

CORTICOSTEROID THERAPY ASSOCIATED WITH COVID-19: AN ALLY OR A RISK FACTOR FOR THE ESTABLISHMENT OF SECONDARY FUNGAL CO-INFECTIONS?

Thaís Ferreira do Amaral¹, Natália Monteiro da Silva Rodrigues Coutinho¹,
Rubia do Nascimento Fuentefria² , Alexandre Meneghello Fuentefria³ ,
Gabriella da Rosa Monte Machado³ 

ABSTRACT

Corticosteroid therapy to combat inflammation caused by SARS-CoV-2 seems to be a risk factor for developing secondary fungal co-infections. PubMed and ScienceDirect databases were searched, with the following word groups: [(aspergillosis OR mucormycosis OR candidiasis) AND (coronavirus disease) AND (corticoids)]. The selected articles present the main risk factors related to the establishment of secondary fungal co-infections in COVID-19 patients. Corticosteroid therapy used to combat inflammation caused by SARS-CoV-2 has been shown to be strongly associated with the establishment of mucormycosis and aspergillosis. Mucormycosis has been the main fungal co-infection related to corticosteroid therapy, causing a high number of deaths in COVID-19 patients. Diabetes mellitus was the most prevalent comorbidity, especially for the establishment of mucormycosis. Dexamethasone use seems to be associated with mucormycosis emergence and death. However, aspergillosis showed a greater relationship with patient recovery. Thus, risk factors such as diabetes mellitus, combined with corticosteroid use, have shown a relationship to the establishment of mucormycosis. The corticosteroids used in COVID-19 patients should be individually analyzed, considering the patient's medical history and the risk/benefit ratio of the use of these drugs.

Keywords: COVID-19, fungal co-infections, mucormycosis, aspergillosis, corticotherapy

Clin Biomed Res. 2022;42(4):369-377

1 Faculdade de Farmácia,
Universidade Federal do Rio Grande
do Sul. Porto Alegre, RS, Brasil.

2 Hospital de Clínicas de Porto Alegre.
Porto Alegre, RS, Brasil.

3 Programa de Pós-Graduação
em Ciências Farmacêuticas,
Universidade Federal do Rio Grande
do Sul. Porto Alegre, RS, Brasil.

Corresponding author:

Gabriella da Rosa Monte Machado
gabbirosam@gmail.com
Laboratório de Micologia
Aplicada, Faculdade de Farmácia,
Universidade Federal do Rio Grande
do Sul
Rua São Luís, 154, Anexo 2
90620170, Porto Alegre, RS, Brasil.

INTRODUCTION

Coronavirus disease – 2019 (COVID-19) is an infection caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that was firstly reported in the city of Wuhan, China, in 2019¹. The most severe cases of infection are characterized by a strong inflammatory condition in the patients' lungs, caused mainly by viral replication and by large release of cytokines that occurs during the inflammation process^{2,3}. Although the respiratory system is the main target of SARS-CoV-2, the virus affects the angiotensin-converting enzyme 2 (ACE-2) receptors. These receptors are present in the lung epithelium, kidneys, gastrointestinal tract, heart, liver, and blood vessels, explaining the emergence of other complications in the patient, such as metabolic acidosis, clotting disorders, and multiple organ failure^{1,2}. Thus, the administration of corticosteroids was started in patients with moderate or severe cases of COVID-19, to minimize the inflammatory process resulting from viral replication, mainly in the lungs, modulating the exacerbated release of cytokines³.

The corticosteroids used to promote immunomodulation have become a risk factor in COVID-19 patients, as they are related to the global increase in cases of secondary fungal co-infections, especially mucormycosis and aspergillosis. Cases of secondary fungal co-infections in COVID-19 patients mainly occurred during the second wave of the disease. In the same period, the World Health Organization (WHO) recommended corticosteroid use in

critically ill COVID-19 patients³⁻⁵. Moreover, other risk factors were also associated with the development of fungal co-infections during SARS-CoV-2 infection, namely: diabetes mellitus, immunodeficiencies, hypertension, and cardiovascular diseases, among others^{3,5}. Thus, we conducted a literature review addressing the main influences related to corticosteroid use and the predisposition of comorbidities, such as diabetes mellitus, arterial hypertension, cardiovascular diseases, and chronic obstructive pulmonary disease (COPD), in the

development of secondary fungal co-infections in COVID-19 patients.

MATERIAL AND METHODS

Data source

The search for scientific reports to compose this study was carried out in the Pubmed and ScienceDirect databases, using the following word groups: [(aspergillosis OR Mucormycosis OR candidiasis) AND (Coronavirus disease) AND (corticoids)] (Figure 1).

