REVIEW ARTICLE

Disseminated Strongyloidiasis in Patients Diagnosed with COVID-19 Treated with Corticoids

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Abstract

The arrival of a new epidemic at the end of 2019 occurred with an outbreak of new cases of people with a clinical picture that ranged from a common cold to serious complications, which included severe acute respiratory syndrome (SARS). With the rapid increase in the number of infected cases, new therapeutic strategies were devised. Among them, the use of corticosteroids is highlighted as a potential reducer of the inflammatory processes caused by the disease, particularly its effect on respiration, which proved to be an important part of the pathogenesis of the disease. The use of glucocorticoids in the treatment of COVID-19, while being efficient, presents problems such as the development of severe strongyloidiasis, especially in those patients who live or have lived in endemic areas for the parasitosis, and thus screening for this condition before therapy is the best immunosuppressive procedure. The evolution to disseminated strongyloidiasis or to hyperinfection in patients co-infected with SARS-CoV-2 undergoing treatment with glucocorticoids increases in chronic, asymptomatic carriers without a previous diagnosis of *Strongyloides stercoralis*, and this is due to the corticosteroid stimulus of the parasite larvae. Corticosteroids are an important risk factor for the development of *S. stercoralis* hyperinfection, which apparently does not depend on the dosage used or duration of treatment. After diagnostic confirmation or after establishing the risk through epidemiological stratification, these patients can be submitted to prophylactic treatment with ivermectin. Therefore, as many patients with COVID-19 are undergoing glucocorticoid therapy and these medications increase the risk of developing strongyloidiasis (disseminated form and form of hyperinfection), especially in risk patients, this study was carried out in the context of this approach theme of the coexistence of this parasitological infection and viral infection by SARS-CoV-2 in patients using the aforementioned immunosuppressive therapy. This is a literature review based on the main data platforms, through which 36 articles published between the years 2020 and 2022 were included for analysis.

Keywords: Disseminated strongyloidiasis; COVID-19; Glucocorticoids.

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Introduction

In December 2019, the first cases of patients infected with the SARS-CoV-2 virus were reported in Wuhan, China. An outbreak of respiratory disease caused by a new strain of virus that had not been previously identified in humans quickly emerged and evolved into a global pandemic, as declared in 2020 by the World Health Organization (WHO).[1] Clinically, the patients had respiratory symptoms such as cough, dyspnea, runny nose, and other less common symptoms such as diarrhea, headache, and abdominal pain, accompanied by fever, anorexia, and fatigue. It was also observed that, among infected patients, those with chronic comorbidities and/or advanced age were severely affected.[2]

There was a boom in new cases of infected individuals and in order to face this quickly established challenge new therapeutic strategies were outlined. Among these, the use of corticosteroids stood out as a potential reducer of the inflammatory process generated by the immune system in the fight against the virus. This justification is based on the alveolar damage caused by the cytokine storm, especially Interleukin 6 (IL-6), which is implicated in the pathogenesis of the disease, causing a cytokine release which leads to an exacerbated inflammatory condition.[3,4] The use of the glucocorticoid Dexamethasone at a dose of 6mg, once a day, for up to 10 days had its effectiveness proven by the reduction of mortality after 28 days in those infected patients who were receiving invasive respiratory support and in those who were receiving oxygen but not invasive respiratory support. The benefit of using the drug was also evidenced in patients undergoing treatment for more than 7 days after the onset of symptoms, a period in which lung damage due to the inflammatory process is more common. These results suggested that these two stages of the disease may be mediated by immunopathological mechanisms, with viral replication having a secondary role.[5] Strongyloidiasis is a parasitic infection caused by the

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nematode *Strongyloides stercoralis*. The infection is acquired through contact with soil that is contaminated with viable larvae of the parasite. Despite the advantages of this therapy against coronavirus, corticosteroids are strongly associated with the development of hyperinfection syndrome (HS) and dissemination syndrome (DS) by *S. stercoralis*, with the use of these substances as a predisposing factor in 67% of these syndromes. Although this nematode more often causes chronic diseases and asymptomatic infections, changes in the immune status normally provoked by the use of immunosuppressive drugs, such as corticosteroids, can lead to progressive larval growth and dissemination, reaching mortality rates of up to 70 to 100%.[6,7] Due to these high mortality rates, adequate screening of at-risk patients (patients who live or have lived in endemic countries) is mandatory before starting immunosuppressive therapy.[7]

