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Sars-CoV-2 and human strongyloidiasis

O Sars-CoV-2 e a estrongiloidíase humana

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ABSTRACT

The Sars-CoV-2, the virus that causes Covid-19 (coronavirus disease 2019), is highly transmissible and of rapid dissemination, and transmitted by respiratory droplets and by direct contact, which can cause respiratory failure and reach multiple organs. Although there is still no effective treatment for the disease, the use of corticosteroids has shown positive results in patients with severe Covid-19, such as dexamethasone, which acts as an immunosuppressant to control cytokine storm syndrome (CSS). In this review, we will abroad the challenge of establishing a balance between risk and benefit in corticosteroid therapy in severe cases of the disease, since corticosteroids can activate the latent infection by *Strongyloides stercoralis* and develop the critical form of strongyloidiasis, the *Strongyloides stercoralis* hyperinflation syndrome (SHS). For these circumstances, screening and empirical treatment with ivermectin is recommended for those patients at moderate to high risk of hyperinfection. The keywords used were "*Strongyloides*" AND "Covid" and the searched databases were PubMed, Scopus, and Web of Science. The selected articles were published from 2020 to 2021 and without language restriction.

Key words: *Strongyloides*; Covid-19; pulmonary cycle; corticoids.

RESUMO

O coronavírus 2 (Sars-CoV-2) é o vírus causador da doença do novo coronavírus (Covid-19), altamente transmissível e de rápida disseminação; é transmitido por gotículas respiratórias e pelo contato direto, podendo causar insuficiência respiratória e atingir múltiplos órgãos. Embora ainda não exista um tratamento eficaz para combater o vírus, o uso de corticoides tem mostrado resultados positivos em pacientes graves da Covid-19, como é o caso da dexametasona, que age como imunossupressor para controlar a síndrome da tempestade de citocinas (CSS). Nesta revisão, dissertaremos sobre o desafio de estabelecer um equilíbrio entre o risco e o benefício na corticoterapia em casos severos da doença, uma vez que os corticoides podem ativar a infecção latente por Strongyloides stercoralis *e desenvolver a forma grave da estrongiloidíase, a síndrome de hiperinfecção por* Strongyloides *(SHS). Para isso, recomenda-se o rastreamento e o tratamento empírico com ivermectina, para aqueles pacientes com risco moderado a alto de hiperinfecção. As palavras-chave utilizadas foram "*Strongyloides*" AND "Covid", e as bases de dados foram PubMed, Scopus e Web of Science. Os textos selecionados foram publicados no período de 2020 a 2021, sem restrição de idioma.*

Unitermos: Strongyloides*; Covid-19; ciclo pulmonar; corticoides.*

RESUMEN

El coronavirus 2 (Sars-CoV-2) es el virus que provoca la enfermedad del nuevo coronavirus (Covid-19), que es altamente transmisible y se propaga rápidamente, transmitiéndose por gotitas respiratorias y por contacto directo, y puede causar insuficiencia respiratoria y afectar a múltiples órganos. Aunque todavía no existe un tratamiento eficaz para combatir el virus, el uso de corticoides ha mostrado resultados positivos en pacientes críticamente enfermos de Covid-19, como la dexametasona, que actúa

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como inmunosupresor para controlar el síndrome de liberación de citocinas (CSS). En esta revisión, discutiremos el desafío de establecer un equilibrio entre riesgo y beneficio en la terapia con corticoides en casos severos de la enfermedad, ya que los corticosteroides pueden activar la infección latente por Strongyloides stercoralis *y desarrollar la forma grave de estrongiloidiasis, el síndrome de hiperinfección por* Strongyloides *(SHS). Para ello, se recomienda el cribado y el tratamiento empírico con ivermectina en aquellos pacientes con riesgo moderado a alto de hiperinfección. Las palabras clave utilizadas fueron "*Strongyloides*" AND "Covid", y las bases de datos fueron PubMed, Scopus y Web of Science. Los textos seleccionados se publicaron de 2020 a 2021, sin restricción de idioma.*

Palabras clave: Strongyloides*; Covid-19; ciclo pulmonar; corticoides.*

INTRODUCTION AND OBJECTIVES

The new coronavirus (Covid-19), caused by coronavirus 2 (Sars-CoV-2), emerged in Wuhan, China, in late 2019, and quickly spread around the world, becoming a pandemic. The pulmonary system is the most affected by Sars-CoV-2, and its clinical manifestations vary according to the severity of the disease. In the severe condition of Covid-19, pneumonia develops with acute respiratory distress syndrome (ARDS), respiratory failure, hypoxia, and/or death[1].

