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ORIGINAL ARTICLE

Inflammatory Bowel Disease and COVID-19: Review

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Abstract

On March 11, 2020, WHO declared the disease caused by SARS-CoV-2 (COVID-19), an RNA virus, initially detected in December 2019, in the city of Wuhan in China, to be pandemic. It is a respiratory disease, transmitted mainly by aerosols and droplets, causing severe acute respiratory syndrome among other manifestations. Crohn's disease, ulcerative colitis and unclassified inflammatory bowel disease are grouped under the generic name of inflammatory bowel disease (IBD). These are autoimmune, chronic, relapsing diseases, with an apparent increase in incidence worldwide. Due to the characteristics of the two diseases, there were concerns about the repercussions of COVID-19 in patients with IBD. This review reports on such concerns.

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Crohn's disease (CD), ulcerative colitis (UC) and unclassified inflammatory bowel disease (IBD-NC), are grouped under the generic name of inflammatory bowel disease (IBD). These are autoimmune, chronic, recurrent diseases, with an apparent increase in incidence worldwide[1]. Children and adolescents account for 20 to 30% of IBDs, being more aggressive and affecting a larger intestine than in adults. It is called very early onset IBD when it manifests before six years of age, being even more severe when started before two years, requiring differential diagnosis with primary immunodeficiencies. The diagnosis of inflammatory bowel disease can be suspected based on clinical and laboratory findings, the diagnosis being confirmed through imaging, endoscopic and histopathological exams[2]. Treatment involves the use of exclusive enteral nutrition, medications such as aminosalicylates, corticosteroids, immunosuppressants and immunobiologicals, and surgery may be required[3].

On March 11, 2020, the WHO declared the disease caused by SARS-CoV-2 (COVID-19), an RNA virus, initially detected in December 2019 in the city of Wuhan in China, to be a pandemic. It is a respiratory disease, transmitted mainly by aerosols and droplets, causing severe acute respiratory syndrome among other manifestations. According to the American Academy of Pediatrics, in the United States 5.6% of the total cases occur in children[4]. Children seem to be less affected and have less severe disease when affected than adults, but severe cases occur in pediatric patients, with infants and preschoolers more prone to severity[5]. Gastrointestinal symptoms such as vomiting, diarrhea and nausea were found in 12% of patients with COVID-19, an increase in liver enzymes of up to 20% and viral RNA in the feces of 41%[6]. Gastrointestinal symptoms are more frequently found in patients with severe infection[7], with isolated gastrointestinal symptoms occurring in 3.4% of cases[8]. There is no evidence of fecal-oral transmission[9].

SARS-CoV-2 binds to target cells through the angiotensin-converting enzyme 2 (ACE-2) present in the epithelial cells of the lung, blood vessels, kidneys, and in large numbers in the terminal ileum and colon. A small amount of soluble ACE circulating in the plasma can sequester the virus, preventing its binding to the membrane. In addition, the entry of the virus into the cell depends on the transmembrane serine protease 2 (TMPRSS2). After penetrating the cell, the virus proteins are translated. In patients with IBD there is an increase in soluble ACE, from TMPRSS2, and in inflamed regions of the terminal ileum and colon, there is an increase in the expression of ACE-2[7,10–12].

Due to the characteristics of the two diseases, there was fear of the repercussion of COVID-19 in patients with IBD. It is believed that IBD is related to an exacerbated immune response, possibly against bacteria present in the intestinal microbiome, and because of the breakdown of tolerance to commensal microorganisms, involving tissue lesions with the release of numerous cytokines[13]. The presence of ACE-2 receptors in enterocytes and colonocytes could function as facilitators of infection, especially in patients with IBD, in whom the increase in these receptors has been proven, regardless of whether the region is inflamed or not[7]. The treatment of IBD is based on immunosuppression, mainly in children, increasing the uncertainties about the possibility of greater risk and severity of COVID-19 in these patients.

Contrary to the initial fears, so far, there seems to be no greater risk of IBD patients becoming ill. The international database Surveillance Epidemiology of Coronavirus Under Research Exclusion (SECURE-IBD)[14], created to monitor COVID-19 in adult and pediatric patients with IBD, reveals that the incidence is low (1,572 patients), that 70% of these patients do not require hospitalization, that 5% of the inmates used ICU and that 3% died. Table 1 depicts the fraction related to children. In Brazil, 47 cases were included, regardless of age, the eighth highest number reported[14]. Data show that, to date, there is no higher incidence of the disease in patients with IBD compared to the general population[15]. In addition, the risk factors for the outcome of the disease in the general population appear to be the same for patients with IBD[16].