From this perspective, considering the possible impact of these immunosuppressive drugs for COVID-19 on the development of severe strongyloidiasis, and considering the high mortality rate of this condition, this review aims to shed light on the importance of a meticulous evaluation of individuals who exhibit the epidemiological profile of *Strongyloides* infection and are also affected by the coronavirus, aiming to enhance clinical approaches.

Methodology

This is a literature review of national and international scientific articles published in journals between the years 2020 and 2022 performed using the methodology mentioned in Figure 1. The research was carried out from the following academic platforms: Google Scholar, Center for Biotechnology Information (PubMed), Science Direct, Scientific Electronic Library Online (SciELO), Virtual Health Library (VHL), Google Academic, and Scopus, using "COVID-19", "Infection", "*S. stercoralis*," "Disseminated Strongyloides", and "Corticosteroid" as descriptors. In all, 50 articles were selected for screening, which was carried out by 4 authors, who were looking for enough information to cover the subject of this review. After analyzing the articles, 24 were excluded because they did not fit the proposed theme and 36 were chosen to be included in this review because they presented relevant information about the hyperinfection syndrome by *S. stercoralis* in patients diagnosed with COVID-19 undergoing therapeutic use of corticosteroids.

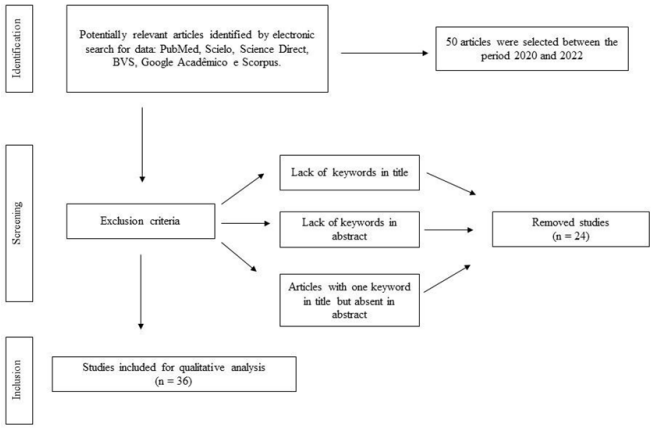

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Figure 1: Scheme of the article's methodology

Discussion

Clinical and epidemiological characteristics of COVID-19

At the time when the first cases were reported with a clinical picture of an acute respiratory disease linked to a seafood market in the Wuhan region, the pathogen had not been previously found in humans. For the identification of the agent, bronchoalveolar lavage samples were collected from patients who had pneumonia of unknown cause in the Wuhan region or who were present at the seafood market shortly before the development of symptoms, these samples were then compared with 7 control samples of patients admitted to the Beijing hospital with pneumonia of unknown cause. Several methods of viral isolation and identification were used until the following result was obtained: the analyzed samples corresponded to the genome of the B lineage of the beta-coronavirus genus and from then on the pathogen was named 2019-nCoV. Although 2019-nCoV is similar to other beta-coronaviruses detected in bats, a phylogenetic analysis showed that this new agent is different from SARS-CoV and MERS-CoV.[8]

Although some epidemiological studies link patients initially diagnosed with pneumonia to the seafood market in Wuhan, the increase in the number of cases that were confirmed later and that show no epidemiological correlation with the market or the region suggests human to human transmission. It is currently known that the main route of transmission is by respiratory droplets and contact.[8,9]