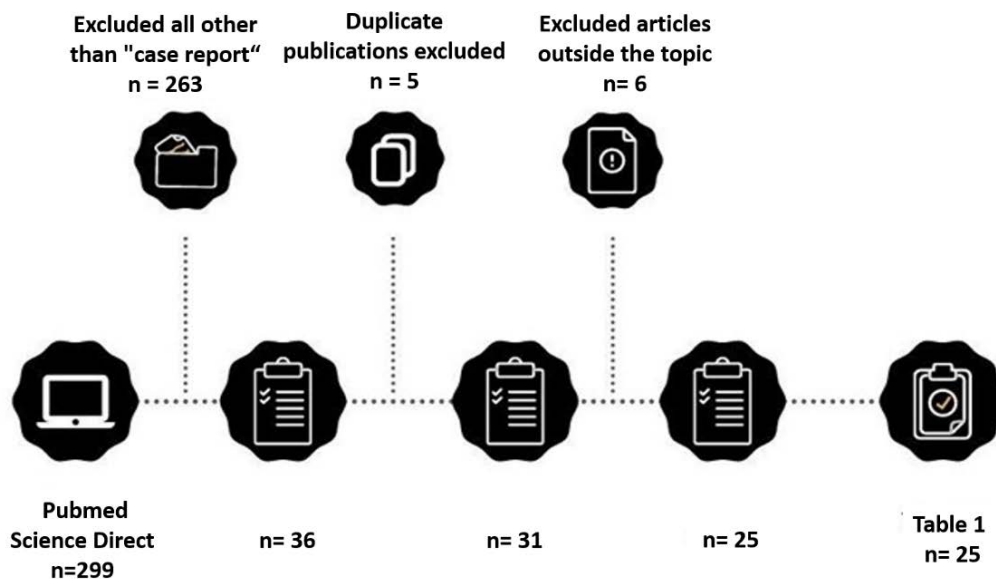


Figure 1: Illustration of the inclusion criteria used to select the articles analyzed in this study.

Selection criteria

Articles published since 2019, case reports, positive patients for COVID-19, and patients who developed fungal infections during or after COVID-19

infection were used. The selected articles present the main risk factors related to the establishment of secondary fungal co-infections in COVID-19 patients (Table 1).

Table 1: Description of fungal co-infections associated with COVID-19, the therapeutic choice used, patient's medical history and clinical outcome.

Reference	Fungal infection	Corticosteroid therapy	Treatment during COVID-19	Treatment for fungal co-infection	Medical history	Gender/ age	Clinical outcome
Alekseyev, Didenko, and Chaudhry ⁶	Mucormycosis	Corticosteroid Association not specified	Hydroxychloroquine	Amphotericin B Surgical debridement Cefepime;	Diabetes mellitus	Man/41	Hospital discharge
Choudhary et al. ⁷	Mucormycosis	Corticosteroid Not specified	Remdesivir	Liposomal Amphotericin B	-	Man/32	Death
Deek et al. ⁴	Mucormycosis	Dexamethasone (6mg/day for 6 days)	Convalescent plasma	Liposomal Amphotericin B	Diabetes mellitus Coronary artery disease Atrial fibrillation	Man/75	Hospital discharge