ACE-2 expression is high in the duodenum and in the terminal ileum, being lower in the cervix, while the expression of TMPRSS2 is higher in the cervix and lower in the terminal ileum, the two areas of greatest involvement in IBD. This characteristic could make the intestine a secondary tropism site for SARS-CoV-2. In experimental models in the presence of acute colitis, there was a decrease in the expression of ECA-2 in colonic epithelial cells and, in chronic colitis, the expression of ACE-2 remained stable or decreased, while that of TMPRSS2 remained stable in those same cells. This seems to indicate that in acute and conical colitis, ACE-2 and TMPRSS2 expression in colonic epithelial cells may be stable or decreased, although in the UC, a slight increase in the expression of ACE-2 was found in active compared to inactive colitis. These animal studies, together with human samples from patients with IBD, may implicate the intestine in the infection by SARS-CoV-2, however the fact of having IBD, even in the inflammation phase, does not seem to increase the expression of ACE- 2 and TMPRSS2, making patients with IBD not at greater risk for contracting COVID-19[17].

On the other hand, patients with IBD may have higher levels of soluble ACE, especially in CD. The soluble form is the

Table 1. COVI-19 in children with inflammatory bowel disease.

Age	Number of cases	Hospitalized	Mechanical ventilation	Deaths
0-9 years	6	1	1	0
10-19 years	83	6	0	0

product of the hydrolysis of the portion that links ACE-2 to the cell membrane, with a very low plasma level. The enzyme responsible for this ACE-2 proteolysis is increased in patients with active IBD. This could justify the plasma increase in soluble ACE in these patients and could generate competition between it and ACE-2 for the link with SARS-CoV-2, with a possible factor of infection limitation and modulation[7].

In severe disease caused by SARS-CoV-2, hyperinflammation occurs due to the release of pro-inflammatory and anti-inflammatory cytokines, as well as chemokines that can attract neutrophils and T lymphocytes, among others, keeping a similarity to the macrophage activation syndrome[18]. This mechanism warned of the possibility of a worse course of the disease in patients with IBD, since they have an exacerbated immune response and this profile is similar to that seen in the inflamed intestine of patients with IBD[11]. In fact, patients with active IBD seem to have worse outcomes[16]. However, patients who are using substances such as cytokine blockers can benefit not only in relation to inflammation of the mucosa in IBD, but also in relation to the prevention of COVID-19[11] pneumonia. The relationship between a worse course in patients with active disease and hyperinflammation has not been established; likewise, it is not known to what extent the medications used to treat IBD positively interfere with COVID-19 hyperinflammation.

Nuances in the gastrointestinal manifestations of IBD can help find the type of disease. Diarrhea and abdominal pain can be common symptoms, but a more indolent course, with abdominal cramps, weight loss, fever and perianal disease can be associated with CD, while small amount diarrhea and the presence of blood in the stool can be related to UC. Changes in laboratory tests often do not help differentiation. The increase in the rate of erythrocyte sedimentation, C-reactive protein and platelets, as well as the fall in albumin or the presence of anemia are nonspecific tests that can point to IBD, without classifying it. Imaging evaluation should generally be done as an integral part of access to the small intestine, looking for fistula lesions and strictures. Computed tomography and magnetic resonance imaging (MRI) with stereography are generally equivalent, but considering irradiation, MRI should be preferred. The diagnosis of IBD as well as its classification is given by endoscopic evaluation, both high and low (ileocolonoscopy), complemented by histopathology.

Safety measures for the clinical follow-up of patients with IBD were proposed during the pandemic. Considering the risk of contamination both on the way and at the service location, outpatient care was proposed by teleconsultation and telephone support. Prevention measures indicated by health authorities such as social distance, hand washing, wearing masks, among others, must be reinforced as well as the guidelines in case of contamination of a family member. There was a recommendation for stratification in relation to the need for endoscopic procedures: performing emergencies, considering emergencies and postponing electives. When the performance was indicated, adequate dressing was described and the use of rooms with negative pressure was indicated[8,19–23].

The treatment of IBD mainly involves the use of immunosuppressive medications. Medication management will vary according to the intensity and presentation of clinical manifestations. Immunosuppression led to fear of increased risk in patients with IBD, as well as increased viral load, prolonged elimination of the virus and impaired antibody response[24].