Epidemiological research has shown that the latency period of the virus can extend up to 24 days, however, the average incubation period is 3 days. Clinical manifestations are varied, from asymptomatic cases to severe and potentially fatal cases. A retrospective study was carried out with 221 patients diagnosed with pneumonia from the new coronavirus confirmed by RT-PCR in pharyngeal swab samples. The mean age of these patients was 55 years and the predominance was male. Among these patients, 55 were severely affected, and the median age of these patients was significantly older: 62 years, and of these 40 had chronic comorbidities (diabetes, hypertension, kidney disease, cardiovascular disease, etc.) with the predominance also being male. The most common clinical symptoms identified include fever, fatigue, and respiratory symptoms such as cough and dyspnea, followed by less common symptoms such as abdominal pain, diarrhea, headache, and anorexia. In severely affected patients, vital signs of increased heart and respiratory rates, body temperature above 38.1°C, dyspnea, and anorexia were observed. Of the 221 patients with COVID-

19, a total of 215 showed bilateral radiographic changes and the remainder had unilateral abnormalities characterized by multiple irregular opacities, lobe consolidation, honeycomb septal thickening, and areas of segmental consolidation. In conclusion, the clinical analysis of the patients shows advanced age, with a higher proportion of males and a higher number of comorbidities in severely affected patients compared with those who were not severely affected. Therefore, age and previous comorbidities are related as risk factors for more severe outcomes.[2,10,11]

Association between Strongyloides and glucocorticoids

Strongyloidiasis is a parasitosis caused by the nematode *S. stercoralis*, which is acquired from contact with soil contaminated with living larvae, in the filarioid form, capable of actively penetrating the skin. The filarioid larva enters the circulatory system and is transported to the lungs, penetrating the alveolar spaces. Subsequently, the larva ascends the trachea and pharynx, is swallowed and reaches the intestine of the host. In the intestine, the larvae release eggs that will be excreted into the environment. The cycle is completed when a new host penetrates the skin. The peculiar characteristic of this soil-transmitted infection is the ability of the agent to reach maturity in the intestine and, thus, reinfect the human host, allowing a chronic, often asymptomatic, infection that can last for decades.[12,13]

A meta-analysis study carried out in 2019 involving immigrants from all over the world showed a seroprevalence of strongyloidiasis of around 12.2%, with immigrants from Asia leading with the highest percentage (17.3%), followed by immigrants from Sub-Saharan Africa (14.6%), and then Latin America (11.4%).[14,15] Although most individuals with strongyloidiasis are asymptomatic, the disease can manifest itself in a more severe way through what is known as the hyperinfection syndrome or disseminated strongyloidiasis. These potentially fatal complications can increase the mortality rate to more than 85%[16,17] and are often associated with the use of immunosuppressant drugs in individuals without a previous diagnosis of chronic infection. Corticosteroids are the most common agent capable of preceding hyperinfection, which apparently does not depend on the dosage used or duration of treatment.[18,19,20] This can be explained by the fact that the increase in the endogenous level of corticosteroids increases the fecundity of parthenogenetic females of S stercoralis, in addition to enhancing the transformation of rhabditoid and filarioid larvae by mimicking the action of ecdysteroid-like hormones that are responsible for this transformation. Thus, there is a greater predisposition to self-infection, considering that, in this process, the filarial larvae invade the intestinal mucosa or the perianal region and carry out the normal parasitic cycle. In addition, corticosteroids also contribute to the development of hyperinfection through alterations in the intestinal barrier and in the host's immune response.[21] The study by Thomas *et al.*, in 1998, demonstrated that corticosteroids can have a stimulating effect on the growth of larvae, similar to that of hormones, even after using a single dose.[22] Something similar was addressed in another study that demonstrated that the use of dexamethasone in rats infected with *S. stercoralis* led to an acceleration of the transformation of rhabditoids larvae into invasive filarioids, promoting hyperinfection and dissemination of larvae to organs other than the lungs, such as the liver, spleen, kidneys, brain, and heart.[23] In lungs, congestion and alveolar hemorrhage may be observed due to the rupture of the pulmonary capillaries during the passage of the larva. Fluid extravasation into the alveolar space is also observed (Figure 2).