Continue

Table 1 - Continuation

Reference	Fungal infection	Corticosteroid therapy	Treatment during COVID-19	Treatment for fungal co-infection	Medical history	Gender/age	Clinical outcome
Jain et al. ⁸	Mucormycosis	Methylprednisolone	-	-	Diabetes mellitus	Woman/57	Death
Krishna et al. ⁵	Mucormycosis	Corticosteroid combination not specified (For 7 days)	Hydroxychloroquine Azithromycin	-	Hypothyroidism	Man/22	Death
Maini et al. ⁹	Mucormycosis	Methylprednisolone; Dexamethasone	Remdesivir	Amphotericin B; Tobramycin BD; Nepalact TDS;	-	Woman/38	Hospital discharge
Metha and Pandey ¹⁰	Mucormycosis	Methylprednisolone; Dexamethasone	Oseltamivir; Meropenem; Tocilizumab	Vancomycin; Amphotericin B	Diabetes mellitus	Man/60	Death
Nehara et al. ¹¹	Mucormycosis	Dexamethasone (For 6 days)	Meropenem Remdesivir Azithromycin	Liposomal Amphotericin B	Diabetes mellitus	Woman/59	Death
	Mucormycosis	Prednisolone	-	Liposomal Amphotericin B; Posaconazole	Diabetes mellitus	Men/52	Hospital discharge
	Mucormycosis	-	-	Liposomal Amphotericin B; surgical debridement	Diabetes mellitus	Woman/62	Hospitalized
	Mucormycosis	Dexamethasone	Antibiotics; Remdesivir	Liposomal Amphotericin B	Diabetes mellitus	Woman/70	Hospitalized
	Mucormycosis	-	-	Liposomal Amphotericin B; Unspecified corticosteroid; Broad-spectrum antibiotics	Diabetes mellitus	Woman/68	Death
Palou et al. ¹²	Mucormycosis	Dexamethasone	-	Liposomal Amphotericin B; Isavuconazole	Hypertension	Man/56	Hospital discharge
Placik, Taylor, and Wnuk ¹³	Mucormycosis	Dexamethasone	Azithromycin; Remdesivir	Amphotericin B	-	Man/49	Death
Rana et al. ¹⁴	Mucormycosis	-	-	Liposomal Amphotericin B; Surgical debridement; Vancomycin	Diabetes mellitus	Man/48	Death
Varshney et al. ¹⁵	Mucormycosis	Unspecified corticosteroid	-	-	Tachycardia; Tachypnea; Hypertension	Man/32	Death
Deana et al. ¹⁶	Aspergillosis	Dexamethasone	Tocilizumab	Liposomal Amphotericin B	Hepatic cirrhosis; Hypertension; Obesity	Man/69	Hospital discharge
Imoto et al. ¹⁷	Aspergillosis	Dexamethasone	Ceftriaxone; Azithromycin; Remdesivir	Voriconazole	Hypertension; Atrial fibrillation; COPD	Man/72	Death
Iwanaga et al. ¹⁸	Aspergillosis	Dexamethasone; Methylprednisolone (replacement of dexamethasone)	Ciclesonide; Ivermectin; Meropenem; Remdesivir	Liposomal Amphotericin B	Diabetes mellitus; Polymyalgia rheumatica	Man/79	Death

Continue

Table 1 - Continuation

Reference	Fungal infection	Corticosteroid therapy	Treatment during COVID-19	Treatment for fungal co-infection	Medical history	Gender/ age	Clinical outcome
Sánchez Martín et al. ¹⁹	Aspergillosis	Methylprednisolone	Hydroxychloroquine; Lopinavir/Ritonavir Tocilizumab	Anidulafungin; Isavuconazole sulfate	Dyslipidemia; Hypertension	Man/71	Hospital discharge
	Aspergillosis	Methylprednisolone	Hydroxychloroquine; Lopinavir/Ritonavir	Isavuconazole sulfate	Diabetes mellitus; Hypertension; Dyslipidemia	Man/73	Hospital discharge
	Aspergillosis	Methylprednisolone	Hydroxychloroquine; Lopinavir/Ritonavir	Amphotericin B; Isavuconazole sulfate	Thalassemia minor	Woman/67	Death
	-	-	BNF; Hydroxychloroquine; Lopinavir/Ritonavir	-	Diabetes mellitus; Hypertension; Dyslipidemia; Obesity; Chronic anemia	Woman/70	Hospital discharge
Sasoni et al. ²⁰	Aspergillosis	Methylprednisolone	Azithromycin; Hydroxychloroquine	Amphotericin B; Fluconazole; Voriconazole	Pulmonary embolism	Man/73	Hospital discharge
Schein et al. ²¹	Aspergillosis	Methylprednisolone	Ceftriaxone; Spiramycin	Voriconazole	-	Woman/87	Hospital discharge
Pasula and Chandrasekar ²²	Aspergillosis	Methylprednisolone	Hydroxychloroquine; Doxacycline; ceftriaxone	Voriconazol	Diabetes mellitus; Hypertension; Obesity; Chronic kidney disease; Smoker	Man/65	Hospital discharge
Trujillo et al. ²³	Aspergillosis	Prednisone	Hydroxychloroquine; Azithromycin; Ceftriaxone; Tocilizumab	Isavuconazole; liposomal Amphotericin B	Kidney transplant	Woman/55	Hospital discharge
Witting et al. ²⁴	Aspergillosis	-	Azithromycin; Tocilizumab	Voriconazole; Micafungin	Smoker	Man/72	Hospital discharge
Abdalla et al. ²⁵	Aspergillosis; Candidiasis	Methylprednisolone	Hydroxychloroquine; Azithromycin; Lopinavir/Ritonavir INF alpha-2a Tocilizumab	Anidulafungin; Liposomal Amphotericin B	Diabetes mellitus; Diabetic nephropathy; Hypertension; Dyslipidemia; Hepatitis B	Man/58	Death
	Aspergillosis; Candidiasis	Methylprednisolone	Hydroxychloroquine; Azithromycin; Lopinavir/Ritonavir; Ribavirin; INF alpha2a	Voriconazole	-	Man/74	Death
Mohamed et al. ²⁶	Aspergillosis; Candidiasis	-	Azithromycin; Hydroxychloroquine	Liposomal Amphotericin B	Diabetes mellitus; Hypertension; Dyslipidemia; Obesity; Former smoker	Man/66	Death
Cai et al. ²⁷	Aspergillosis; Pneumocystosis	Methylprednisolone	Oseltamivir; Lopinavir; Ritonavir; Tocilizumab	Caspofungin	Rheumatoid arthritis	Woman/72	Hospital discharge
Thyagarajanc Mondy, and Rose ²⁸	Cryptococcosis	Dexamethasone	Convalescent plasma	-	Diabetes mellitus; Hypertension; Obesity; Osteoarthritis	Woman/75	Death