So far, it is known that the virus is transmitted by direct contact and respiratory droplets, while other forms of transmission are being studied. Treatment for severe cases of the disease is still a challenge, although immunosuppressive therapy has shown positive results for the control of cytokine storm syndrome (CSS) in severe patients[1].

Strongyloidiasis is caused by *Strongyloides stercoralis*, a nematode that infects 10% to 40% of the population in tropical and subtropical countries. Considered endemic, especially in Central Europe, Southeast Asia, Latin America, and sub-Saharan Africa, it is also found in non-endemic regions by immigrants or travelers from endemic countries, as well as by agricultural workers who work with the soil[2].

Strongyloidiasis is usually asymptomatic in immunocompetent individuals[3]; however, individuals on corticosteroid treatment, alcoholics, patients with human T-cell lymphotropic virus 1 (HTLV-1) or human immunodeficiency virus (HIV) infection, as well as those with hematologic diseases or transplanted organs may progress to *Strongyloides* hyperinfection syndrome (SHS) or to the potentially fatal disseminated form[4, 5].

Therefore, the initial objective of this study was to evaluate the interface of two etiological agents, viral and parasitic, in the human body, since *Strongyloides* cycles in the lungs and Sars-CoV-2 primarily affects the pulmonary system. Based on this, we found several published studies associating the use of corticosteroids in patients with moderate to severe Covid-19 infection with the development of hyperinfection in individuals at risk for *Strongyloides* infection. This was the direction of our study.

MATERIAL AND METHODS

The study consists of a literature review that was performed in the PubMed, Web of Science, and Scielo databases. The search strategy was: "*Strongyloides*" AND "Covid"; there were no language restrictions for the search and no other filters were applied. As an eligibility criterion, studies addressing the complications of strongyloidiasis in Covid-19 patients were included – all articles reported treatment with the use of corticosteroids.

As an inclusion used after the references were found, we selected an article that was extracted from the references of one of the pre-selected studies, which described the dissemination and hyperinfection syndrome, in a concise and complementary way to the rest of the elected studies. The therapeutic management proposed by the Centers for Disease Control and Prevention (CDC) for acute and chronic strongyloidiasis and hyperinfection was also included. The excluded studies were outside the proposed topic: two of them referred to the Covid-19 pandemic with other diseases; two other articles addressed the antimicrobial treatment in strongyloidiasis; and one reported *Strongyloides* and Covid-19 virus as causative agents of reactive arthritis.

RESULTS

During the search, we found 38 articles; 15 of them met the objective of this review (**Figure**). Initially, the selection was made by reading the title, already excluding duplicate articles among the databases. After reading the abstract, we made the final selection by applying the inclusion and exclusion criteria.

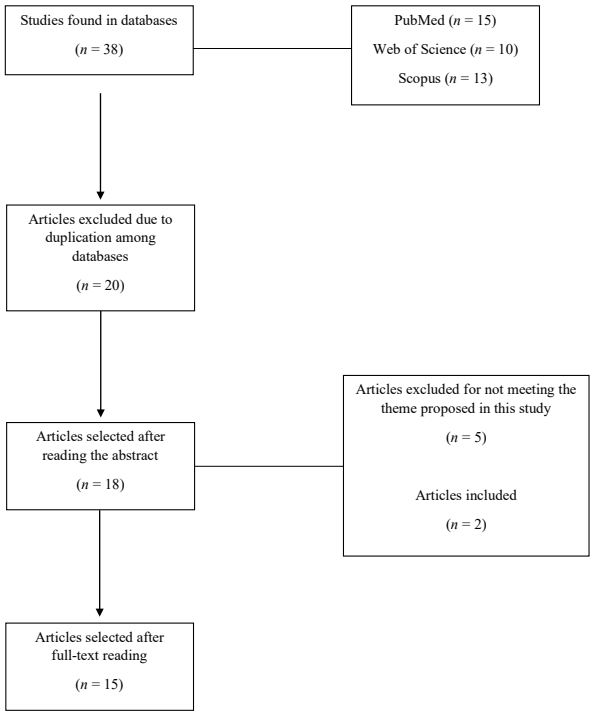

FIGURE – *Flowchart of the process of inclusion and exclusion of studies for review*

DISCUSSION AND CONCLUSION

CSS is among the most serious manifestations of Covid-19, leading patients to multiple organ failure and death. One of the symptoms is the unexpected increase in circulating levels of pro-inflammatory cytokines [interleukin-1 (IL-1) and 6 (IL-6), interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α), which causes hyperinfection and CSS. When CSS occurs, different cells of the immune system (neutrophils, macrophages, and T cells) migrate to the site of infection, resulting in a cascade of damage to the vascular barrier, diffuse alveolar damage, lung injury, and multiple organ failure[1].