In this sense, treatment with corticosteroids is capable of inducing an increase in fertility of the adult female of the nematode *in vivo*, resulting in a greater production of eggs that, when hatched, release infective larvae inside the intestinal mucous membranes of the host. Thus, this enables larval dissemination to distal organs of the host, such as spleen, liver, brain, and lung. The explanation for the occurrence of these phenomena, although little clarified, is based on two hypotheses. The first is that the worms have receptors for eicosanoids, cytokines and chemokines from the host, responding to these mediators with the production of their own reproductive and growth hormones. Thus, the administration of corticosteroids increases the production of molecules similar to ecdysteroids, which control the molt of the *S. stercoralis* larva, increasing the molting rate and, consequently, increasing the number of worms.[16,24] The second hypothesis is that the parasites benefit from the suppression of the innate and adaptive immune responses of patients undergoing treatments with immunosuppressive drugs, contributing to their reproduction, invasion, and dissemination.[25,26]

Association between SARS-CoV-2 and glucocorticoid use

Figure 3 shows the histological section of lung from a patient infected with Strongyloides under glucocorticoid use. With

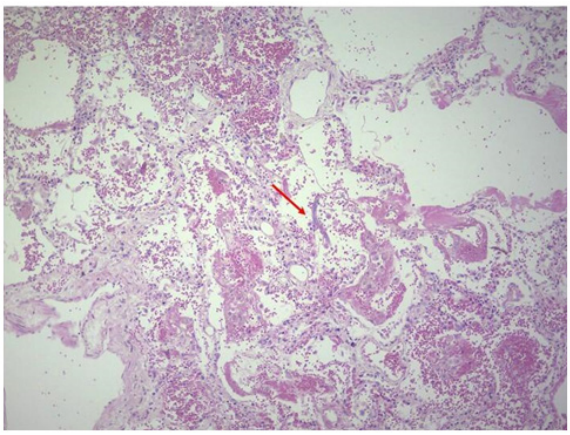

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Figure 2: Disseminated strongyloidiasis. Patient using glucocorticoids. Histological section of lung from a patient infected with *Strongyloides* under glucocorticoid use. The arrow indicates the presence of the larvae in the alveolar space.

the scenario of the SARS-CoV-2 pandemic, several therapies have been used with the aim of reducing or avoiding diffuse lung damage, including the use of glucocorticoids, which have the function of modulating the extent of the impacts caused by inflammation and, by extension, consequently, prevent progression to a worse clinical prognosis. Among the drugs adopted from this class is the glucocorticoid dexamethasone, which has shown positive results when used in patients undergoing invasive mechanical ventilation or just oxygen. One study revealed a lower incidence of deaths in the group of patients on mechanical ventilation (29.3% vs. 41.4%) or on oxygen alone (23.3% vs. 26.2%) who received a daily dose of 6mg of the drug when compared with the group with the same clinical situation and with normal care.[27]

In another study, the efficacy and safety of the use of corticosteroids was estimated in patients with severe pneumonia due to COVID-19, and from a sample of 46 patients, 26 received intravenous administration of methylprednisolone at a dose of 1 to 2 mg/kg/ d for 5 to 7 days, while the rest did not. The results showed that the group using glucocorticoids showed a faster improvement in symptoms and improved pulmonary evaluation from chest computed tomography.[28]

From a general perspective, corticosteroids, including dexamethasone, methylprednisolone, hydrocortisone, and prednisone, can be used in different ways to combat SARS-CoV-2, they are accessible and can be for any age group, which is of paramount importance in a highly contagious scenario. Dexamethasone, as previously discussed, showed evidence of its effects in reducing mortality in patients in the scenario of ventilatory assistance and with oxygen supply. This was also seen in methylprednisolone, hydrocortisone, and prednisolone, all of which also demonstrated significant effects in therapy. This is due to the fact that corticoids act by blocking the exacerbated immune response, either by an anti-inflammatory action or by a decrease in the activation of defense cells (T lymphocytes, macrophages, and monocytes). Thus, the use is related to the attempt to block the so-called "cytokine storms", which reduces damage to the lungs.[29]

However, one of the problems in the use of glucocorticoids is the side effects they cause, since corticosteroids have potent anti-inflammatory and immunosuppressive effects on primary and secondary immune cells. In view of this, this suppression of the immune system can reduce the patient's symptoms as well as side effects. Thus, signs of slow recovery, bacterial infections, hypokalemia, and other secondary infections may be hidden. For this reason, its indication for use is just for critically ill patients, and its use is not indicated for the treatment of less severe cases of COVID-19.[29,30]

Strongyloidiasis, COVID-19 and use of glucocorticoids.