DISCUSSION

Immunosuppressive therapy as a way to combat COVID-19 and the risk of secondary fungal co-infections

The SARS-CoV-2 infection varies in severity, from milder manifestations to severe cases of the disease. Symptoms such as fever, dry cough, and difficulty breathing are the most common. However, some patients develop a sore throat, headache, fatigue, and diarrhea³. Approximately 80% of patients have a mild or moderate infection, and they may be asymptomatic or develop milder symptoms, without the need for hospital admission. However, the other 20% develop the most severe form of the infection, and require hospitalization, often in an intensive care unit (ICU)²⁹.

Similarly to other viral infections, such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS), SARS-CoV-2 replication can stimulate an uncontrolled systemic immune response in the patient's body, caused by the phenomenon known as "cytokine storm"³⁰. This phenomenon occurs because of the exacerbated release of pro-inflammatory cytokines via lymphocytes, monocytes, fibroblasts, and bronchial epithelial cells, mainly releasing Interleukin-6 (IL-6), which is higher in COVID-19 cases²⁹. SARS-CoV-2 also induces other cytokines, such as IL-1, IL-2, IL-8, IL-17; tumor necrosis factor alpha (TNF- α); Interferon gamma-induced protein 10 (CXCL10); and monocyte chemotactic protein 1 (MCP-1). In addition to cytokines, other pro-inflammatory parameters are also induced, such as C-reactive protein, D-dimers, and ferritin. These events are associated with the severity of the viral infection in the patient, which in the long term causes damage and fibrosis in the lungs of those infected^{3,31}.

Hyperinflammation caused by cytokine storms represents a high risk to the patient. Thus, immunomodulatory therapy has become necessary in cases of hospitalized COVID-19 patients²⁹. Immunomodulatory drugs alter the body's immune function. Corticosteroids are part of this group, as they potentially induce suppression of the patient's immune system via numerous mechanisms that interfere with the number of cells and their functions³². As with MERS, SARS, and H1N1, corticosteroids have been widely used to control the immune response in critically ill and hospitalized COVID-19 patients^{3,30}. According to Horby et al.³³, favorable results for the use of dexamethasone, and hydrocortisone for 10 days in COVID-19 patients who required mechanical ventilation were observed, reducing the mortality rate. Despite the positive therapeutic response in severe cases, corticosteroid must be rationally and responsibly administered, since these drugs demonstrate adverse events, such as glucose

intolerance, hypertension, and susceptibility to viral, fungal, and bacterial infections—which can harm and further endanger the patient's health³².

Among the 33 case reports analyzed (Table 1), 28 studies recommended the use of at least one corticosteroid for more than five days during COVID-19 treatment. On the other hand, 24 patients developed some secondary manifestation, such as fungal co-infection during hospitalization or shortly after hospital discharge. Still in this group, 13 patients died. The prolonged use of very high doses of these drugs is not recommended precisely because of the high risk of developing other diseases due to suppression of the immune system³⁴.

Influence of medical history on the establishment of secondary fungal co-infections in COVID-19 patients

Opportunistic fungal infections primarily affect immunocompromised patients. Candidiasis, pulmonary aspergillosis, pulmonary mucormycosis, and rhinocerebral mucormycosis are common in immunocompromised patients. Risk factors, such as leukemia, bone marrow, and organ transplants, acquired or genetic immunodeficiency, and high doses of corticosteroids are associated with a greater susceptibility to the establishment of a fungal infection in the patient³⁵. In addition to the risk factors presented, there are chronic diseases that may be associated with the appearance of specific fungal infections, as described below.

Diabetes mellitus is a chronic disorder related to increased blood glucose concentration associated with defects in insulin secretion or action. Mucormycosis is a rare but potentially lethal fungal infection caused by fungi of the order Mucorales, found in soil, on decaying plants, and vegetables³⁶. This infection presents the highest prevalence associated with diabetes mellitus. The lack of diabetes control can lead to ketoacidosis in humans, reducing the plasma pH and, therefore, the binding of iron to transferrin. This fact leads to a higher concentration of plasma-free iron concentration, available for the fungal pathogen, which uses iron for its growth and expression of virulence factors in the host^{2,36}. In the studies analyzed (Table 1), 27 patients present some comorbidity, and 17 are patients with diabetes mellitus (DM), the most prevalent medical history. Among the patients with DM, mucormycosis was the most prevalent fungal co-infection, diagnosed in 10 cases and five of these died.

