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REVIEW ARTICLE

The use of corticosteroid therapy for COVID-19 patients: an evidence-based overview

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ABSTRACT

Since the World Health Organization declared the COVID-19 pandemic, the scientific community has raised considerable efforts to promote better patient treatment. One of the most effective therapies is the administration of corticosteroids at specific stages of the disease, once that severe COVID-19 pathophysiology evolves into an exuberant inflammatory response, resulting in uncontrolled pulmonary inflammation and multisystem damage. However, it is still discussed whether some drugs, such as dexamethasone, are more effective than others, such as hydrocortisone and methylprednisolone. Therefore, we constructed a comprehensive overview based on clinical studies with detailed methodological procedures regarding the role of corticosteroids in COVID-19 treatment. We addressed how the current evidence supports their use in this scenario.

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INTRODUCTION

In March 2020, coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic by the World Health Organization (WHO), becoming the most severe pandemic of this century so far[1]. After that, several strategies for prevention, treatment, and possible eradication of the virus became available. In December 2020, the Food and Drug Administration issued the first emergency use authorization for a vaccine[2]. Nevertheless, the disease is still affecting millions of people worldwide[1].

Multisystem inflammatory reactions play a central role in the progression of COVID-19 and are a leading cause of case fatality[3]. High levels of cytokines damage the lung and intensify the destructive multi-organ failure associated with acute respiratory distress syndrome (ARDS) and hypoxic respiratory failure[3]. Patients with SARS-CoV-2 infection show elevated cytokine interferon (IFN)-γ, proinflammatory cytokines interleukin (IL)-1β, IL-6, IL-8, IL-12, as well as excessive infiltration of monocyte/macrophages and neutrophils to the site of infection[4]. This intense inflammatory response, called "cytokine storm", is the critical characteristic of COVID-19 pathophysiology, eliciting microcirculation dysfunctions and thromboinflammation[5].

For this reason, corticosteroids have been demonstrated as one of the most effective therapeutic options for COVID-19 treatment to reduce the hyperinflammatory state[6]. They are a class of drugs that may dramatically reduce the immunological response, inhibiting the gene expression of some proinflammatory cytokines and chemokines, thereby mitigating the cytokine storm[7]. They were commonly used during the 2002–2004 severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) outbreak because they effectively controlled the rapid deterioration of the clinical condition[8].

Several clinical studies have demonstrated the ability of corticosteroid therapy to reduce the COVID-19 severity, reducing the mortality rate and the need for mechanical ventilation[9]. Although most of the evidence highlights dexamethasone as the major option, other drugs of this class, such as methylprednisolone and hydrocortisone, have shown some clinical benefit[10]. Here, we present a critical appraisal of the role of corticosteroids in COVID-19 treatment, exploring the biological plausibility and the clinical evidence regarding their use.

CORTICOSTEROIDS FOR TREATING VIRAL INFECTIONS

Viral infections are the leading cause of respiratory pathologies and, despite significant advances in research on the treatment of these conditions, until the early 2000s, they still contributed to about 20%-30% of annual deaths from respiratory diseases[11]. In this scenario, the development of ARDS, an intense inflammatory process of the lungs, is the typical presentation of several infectious diseases in critical stages, most frequently characterized by alveolar injury, acute hypoxemic respiratory failure, and bilateral pulmonary infiltrates on chest imaging[12].

Corticosteroids, a class of steroid hormones, represent drugs commonly used in treating patients with inflammatory-induced respiratory distress due to their various effects on the immune system[13]. In most cases, their clinical indication is based on the pathogenesis of some diseases that evolve through the overproduction of proinflammatory cytokines or chemokines, especially in infections such as those caused by the influenza virus[13]. The anti-inflammatory action of these drugs occurs through two main mechanisms that have justified their use in different scenarios, particularly in patients with severe sepsis and septic shock[14]. First, corticosteroids interact with transcription factors of kB and AP-1, inhibiting the release of several inflammatory substances (e.g., IL-1, IL-2, IL-3, and IL-6; IFN-gamma and TNF-alpha)[15]. This mechanism can prevent the migration of inflammatory cells from the circulation to the site of infection, blocking the synthesis of several chemokines[15].

Second, corticoids inhibit the phospholipase A2 synthesis, which will result in blocking the eicosanoid production, and further inhibiting various leukocyte inflammatory events, an important inflammatory response[15]. As a result, causes the inhibition of prostaglandin synthesis and cyclooxygenase (COX-1 and COX-2), potentiating the anti-inflammatory effect[15]. Moreover, beyond their effects on the cytokine storm, corticosteroids have been suggested to be able to attenuate lung injury, reducing capillary permeability and increasing alveolar edema fluid clearance, resulting in improved barrier function[16]. Hence, their use would change pulmonary and systemic inflammation and prevent disease progression to ARDS[16].

Despite this, studies evaluating these drugs' effectiveness in treating respiratory infections are still controversial. For instance, a retrospective database analysis evaluating two groups of patients treated for influenza A with or without corticosteroids (such as methylprednisolone, prednisolone, dexamethasone, and/or hydrocortisone) found in the subgroup analysis that low-to-moderate dose corticosteroids (25 mg-150 mg d-1) was related to a reduction in 30-day mortality[17].This finding was restricted to patients with a ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen < 300 mmHg[17].