Although there are no definitively effective drugs to treat Covid-19, immunosuppressive therapy shows promising results for the control of CSS in severe Covid-19 patients[6]. This is the case of dexamethasone, which has become the standard of care for Covid-19 in patients who require mechanical ventilation or supplemental oxygen[7]. On the other hand, it is an important risk factor for opportunistic infections such as *Strongyloides stercoralis*[1].

A UK-based Randomized Evaluation of COVID Therapy (RECOVERY) randomized clinical trial provides evidence that the treatment with dexamethasone at a dose of 6 mg once daily for up to ten days reduces 28-day mortality in Covid-19 hospitalized patients who are receiving oxygen supply, but not among those not receiving respiratory support[8].

The *Strongyloides stercoralis* life cycle is complex, alternating between parasitic cycles – in the host, where autoinfection can occur – and free-living – which occurs in the soil. Rhabditoid larvae can develop into filarioids in the intestine and penetrate the intestinal mucosa or skin of the perianal area, resulting in autoinfection. This process, when dysregulated, causes a large number of infective larvae to enter the intestine, reach the lungs and return to the intestine, leading to hyperinfection. When larvae reach ectopic regions, disseminated strongyloidiasis occurs[4].

SHS and the disseminated form are the most severe clinical manifestations of the disease, with a high mortality rate. The former is related to different types of immunocompromising, and the latter is caused by the migration of larvae to other organs, in addition to the pulmonary cycle of autoinfection; it is usually associated with secondary bacterial infections[4]. Uncontrolled proliferation and spread of the parasite manifest with fever, respiratory and gastrointestinal symptoms, as well as the occurrence of sepsis from Gram-negative organisms or meningitis. Asymptomatic individuals who become immunosuppressed, most commonly those undergoing treatment with corticosteroids, undergoing chemotherapy, and individuals with HTLV-1 or HIV infection, are susceptible to developing hyperinfection[3].

In this context, we observe the use of dexamethasone – a glucocorticoid – in patients co-infected with *Strongyloides stercoralis* as a potentiator to cause SHS. The current recommended dose of dexamethasone by Covid-19 Treatment Panel is 6 mg for 10 days. Therefore, there have been cases of *Strongyloides* hyperinfection in a shorter period and/or at a lower dose, and also cases after a single dose of dexamethasone, which led researchers to believe in the occurrence of the disease regardless of the dose, duration, or route of administration[9].

Therefore, assessment for the risk of strongyloidiasis is recommended in all cases of Covid-19 that require corticosteroid therapy, especially in individuals from low- and middle-income countries (LMICs) and in high-risk patients, to prevent strongyloidiasis-associated morbidity[5]. Of patients with microscopically proven strongyloidiasis, 77% have eosinophilia and 81% have positive serology; therefore, peripheral eosinophilia is usually a good clinical marker for *Strongyloides* parasitic infection, although the use of steroids can interfere in this process[3]. Another negative factor for the diagnosis is that asymptomatic patients usually have negative microscopy[3].

The following **Table** presents the four case reports selected for this review.

TABLE – Case reports included in the literature review

Article	Authors	Country (Birth/residence)	Age	Corticoid	Dose	Time
1. Reactivation of *Strongyloides stercoralis* in patients with Sars-CoV-2 pneumonia receiving dexamethasone	Feria L, Torrado M, Anton-Vasquez V	Bolivia/Spain	44	Dexamethasone	6 mg/dia	7 days
		Honduras/Spain	74	Dexamethasone	6 mg/dia	10 days
2. Case report: Disseminated strongyloidiasis in a patient with Covid-19	Lier AJ *et al.*	Ecuador	68	Methylprednisolone	40 mg/8 h	8 days
3. *Strongyloides* infection manifested during immunosuppressive therapy for Sars-CoV-2 pneumonia	Marchese V *et al.*	Italy	59	Dexamethasone	20 mg/day reduced to 10 mg/day	5 days 6 days
4. Covid-19-associated eosinopenia in a patient with chronic eosinophilia due to chronic strongyloidiasis	Stylemans D *et al.*	Ecuador/Belgium	59	Methylprednisolone	80 mg	Gradual reduction over a month

In the four case reports included in this review, patients received high-flow oxygen therapy and ivermectin as the first choice for the treatment of strongyloidiasis. The two patients in the first report[10] had negative serology for HIV-1/2, viral hepatitis, and HTLV-1/2 and remained asymptomatic with positive serology for *Strongyloides stercoralis* over the course of three months. Also noteworthy is the absence of eosinophilia, possibly due to treatment with dexamethasone.