Unlike mucormycosis, aspergillosis seems to be more associated with chronic obstructive pulmonary disease (COPD) and severe cases of influenza or pneumonia^{35,36}. Aspergillosis is caused by the *Aspergillus* spp., anemophilous, opportunistic, and emerging fungi present in different environments, such as hospitals. The main human contagion

by this microorganism occurs via the airways, initially affecting the lungs and consequently being able to spread through the lymphatic system and bloodstream. COPD is the obstruction of air passage in the lungs, mainly caused by smoking or other harmful compounds. In these cases, the lung injury is irreversible. In addition, as in severe cases of viral respiratory infections, COPD patients also use corticosteroid therapy¹⁶. Thus, the establishment of aspergillosis seems to be substantially linked to the association of two factors: a) suppression of the immune system and b) physical integrity of the lung³⁵.

In this review, only one patient had a COPD history and died. Although COPD was not frequent in the analyzed cases, other factors, such as smoking history and pulmonary embolism (which can affect lung integrity) were also observed (Table 1). All these COVID-19 patients, in addition to the lung damage being more pronounced, received corticosteroid therapy.

Main fungal co-infections in COVID-19 patients

During the first COVID-19 global wave the main objective of corticosteroid use was to promote the maintenance of severe symptoms caused by the exacerbated immune response and the search for therapies that could reduce disease-related mortality^{31,35}. Thus, these drugs—mainly dexamethasone—were used worldwide². However, during the second COVID-19 global wave, reports of fungal infections secondary to COVID-19 increased, demonstrating that the therapeutic management related to corticosteroids administration should be carried out with greater caution, considering the patient's medical history and the risk/benefit ratio of the treatment^{7,37,38}. From alterations in the therapeutic approach for the administration of corticosteroid, an increase in the number of cases, mainly of mucormycosis and aspergillosis associated with COVID-19, was observed. These cases may be directly associated with corticosteroid use in this group. This hypothesis is justified since these drugs can cause an uncontrolled release of sugar, which helps the growth and accelerated replication of fungi, in addition to suppressing the immune system, the main defense of the host against infections⁴.

The main risk factor associated with the establishment of secondary aspergillosis in respiratory infections is the impairment of the immune system. In addition, another factor strongly related to this complication is a primary viral infection. Similarly to the infections caused by influenza viruses (mainly H1N1, H3N2, and H7N9), infections caused by SARS-CoV-2 promote an abnormal activation of CD8 T lymphocytes, CD4 T lymphocytes, and natural killer cells (NK cells), damage to the lung epithelium and in mucociliary clearance, creating an environment conducive to fungal infections¹⁶.

Based on these reports, 32 COVID-19 patients developed some secondary fungal co-infection, of which mucormycosis is the most frequent (16 cases) and responsible for the highest number of deaths in patients who received corticosteroids—mainly dexamethasone. Among this group, 17 patients have a medical history of diabetes mellitus, which is the main comorbidity associated with the development of fungal co-infections in COVID-19 patients. Reports of other fungal co-infections—such as aspergillosis, candidiasis, pneumocystosis, and cryptococcosis—in these patients have also been described (Table 1).

When compared with mucormycosis, the establishment of aspergillosis associated with COVID-19 also proves to be recurrent, however, the mortality rate is lower (3/12 cases) when compared with that observed in mucormycosis (9/16 cases). Corticoids assist the *Aspergillus* spp. development only by immunosuppression, and there is no relationship between the fungal growth and the metabolic dysfunctions that the drug can cause in the human organism (Table 1).

Corticosteroid therapy as a triggering factor of secondary fungal co-infections in COVID-19 patients

Corticosteroids can be divided into two large groups: mineralocorticoids, which regulate the body's fluid and electrolyte balance, and glucocorticoids, which act both on carbohydrate and protein metabolism and on the host organism's defense mechanisms. Glucocorticoids are more used in COVID-19 patients due to its anti-inflammatory and immunosuppressive action³⁹.

