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Review Article

# Corticosteroid therapy associated with COVID-19: an ally or a risk factor for the establishment of secondary fungal co-infections?

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## 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*

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## 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 2019[1]. 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 cytokines[3].

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 patients[3-5]. 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).

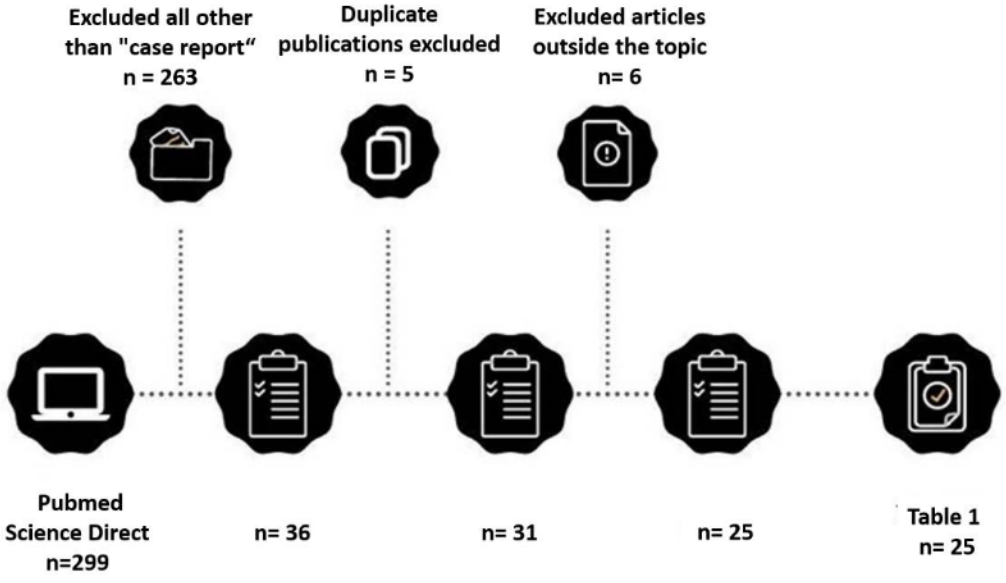


Figure 1: Illustration of the inclusion criteria used to select the articles analyzed in this study.

### *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 | Amphortericin 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; Vancomicin | 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 |
| | - | - | BINF; 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 diarrhea[3]. 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 cases[29]. 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 patients[29]. Immunomodulatory drugs alter the body's immune function. Corticosteroids are part of this group, as they potently induce suppression of the patient's immune system via numerous mechanisms that interfere with the number of cells and their functions[32]. 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 health[32].

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 system[34].

### *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 patient[35]. 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 vegetables[36]. 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 therapy[16]. 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 lung[35].

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 worldwide[2]. 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 infections[4].

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 infections[16].

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 action[39].

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 patient[40]. 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 infections[31].

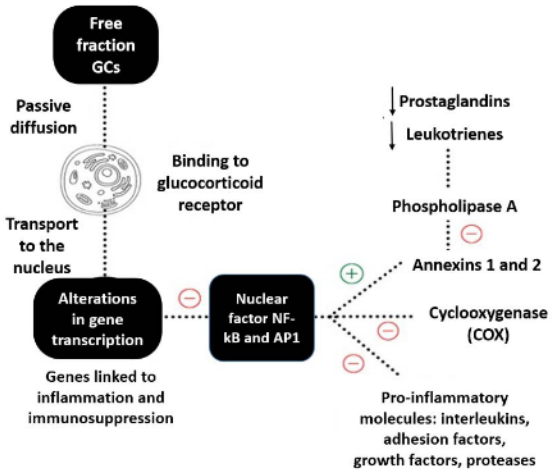


Figure 2: Mechanism of the immunomodulatory action of glucocorticoids.

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 them[32].

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.

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