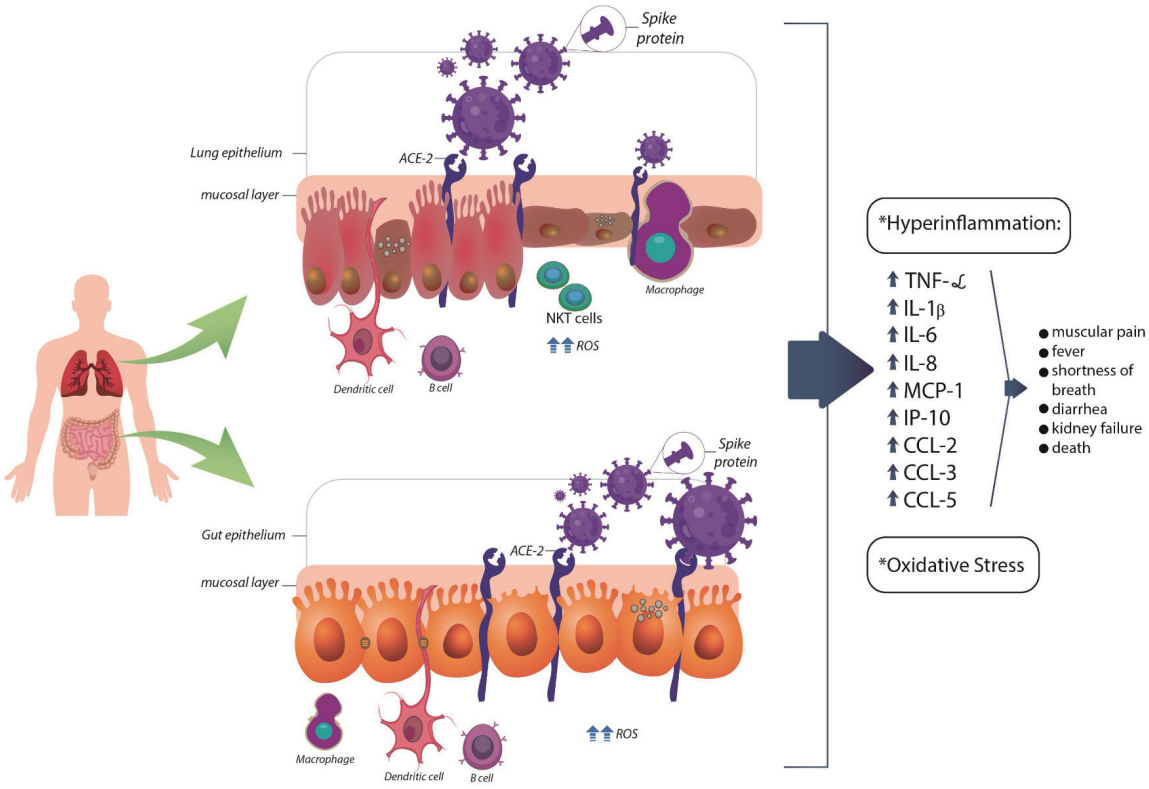

Figure 5. Possible pathogenesis for SARS-CoV-2 infection in lung and gut epithelium. ACE-2: angiotensin-converting enzyme 2; CCL: C-C motif chemokines ligand; IP-10: interferon-inducible protein 10; DC: dendritic cell; IFN-γ: interferon gamma; IL: interleukin; MCP-1: monocyte chemoattractant protein-1; NKT: natural killer T cell; ROS: reactive oxygen species; TNF-α: tumor necrosis factor-α.

of the symptoms through the saliva, respiratory droplets, urine, feces, conjunctiva, and fomites. The transmission may also occur during the clinical recovery of the disease, and the most common clinical manifestations are fever, dry cough, headache, fatigue, muscle pain, dyspnea, pneumonia, and SARS. COVID-19 pneumonia affects the chest that exhibits imaging abnormalities, even in asymptomatic patients, and a rapid evolution from focal and unilateral presentation to diffuse bilateral ground-glass pattern that progress to consolidations within 1 - 3 weeks. The symptoms also vary with the patients' ages [47-49].