In this spectrum, with the global pandemic, many studies were carried out regarding viral and bacterial coinfections, however, at first, little was investigated about parasitic coinfections. Patients with COVID-19 have been widely treated with corticosteroids, which is a risk factor for disseminated strongyloidiasis. A case report published in 2020 demonstrated the medical evolution of a 68-year-old man hospitalized with positivity for SARS-CoV-2. The patient was an immigrant who came from Ecuador 20 years ago, where he worked in soil cultivation. The patient underwent treatment with methylprednisolone from the 4th day of hospitalization and developed a picture of disseminated strongyloidiasis on the 19th day, subsequently evolving into a picture of bacterial meningitis. The patient probably acquired the parasite in Ecuador while working with the soil, and the use of immunosuppressant medication probably enabled the complication of the infection.[31] The same evolution was presented in other works, as in the case report that was described in an article by Lier *et al.*, in 2020, relating a condition of disseminated strongyloidiasis with a subsequent evolution to bacterial meningitis. Both cases describe patients who were being treated for bacterial coinfections associated with COVID-19, whose use of antibiotics was discontinued after the improvement of the bacterial condition. Thus, with the emergence of the parasitic condition, therapy with ivermectin was used, without reestablishing antimicrobial therapy, which may have contributed to the complication.[31]

In another similar case, a 45-year-old patient from Ecuador who tested positive for COVID-19 was treated with dexamethasone. On the 7th day of hospitalization, the individual showed progressive worsening, presenting cutaneous lesions duly investigated and revealed to be a coinfection by a parasite, with a positive result for *S. stercoralis.* Treatment with ivermectin was started on the 12th day of hospitalization and 48 hours later the patient no longer presented symptoms.[32]

Corroborating the relationship between asymptomatic chronic carriers of strongyloidiasis and the development of hyperinfection after the use of corticosteroids in the treatment of COVID-19, the 2022 study by Lorenzo *et al.* showed that 5 out of 86 patients positive for COVID-19 from endemic areas for *S. stercoralis* presented the symptomatic form of the disease after immunosuppressive treatment with dexamethasone. Thus, it was concluded that the use of dexamethasone in patients with previously undetected strongyloidiasis may lead to a worsening of the clinical picture and to more severe consequences such as hyperinfection.[33]

Another work presented by Stylemans and collaborators, in 2021, demonstrated a 59-year-old Ecuadorian patient who sought medical help after 10 days with COVID-19. The individual was hospitalized and required intubation due to his worsening condition. During the acute period of the disease, the patient remained with eosinopenia. After 49 days in the hospital bed, the doctors observed a slight increase in the levels of eosinophils, alerting them to initiate further investigations into possible new infections. Based on an analysis of the patient's previous medical records, chronic eosinophilia was detected, which increased the suspicion of a parasitic condition. Their results showed positive serological tests for *S. stercoralis,* which allowed them to re-evaluate the patient's treatment, initiating Ivermectin treatment. The