The biologically active form of glucocorticoids (GC) is the free fraction, which is not bound to plasma proteins. Synthetic GC have a lower affinity for these proteins than endogenous GCs, so approximately only 70% are bound. This results in a higher concentration of the free fraction and, consequently, a greater pharmacological activity in the patient⁴⁰. GCs act on inflammatory cells, reducing the mobilization and activation of neutrophils, in addition to reducing the activation of macrophages and T-helper (Th) cells. In addition, the transcription of genes associated with inflammation and immunity is also influenced by the binding of the free fraction of the molecule with the glucocorticoid receptor (GR), present in most cells of the body^{38,40} (Figure 2). These alterations lead to a reduction in the production of pro-inflammatory ILs—such as IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, and IL-8. The main effect of suppressing the immune response reported in these cases is the increased susceptibility to the development of fungal infections³¹.

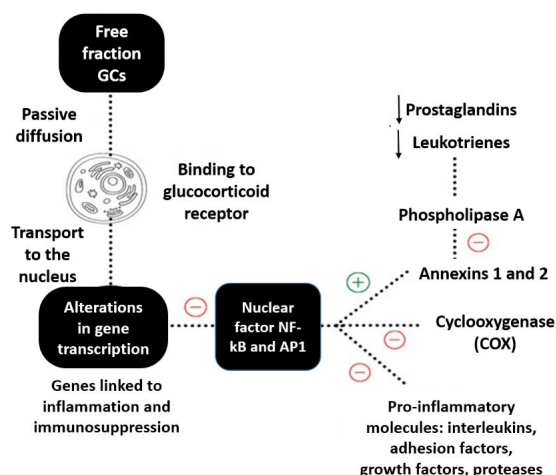


Figure 2: Mechanism of the immunomodulatory action of glucocorticoids.

The chemical structure of the corticosteroids has some similar features, such as a double bond between the C-1-2 position and a ketone at the C-3 position of the molecular structure, which enhances glucocorticoid activity. These structural differences also determine some factors, such as the potency and the glucocorticoid and mineralocorticoid activity. Dexamethasone has a 30-fold higher glucocorticoid activity compared to hydrocortisone (activity=1), which can be explained by the different methylations that occur in the first drug. On the other hand, methylprednisolone, prednisone, and prednisolone have similar action potentials, which can be explained by the structural similarity between them³².

Among the 33 studies, 28 reported the use of corticosteroids in COVID-19 patients (Table 1). Of these, methylprednisolone (n=11), dexamethasone (n=9), prednisone (n=1), and prednisolone (n=1) were used in 26 patients. The other six cases only reported "corticosteroid use" or "corticosteroid combination use." Despite the higher prevalence during corticosteroid therapy in COVID-19 patients, dexamethasone was the main drug associated with death (5/9). Methylprednisolone ranked second in deaths (5/11). In addition, dexamethasone (alone or associated with other corticosteroids) seems to be more closely related to cases of mucormycosis (7/13). On the other hand, aspergillosis was more frequent in COVID-19 patients who used methylprednisolone (7/11). Among the 13 patients with DM and received some corticosteroid, eight had mucormycosis (associated with five deaths) and three patients had aspergillosis (associated with one death). Only one cryptococcosis case in a patient with DM who used dexamethasone was reported.

Fungal co-infections, such as aspergillosis and mucormycosis, have been frequent in COVID-19 patients, increasing the mortality rate in these cases. According to the reports described, corticosteroid therapy is strongly associated with the establishment of fungal co-infection in patients previously infected with

SARS-CoV-2, especially in older people. Mucormycosis was the most lethal secondary fungal co-infection in COVID-19 patients. In addition, patients with DM medical history had the highest death rates associated with this co-infection. Notably, aspergillosis is more related to recovery and a favorable clinical outcome for patients, highlighting its prevalence in COPD patients, smokers, and respiratory viral infections, such as COVID-19.

Corticosteroid use, such as dexamethasone, proved to be very influential in the secondary fungal co-infections appearance, especially in patients with DM medical history, leading to the death of most patients. The triad: mucormycosis, use of dexamethasone, and DM resulted in a poor clinical outcome and in the death of most patients. Both mucormycosis and aspergillosis present a major health risk to COVID-19 patients. In both cases, corticosteroid therapy has developed a fundamental role at the beginning of the fungal co-infection since the suppression of the immune system facilitates the entry and installation of these microorganisms in the patient's organism. Finally, we suggest that the use of corticosteroids should be analyzed individually, considering the patient's medical history and the risk/benefit ratio of using these drugs.

Conflicts of interest

The authors declare that they have no known competing interests or personal relationships that could influence the work reported in this paper.

Funding

This study was partly financed by the Coordination for the Improvement of Higher Education Personnel – Brasil (CAPES) – Finance Code 001 and partly by the Brazilian National Council for Scientific and Technological Development (CNPq), grant 302752.