SARS-CoV or Middle East respiratory syndrome coronavirus (MERS-CoV) infected animals exhibit marked inflammatory and immune responses leading to a cytokine storm [50] (Fig. 5). The sequence of events includes a reduced release of antiviral IFNs and increased synthesis of biomarkers such as IL-1β, IL-2, IL-6, IL-8, IFN-α/β, TNF-α, IP-10, and C-C motif chemokines ligand (CCL2, CCL-3, CCL-5). Due to the genetic homology and pathologic characteristics, it is possible to predict that similar events will occur with COVID-19. Interestingly is that the anti-inflammatory IL-10 is frequently augmented in COVID-19 patients. The consequences of this scenario are apoptosis of lung epithelial and endothelial, vascular leakage, imbalanced T cell, dendritic cell, and macrophages responses that culminate in vascular alveolar edema, hypoxia, and death [41, 45, 51-53].

The release of IL-6, at high levels, has been suggested as a potential trigger for ARDS in SARS-CoV-2 infections, which may favor serious and even fatal outcomes. The levels of IFN-γ and TNF-α have also been associated with severe SARS-CoV infection [10, 54].

The cytokine storm is also associated with pronounced oxidative stress due to the synthesis of reactive oxygen species that can contribute to ARDS, which is one of the most relevant causes of deaths in the infected patients (Fig. 5) [55, 56].

Are IBD patients more vulnerable to influenza or COVID-19?

We did not find RCTs investigating IBD and COVID-19, but we can find clinical trials evaluating the influenza vaccine in these patients. Vaccine studies show that varying degrees of serologic response can be observed with vaccination (Table 1) [5, 18-26]. Higher levels of antibodies induced by vaccination can reduce the risk of illness and leads to protection against infections. One possibility to improve the immune response of the vaccine with infliximab therapy could be the use of a more concentrated vaccine [18, 57] once the administration of a booster vaccine in IBD patients has not shown to be effective [23].

Similar to influenza, COVID-19 affects the respiratory

tract due to the direct viral infection or due to impairment in the immune response. An Italian study showed that hospitalizations between 2007 - 2016 for encapsulated bacterial infections were 74.5% for *Streptococcus pneumoniae* (*S. pneumoniae*), 16.3% for Neisseria meningitidis (*N. meningitidis)*, and 9.3% for Haemophilus influenzae (*H. influenzae*) [58].

As pointed before, coronaviruses can bind to the target cells through ACE-2 receptor that is expressed in epithelial cells of the lung and largely the colon and the terminal ileum (amongst the highest in the body). Once the SARS-CoV-2 RNA was detected in the stool, much attention has been directed to the gastrointestinal system. More than 50% of the patients infected with COVID-19 exhibit positive tests in feces, and about one-fifth remained positive in feces even with a negative test in respiratory samples. These findings may explain the reasons why some infected patients present gastrointestinal symptoms [11].

Authors have found that diarrhea might be the first symptom before diagnosis and can occur in 49.5% of the patients, and about 22.2% of them presented this symptom before diagnosis [59].

Both key enzymes of the renin-angiotensin system (ACE and ACE-2) are expressed in high amounts in the small bowel and the colon. Some authors have found that the inflamed gut has over-expression of ACE-2 (Fig. 5). Large amounts of angiotensin I and II are found in the mucosa of recto-sigmoid biopsies obtained from patients with CD when compared to UC patients or healthy individuals. Therewithal, IBD patients have increased circulating alternative renin-angiotensin system components than patients without IBD. The treatment of these subjects with angiotensin-receptor blockers leads to reduced mucosal pro-inflammatory biomarkers than controls. Indeed, the interference in the renin-angiotensin system has been shown to play a beneficial role in some animal models of colitis [60-64], and targeting drugs could be beneficial for the human therapeutic approach.

The components of the classical and alternative axes of the renin-angiotensin system were found in the intestinal wall of IBD patients and controls, suggesting that all the components can be synthesized within the gastrointestinal tract, and probably has crucial actions in the maintenance of homeostasis or can be perturbed in intestinal inflammation [60].