In the report by Lier *et al*. (2020)[11], the patient had no clinical response to ivermectin, so 400 mg albendazole was added, orally (PO), every 12 hours, and his serum antibody for *S. stercoralis* was negative and serologies for HIV and HTLV-1 were also negative.

For ten years, the patient in the Marchese *et al*. (2021) study had been chronically treated with low-dose prednisone for Still's disease. After administration of dexamethasone, the first signs that raised the suspicion of *Strongyloides stercoralis* infection were an abrupt increase in eosinophil count associated with abdominal pain and itching. However, there was no worsening in the patient's clinical condition[8].

A review of medical records of the patient from the study by Stylemans *et al*. (2021)[12] revealed persistent eosinophilia over a seven-year period due to chronic *S. stercoralis* infection. In *S. stercoralis* infection, eosinophilia is more frequent when compared to some parasitosis, as the parthenogenetic female inhabits the submucosa of the intestine rather than the lumen. During Covid-19, the authors observed absolute depletion of eosinophils and, as is already known, eosinopenia is a frequent laboratory finding in Covid-19, present in approximately 50% to 70% of hospitalized patients. As the patient recovered, there was an increase in eosinophils and then a decrease after treatment with ivermectin[12].

The World Health Organization (WHO) guidelines recommend corticosteroids in patients with severe or critical Covid-19, so they may carry risks of reactivation of latent infections, such as *Strongyloides stercoralis*[7]. Therefore, it becomes a challenging task to maintain a risk-benefit balance for the use of immunomodulators[13].

The strategy to be adopted with an intent to minimize the impact of corticotherapy on *Strongyloides stercoralis* infection is the screening before the administration of immunosuppressive therapy, so that a presumptive treatment with ivermectin is adhered to, for patients at higher risk of infection by *Strongyloides* and SHS[14]. It is known that the SHS fatality rate is reported to be 100% if untreated, and when treated with ivermectin this rate decreases to 47%[3].

The Hospital for Tropical Diseases London clinical guideline for the assessment and risk management of SHS in hospitalized patients by Covid-19 advises on the assessment of individuals with a history of travel or migration to endemic areas – tropical and subtropical regions – and some temperate regions, such as Japan, Italy, Australia, Spain, and America; it also considers high-risk exposure to *Strongyloides*: farmers, miners, military, individuals living in rural areas and in places with poor sanitation, patients in contact with human waste or wastewater, and those who have the habit of walking barefoot.

There are two protocols to follow: 1. in patients considered to be at high risk for strongyloidiasis (individuals with moderate to severe Covid-19 who require dexamethasone therapy and fit into the two situations mentioned above – travelers or migration to endemic areas and with high-risk exposure), it is essential to start empirical treatment with ivermectin and send both *Strongyloides* serology and stool and sputum/bronchoalveolar lavage sample to the parasitology laboratory for microscopy and *Strongyloides* culture; 2. in non-high-risk patients (with

a history of travel to an endemic region, but who do not meet the criteria for a high-risk patient, or who have mild Covid-19 with no dexamethasone requirement), the recommendation is to monitor the development of signs and symptoms suggestive of SHS (respiratory deterioration on immunosuppressive therapy, diarrhea and skin rash, Gram-negative sepsis, and bilateral pulmonary infiltrates). Under these conditions, or if the patient requires immunosuppressive therapy, it is advisable to discuss the possibility of SHS and consider the need for ivermectin; stool and sputum/bronchoalveolar lavage sample should be sent to parasitology for microscopy and *Strongyloides* serology should be performed[3].

In addition, according to the CDC, the treatment of choice for acute and chronic strongyloidiasis is ivermectin 200 µg/kg, PO, once a day, for two days, or, alternatively, albendazole 400 mg, PO, twice a day for seven days[15].

Cytokines play an important role in the immune response against the Sars-CoV-2 virus, however, when released in excess, they cause the body to go out of control and some defense cells decrease, configuring the severity of Covid-19. To handle it, the use of corticosteroids, such as dexamethasone, attenuates the immunological chaos due to its immunosuppressive effect. However, the glucocorticoid administration in individuals co-infected with *Strongyloides stercoralis* demonstrated a high risk of developing SHS. Therefore, it is necessary to define a management protocol for patients with moderate to severe Covid-19 and who qualify as candidates for possible *Strongyloides* infection, such as the history of travel or residence in endemic areas, living in regions with poor sanitation, rural work, etc. The purpose of this protocol is to ensure safety for the administration of corticotherapy and concomitantly treat *Strongyloides*, without worsening the infection.

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