REFERENCES

- Hosseini SE, Kashani RN, Nikzad H, Azadbakht J, Bafrani HH, Kashani HH. The novel coronavirus Disease-2019 (COVID-19): mechanism of action, detection and recent therapeutic strategies. *Virology*. 2020;551:1-9.
- Ibrahim SA. Host-iron assimilation: pathogenesis and novel therapies of mucormycosis. *Mycoses*. 2014;57(Suppl 3):13-7.
- Moreno G, Rodríguez A, Reyes FL, Gomez J, Sole-Violan J, Diaz E, et al. Corticosteroid treatment in critically ill patients with severe influenza pneumonia: a propensity score matching study. *Intensive Care Med*. 2018;44(9):1470-82.
- Deek JA, Boukovalas S, Rathfoot JC, Gotcher JE. Rhinocerebral mucormycosis as a sequelae of COVID-19 treatment: a case report & literature review. *J Oral Maxillofac Surg*. 2022;80(2):333-40.
- Krishna V, Morjaria J, Jalandari R, Omar F, Kaul S. Autoptic identification of disseminated mucormycosis in a young male presenting with cerebrovascular event, multi-organ dysfunction and COVID-19 infection. *IDCases*. 2021;25:e01172.
- Alekseyev K, Didenko L, Chaudhry B. Rhinocerebral mucormycosis and COVID-19 Pneumonia. *J Med Cases*. 2021;12(3):85-9.
- Choudhary GR, Aggarwal A, Jain V, Jena R. COVID-19 and fatal renal mucormycosis: contributory or coincidental? *Indian J Urol*. 2021;37(3):270-3.
- Jain M, Tyagi R, Tyagi R, Jain G. Post-COVID-19 gastrointestinal invasive mucormycosis. *Indian J Surg*. 2022;84(3):545-7.
- Maini A, Tomar G, Khanna D, Kini Y, Mehta H, Bhagyasree V. Sino-orbital mucormycosis in a COVID-19 patient: a case report. *Int J Surg Case Rep*. 2021;82:105957.
- Metha S, Pandey A. Rhino-orbital mucormycosis associated with COVID-19. *Cureus*. 2020;12(9):e10726.
- Nehara HR, Puri I, Singhal V, Ih S, Bishnoi BR, Sirohi P. Rhinocerebral mucormycosis in COVID-19 patient with diabetes a deadly trio: case series from the north-western part of India. *Indian J Med Microbiol*. 2021;39(3):380-3.
- Palou EY, Ramos MA, Cherenfant E, Duarte A, Fuentes-Barahona IC, Zambrano LI, et al. COVID-19 associated rhino-orbital mucormycosis complicated by gangrenous and bone necrosis-a case report from Honduras. *Vaccines (Basel)*. 2021;9(8):826.
- Placik DA, Taylor WL, Wnuk NM. Bronchopleural fistula development in the setting of novel therapies for acute respiratory distress syndrome in SARS-CoV-2 pneumonia. *Radiol Case Rep*. 2020;15(11):2378-81.
- Rana G, Gautam S, Mawari G, Daga MK, Kumar N, Raghu RV. Massive hemoptysis causing mortality in a post COVID-19 infected Asian male patient: presenting as pulmonary mucormycosis, pulmonary tuberculosis and later sino-nasal mucormycosis. *Respir Med Case Rep*. 2021;34:101511.
- Varshney VK, Swami A, Thirunavukkarasu B, Agarwal A, Baid G. Synchronous small bowel gangrene with pyelonephritis secondary to mucormycosis: a disastrous complication of COVID-19 pandemic. *Cureus*. 2021;13(6):e15911.
- Deana C, Vetrugno L, Bassi F, De Monte A. Tocilizumab administration in COVID-19 patients: water on the fire or gasoline? *Med Mycol Case Rep*. 2021;31:32-4.
- Imoto W, Himura H, Matsuo K, Kawata S, Kiritoshi A, Deguchi R, et al. COVID-19-associated pulmonary aspergillosis in a Japanese man: a case report. *J Infect Chemother*. 2021;27(6):911-4.
- Iwanaga Y, Kawanami T, Yamasaki K, Sakakibara H, Ikushima I, Ikegami H, et al. A fatal case of COVID-19-associated invasive pulmonary aspergillosis. *J Infect Chemother*. 2021;27(7):1102-7.
- Sánchez Martín C, Madrid Martínez E, González Pellicer R, Armero Ibáñez R, Martínez González E, Liau Pitarch JV. Invasive pulmonary aspergillosis in patients with acute respiratory syndrome by COVID-19. *Rev Esp Anestesiol Reanim*. 2022;69(1):48-53.
- Sasoni N, Rodriguez Müller M, Posse G, González J, Leonardelli F, Garcia-Effron G. SARS-CoV-2 and Aspergillus section Fumigati coinfection in an immunocompetent patient treated with corticosteroids. *Rev Iberoam Micol*. 2021;38(1):16-8.
- Schein F, Munoz-Pons H, Mahinc C, Grange R, Cathébras P, Flori P. Fatal aspergillosis complicating severe SARS-CoV-2 infection: a case report. *J Mycol Med*. 2020;30(4):101039.
- Pasula S, Chandrasekar P. Spontaneous hemoptysis in a patient with COVID-19. *Chest*. 2021;160(1):e39-44.
- Trujillo H, Fernández-Ruiz M, Gutiérrez E, Sevillano Á, Caravaca-Fontán F, Morales E, et al. Invasive pulmonary aspergillosis associated with COVID-19 in a kidney transplant recipient. *Transpl Infect Dis*. 2021;23(2):e13501.
- Witting C, Quaggin-Smith J, Mylvaganam R, Peigh G, Angarone M, Flaherty JD. Invasive pulmonary aspergillosis after treatment with tocilizumab in a patient with COVID-19 ARDS: a case report. *Diagn Microbiol Infect Dis*. 2021;99(4):115272.
- Abdalla S, Almaslamani MA, Hashim SM, Ibrahim AS, Omrani AS. Fatal Coronavirus Disease 2019-associated pulmonary aspergillosis; a report of two cases and review of the literature. *IDCases*. 2020;22:e00935.
- Mohamed A, Hassan T, Trzoz-Grzybowska M, Thomas J, Quinn A, O'Sullivan M, et al. Multi-triazole-resistant *Aspergillus fumigatus* and SARS-CoV-2 co-infection: a lethal combination. *Med Mycol Case Rep*. 2021;31:11-4.
- Cai S, Sun W, Li M, Dong L. A complex COVID-19 case with rheumatoid arthritis treated with tocilizumab. *Clin Rheumatol*. 2020;39(9):2797-802.
- Thyagarajan RV, Mondy KE, Rose DT. *Cryptococcus neoformans* blood stream infection in severe COVID-19 pneumonia. *IDCases*. 2021;26:e01274.