For the establishment of SARS-CoV-2 infection, there must be a connection with the ACE-2 and the fusion of the capsule of the virus with the host cell membranes (Fig. 5). This process occurs through the spike surface glycoprotein, in which activation is mediated by a proteolytic cleavage induced by host cell proteases whose activity is up-regulated in IBD patients [65]. It is also noteworthy to say that there are two isoforms of ACE-2. One is anchored to the membrane (and may serve as SARS-CoV-2 receptor), and the other is circulating. The soluble form seems to compete with SARS-CoV, inhibiting the binding of the viral particle to the surface-bound in the other isoform. Noticeable is that the levels of the soluble protein are up-regulated in the peripheral blood of patients with IBD, suggesting a possible contribution to reducing the virus infection [66-68]. Indeed, with these observations it is possible to suggest that human intestinal tract could be an alternative route for SARS-CoV-2 [69, 70].

The conventional therapies used by IBD patients may also interfere in the COVID-19 infection. Immune-suppressors agents are associated with a higher risk of infections due to the inhibition of intracellular signals necessary to the host act against pathogens. Still, it is necessary to remember that the drugs related to the suppression of the production of cytokines in IBD could bring benefits both to reduce mucosal inflammation and for preventing pneumonia caused by COVID-19. Increased risk of pneumonia has already been reported in patients with IBD compared to healthy individuals, and this relationship is even more evident in patients using medications such as corticosteroids [49, 71-73].

Moreover, TNF and IL-6 targets can increase the risk for bacterial infections but show fewer effects on viral infections such as influenza. The drugs that target pro-inflammatory cytokines such as infliximab, adalimumab, ustekinumab, besides being immune suppressors and could be considered harmful in COVID-19 infection, are also associated to the capacity or neutralizing individual mediators of the inflammation process and may mitigate the hyper-inflammatory state observed in the severity of COVID-19 pathophysiology. The Janus kinase (JAK1 and 3) inhibitors used for the therapeutic approach of CD patients can interfere in the function of cytokines involved in antiviral responses such as type I INF, IL-2, IL-15, and IL-21. These inhibitors could, at least in part, inhibit the clearance of SARS-CoV-2. On the other hand, the inhibition of JAK2 seems to block the viral entrance of SARS-CoV-2 [72].

Authors also have shown that COVID-19 patients with gastrointestinal symptoms present lengthy illness duration, and it seems that the average age of positive test in the stool is 49 years, suggesting that aging is related to the ease of virus invasion [74, 75].

The above discussion may suggest that the inflamed gut of IBD patients could be an optimal door to the entrance of the virus in humans. Nevertheless, there is still much lack of evidence that the over-expression of ACE-2 in the colon and ileum could influence the entry and replication of the virus in the intestinal cells and facilitates its transmission in another extra-respiratory route [66].

Bezzio et al suggested that the presence of active IBD, older age patients with comorbidities have been associated with a higher risk of development of COVID-19 pneumonia and death in IBD patients. Moreover, concomitant treatment with immunosuppressants and biologics did not associate with worse COVID-19 prognosis in these patients [76].

According to Nakase et al, there is still no evidence that IBD itself can augment the risk of SARS-CoV-2 infection; and, for these reasons, there is no need for doctors to suddenly discontinue immunomodulatory or biologic treatment in quiescent IBD subjects. Besides that, there is a need for careful observation of older age patients (> 60 years old) and those subjects receiving corticosteroid therapy during the COVID-19 pandemic [77].

Evidence shows that COVID-19 can exacerbate symptoms of IBD, and it is important to distinguish between an IBD exacerbation and symptoms caused by COVID-19. Patients with active severe IBD and with COVID-19 can go through progressive pneumonia, ARDS and multi-organ failure due to the cytokine storm syndrome associated with hyper-inflamma-

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tion [78, 79].

Regardless, once the cytokine storm observed in COVID-19 patients is similar to the cytokine pattern observed in the acute period of the inflammatory process of IBD patients (during the disease flares), the advice is that avoiding the infection is still an optimal option for IBD subjects.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Conceptualization and design: SMB, JNM, UAPF, and RAG; methodology: SMB, JNM and RAG; writing (original draft preparation): SMB, JPGP, JFSH, CHR, PB; writing (review and editing): SMB, MAPJ, and ACAC. All authors have read and agreed to the published version of the manuscript.

Data Availability

Any inquiries about supporting data availability of this review should be directed to Doctor Sandra M. Barbalho, smbarbalho@gmail.com.

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