Evaluation of the drugs used in IBD patients can be done during the pandemic in some treatment centers. Aminosalicylates, 5-ASA and sulfasalazine, despite being related to the risk of serious infection[25], are considered safe, and treatment suspension is not recommended even under COVID-19[20,22,26]. Corticosteroids, used to induce remission of the disease and relapse, do not have their safety defined in cases of SARS-CoV-2 infection. Considering the experience with the H1N1, SARS-CoV and MERS-CoV viruses, they can impair virus clearance and prolong viremia[27]. Its use can be restricted to relapses, in lower doses than usual, and in patients who were already in use, and the dose should be reduced to a tolerable minimum[20,22,26,27]. Immunomodulators (azathioprine, mercaptopurine, thioguanine, methotrexate, tacrolimus, and mycophenolate mofetil) do not appear to increase the risk of COVID-19. Reports involving SARS-CoV1, 2 and MERS-CoV findings, indicate that thiopurines appear to inhibit viral replication as well as calcineurin inhibitors (tacrolimus and cyclosporine). Starting monotherapeutic treatment with immunomodulators should be avoided due to the long-term therapeutic effect, and combined use with biologicals should be initiated only in severe cases. In the case of children with IBD with symptoms of SARS-CoV-19, with a positive test or not, the immunomodulator should be suspended until asymptomatic. In cases of a positive test and the child being asymptomatic, the decision to maintain or suspend the medication must be made on a case-by-case basis[9,20,22,23,27].

Biologicals are widely used in the treatment of IBD. At the beginning of its use, the prognosis of patients change. Anti-TNF-α (approved for use in children: infliximab and adalimumab) initially raised concerns about COVID-19, as they could potentially alter antiviral immunity and TNF-α cytokine is greatly increased in SARS- CoV1, 2 and MERS-CoV. A study on the use of anti-TNF-α in patients with septic shock in the ICU did not show a risk of worsening the infection. So far, there is no evidence on the potential increased risk for COVID-19. Thus, patients using these medications must maintain their dose regimen, interval between doses and route of administration, even considering the possibility of subcutaneous application that can be done under guidance at home. The care defined for the venous medication infusion environment can guarantee safety in maintaining this route. When starting treatment in the current context, preference should be given to adalimumab, not only through the route of administration, but also

because of the lower potential for antibody formation. The use of combined therapy, anti-TNF-α in conjunction with an immunomodulator, should be reassessed, as the association appears to have a greater relationship with hospitalization, ICU admission and mortality. The use of this combination is recommended in order to reduce the formation of antibodies against the drug; this justifies the preference for, at that moment, starting treatment with adalimumab[7,9,20,22,23]. There was a proposal to incorporate the testing of SARS-CoV-19 before starting treatment with a biological agent, as is already done with other diseases[24], and its real need remains in doubt, since if the test is positive, there is no treatment for the virus and there will only be a delay in the start of treatment due to the need for social isolation[28].

Other agents are used in the treatment of IBD in adults, not being approved for use in children. Anti-integrin-a4b7 (vedolizumab) does not appear to increase the risk of infection by SARS-CoV-19, appearing to have a good safety profile, and should be stopped in case of COVID-19 symptoms[7,9,20,22]. Treatment with anti-IL12/23 (ustekinumab) also does not appear to increase the risk of this infection. These interleukins are part of the storm caused by SARS-CoV-2, but there is insufficient data to indicate their use for this purpose. Its safety profile is good, and should be interrupted in the case of this infection[7,9,20,22,27]. Janus kinase inhibitors (tofacitinib) inhibit the activity of interferon alfa, which may increase the risk of viral diseases. On the other hand, they inhibit several cytokines, including IL-6, having an antiviral role. There is no evidence of an increased risk of infection from SARS-CoV-19[9,20,22,27].

Elective surgeries, in general, were suspended, but it is reasonable to assess them on a case-by-case basis. The guidelines dictated by the consensus involving surgical practices must be respected. The use of personal protective equipment is mandatory and the procedure must be performed in a room under negative pressure. The surgery must be judged individually. In general, there is a consensus that perianal abscesses and other emergency procedures, such as colectomy in severe UC and resection in penetrating CD, should not be postponed. Other surgical procedures should be postponed, after evaluating each case[20,22,23].

In conclusion, there seems to be no greater risk for children with IBD to contract COVID-19 than the general population. Social isolation and detachment protocols must be followed in agreement with the health authorities in order to reduce the possibility of infection. Clinical monitoring of patients is essential for maintaining control and diagnosis of relapses. The use of teleconsultations is justified, but face-to-face service can become essential. There is no evidence that the treatment of IBD increases the risk of infection by SRAS-CoV-19. The use of aminosalicylates and immunomodulatory medication does not seem to increase the risk of infection by SARS-CoV-19, neither does the use of biologicals. In case of infection with this virus, medications, with the exception of aminosalicylates, should be discontinued, although there is no certainty of this need. There is no justification for the replacement of anti- TNF-α, and there is justification for adalimumab in patients who will start treatment. Infusion centers must be equipped to prevent infection and recognize the possibility of the patient having the disease. The use of corticosteroids should be judicious, being accepted in relapses, but the dose should be decreased as soon as possible. Endoscopies and surgeries, when necessary, must be evaluated in each case, but maintaining emergency ones. An initial treatment option is exclusive enteral therapy, within its restricted indications[29].

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