29. Meskini M, Rami MR, Maroofi P, Ghosh S, Siadat SD, Sheikhpour M. An overview on the epidemiology and immunology of COVID-19. *J Infect Public Health*. 2021;14(10):1284-98.
30. Khosroshahi LM, Rokni M, Mokhtari T, Noorbakhsh F. Immunology, immunopathogenesis and immunotherapeutics of COVID-19; an overview. *Int Immunopharmacol*. 2021;93:107364.
31. Bacca E, Digaetano M, Meschiari M, Franceschini E, Menozzi M, Cuomo G, et al. Immunomodulation for the management of severe SARS-CoV2 infections. State of the art and review of the literature. *Biochem Biophys Res Commun*. 2021;538:151-5.
32. Nelson RP Jr, Ballou M. 26. Immunomodulation and immunotherapy: drugs, cytokines, cytokine receptors, and antibodies. *J Allergy Clin Immunol*. 2003;111(2 Suppl):S720-32.
33. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. 2021;384(8):693-704.
34. Rello J, Waterer WG, Bourdiol A, Roquilly A. COVID-19, steroids and other immunomodulators: the jigsaw is not complete. *Anaesth Crit Care Pain Med*. 2020;39(6):699-701.
35. Boroujeni ZB, Shamsaei S, Yarahmadi M, Getso MI, Khorashad AS, Haghighi L, et al. Distribution of invasive fungal infections: molecular epidemiology, etiology, clinical conditions, diagnosis and risk factors: a 3-year experience with 490 patients under intensive care. under intensive care. *Microb Pathog*. 2021;152:104616.
36. Fernández-García OA, Cuellar-Rodríguez JM. Immunology of fungal infections. *Infect Dis Clin North Am*. 2021;35(2):373-88.
37. Cai S, Sun W, Li M, Dong L. A complex COVID-19 case with rheumatoid arthritis treated with tocilizumab. *Clin Rheumatol*. 2020;39(9):2797-802.
38. Chein LYC, Hoiland RL, Stukas S, Wellington CL, Sekhon MS. Confronting the controversy: interleukin-6 and the COVID-19 cytokine storm syndrome. *Eur Respir J*. 2020;56(4):2003006.
39. Rang H.P, Ritter JM, Flower RJ, Henderson G. *Rang & Dale: pharmacologia*. 8th ed. Rio de Janeiro: Elsevier; 2016.
40. Pereira ALC, Bolzani FCB, Stefani M, Charlín R. Uso sistêmico de corticosteroides: revisão da literatura. *Med Cutan Ibero Lat Am*. 2007;35(1):35-50.

Received: May 18, 2022

Accepted: Jul 18, 2022