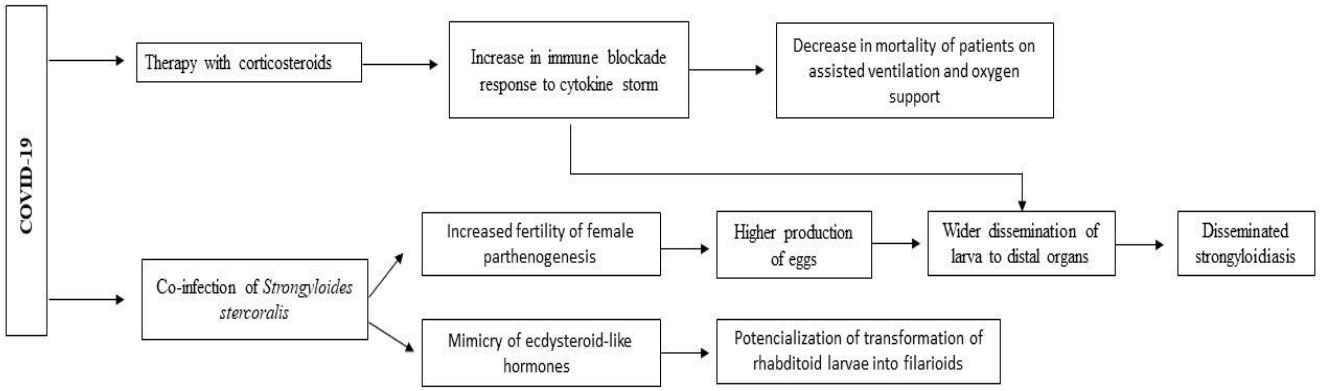

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Figure 3: Diagram of the relationship between corticosteroid therapy, COVID-19 and coinfection with *S. stercoralis*

patient showed significant improvement after 1 week and was discharged. In this context, it is noteworthy that, in view of the Covid-19 situation, the level of eosinophils suffered an abrupt drop, with an increase only in the recovery stage. Thus, the need for strongyloidiasis screening is recommended in all patients selected for immunosuppressive therapy, especially when this therapy is empirical.[34]

On the other hand, there are reports that eosinopenia was not present during the peak of the infection, as in the study carried out by Patel *et al.*, in 2021, which reports the case of a 72-year-old patient from Nicaragua diagnosed with COVID-19 who was admitted to the hospital and initially treated with Dexamethasone. The individual rapidly worsened, being intubated and transferred to the ICU. His exams showed high levels of eosinophils, indicating parasitic coinfection. Doctors made the proper investigations and the results were positive for *S. stercoralis*. After treatment with ivermectin was started, the patient's hyperinfection condition was reversed. Therefore, it is essential that the medical team is aware of latent infections, such as *S. stercoralis*, which may be discovered during treatment.[35]

To summarize, the purpose and importance of this analysis are based on the need for reductions of complications in the treatment of COVID-19 due to the development of this parasitic disease secondary to the use of corticosteroids, thus reducing iatrogenic events and the mortality rate of patients undergoing immunosuppressive therapy through screening for *stercoralis*. The increase in the indiscriminate use of corticosteroids, such as dexamethasone, as part of the therapeutic strategy for COVID-19, there is an increase in the risks of the development of this viral and parasitic coinfection, which can often have fatal outcomes. Therefore, It is evident that health platforms should consider creating effective strategies such as applying new or existing protocols to prevent these negative outcomes.[9] In this sense, screening programs for *S. stercoralis* should be implemented during the SARS-CoV-2 pandemic, mainly in regard to areas with a high incidence of strongyloidiasis or with a significant movement of immigration. Despite ELISA serology having greater specificity and sensitivity, the test is not widely accessible.[23] The use of more sensitive techniques, such as the Baermann-Moraes method (parasitological examination of feces), agar culture and PCR, which can be combined with serology, have the potential to be implemented in screening systems. However, these techniques have some limitations because of the delay in culture results or the difficulty in collecting larvae in stool samples.[36] Given the impossibility of performing more sensitive techniques, an epidemiological stratification is proposed for patients with COVID-19 at risk of previous exposure to the worm, which should be done according to criteria such as country of birth, current residence, and having made long journeys. In this way, it is possible to identify patients at greater risk and submit them to preventive therapy with ivermectin, which is 85% effective in a single dose.[23]

Conclusion

In this light, it was concluded that, in the context of the global pandemic caused by COVID-19, glucocorticoids play an essential role as part of the treatment protocol for severe forms of the disease. However, their indiscriminate use and without any type of screening can contribute to the emergence of serious forms of diseases, at first undiagnosed, such as strongyloidiasis. In this sense, treatment with glucocorticoids without the necessary screening, given the scenario of COVID-19 and coinfections, creates a therapeutic inconsistency. As previously discussed, this contradiction is avoided by treating the parasite with ivermectin, and should start from the screening of strongyloidiasis in patients with suspicious clinical features or a previous history in compatible territories, with an emphasis on endemic areas for the *S. stercoralis* parasite. Therefore, in view of the cases presented, the need for a more careful look at this possible coinfection is clear, since the fatal consequences can be avoided with the establishment of a screening protocol.

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