In turn, a meta-analysis of nine small controlled clinical trials showed that prolonged use of methylprednisolone or hydrocortisone in infection-induced ARDS leads to a significant reduction in inflammatory parameters and reduced length of stay in the intensive care unit and the duration of mechanical ventilation[18]. Regarding dexamethasone, Villar et al.[19]conducted the most consistent randomized controlled trial (DEXA-ARDS trial) to assess the effects of this drug in ARDS.They demonstrated that early administration of dexamethasone (20 mg once a day for five days, after that 10 mg once a day for five days) could reduce the duration of mechanical ventilation (between-group difference 4.8 days [95% CI 2.57 to 7.03]; p < 0.0001) and overall mortality in patients with established moderate-to-severe ARDS.

However, a retrospective study, which evaluated the treatment of patients with severe acute respiratory

syndrome during the 2002 epidemic in China, concluded that treatment with methylprednisolone, the principal steroid used, did not show any benefits on the death rate and hospitalization days in noncritical patients, although a shorter length of stay was observed in severe cases[20]. The incidence of complications was significantly associated with the need for invasive ventilation, although it was not related to corticosteroid use20. In contrast, in patients with severe influenza, a meta-analysis of observational studies demonstrated that corticosteroids were associated with an increased risk of mortality[21].Another systematic review also noted that corticosteroids, mainly methylprednisolone and prednisone, were associated with severe adverse events, including antiviral resistance, opportunistic infections, and prolonged virus replication[22].

CORTICOTHERAPY IN COVID-19

Clinical judgments and observational assessments

Earlier in the SARS-CoV-2 pandemic, some clinicians and researchers were discordant about whether corticosteroids were safe and could reduce mortality in patients with COVID-19. For instance, Shang et al.[23] recommended prudent use of corticosteroids at a low-to-moderate dose (≤ 0.5–1 mg/kg per day methylprednisolone or equivalent), especially for critically ill patients, during a short duration (≤ 7 days), considering the previous findings showing a reduction of mortality and shorten the length of stay in the hospital for patients with severe acute respiratory syndrome. Additionally, several clinicians started to use methylprednisolone, based on studies before the pandemic, which suggested that this drug represents the best corticosteroid option for ARDS, mainly because of its greater pulmonary penetration[24].

Alternatively, Russell et al.[25] published a review based on previous studies on influenza, respiratory syncytial virus, SARS-CoV, and MERS-CoV, showing several negative conclusions about the use of corticosteroids, including endocrine complications, psychosis, and increased mortality. Hence, they highlighted that it was impossible to make any recommendation on this point because the totality of available data was inconclusive regarding their safety and clinical benefits (e.g., in mortality rate), and it might be more likely to be harmful.

For this reason, diverse corticosteroid strategies were used in observational studies to address whether these drugs could be helpful in COVID-19 treatment. Dexamethasone, methylprednisolone, and hydrocortisone have been the most commonly evaluated, some in studies that allowed multiple corticosteroid regimens[26]. For instance, Wu et al.[27], in a single-center cohort study with a limited sample size, demonstrated that the administration of methylprednisolone reduced the risk of death in patients with ARDS (HR, 0.38; 95% CI, 0.20-0.72; p = 0.003). Moreover, Wang et al.[28], in a retrospective cohort study with 46 severe patients, found a benefit in reducing the length of hospitalization and improvement in chest imaging parameters in patients with methylprednisolone treatment (1–2 mg/kg/day for 5–7 days), as well as improvement in the likelihood of receiving mechanical ventilation.

Nevertheless, these two observational studies shared procedural problems beyond their small sample size. For instance, the variety of other drugs (e.g., antivirals and antibiotics) used simultaneously, as well as the inaccurate different dosages and duration of methylprednisolone treatment according to clinical manifestations and laboratory parameters, increased the confounding factors in detecting clinical effects.

Evidence from clinical trials

Further, randomized clinical trials started to investigate corticosteroid regiments in COVID-19 to provide conclusive evidence, as summarized in Table 1. In most studies, corticosteroids have shown important outcomes related to the need for and the duration of mechanical ventilation, length of stay, and case fatality.

For instance, the REMAP-CAP study randomized 384 severe COVID-19 patients to determine whether hydrocortisone improves organ support-free days within 21 days[29]. At a 7-day fixed-dose course (50 mg, every 6 h for 7 days) or shock-dependent dosing, the median organ support-free days have not shown a significant difference compared to placebo[29].Furthermore, the trial was stopped early, and no treatment strategy met the prespecified criteria for statistical superiority[29]. Likewise, another clinical trial found that low-dose hydrocortisone did not significantly reduce the proportion of COVID-19 patients receiving mechanical ventilation on day 21[30].

Regarding methylprednisolone, a small Brazilian randomized, double-blind, phase IIb, placebo-controlled trial found that the mortality rate on day 28 was not different between groups[31]. Additionally, it was observed that patients in the methylprednisolone arm tended to need more insulin therapy, and no difference was seen in virus clearance in respiratory secretion until Day 7[31]. An Iranian randomized controlled trial found that methylprednisolone has better effects than dexamethasone on clinical status and mechanical ventilation dependence for patients hospitalized with Covid-19[32].However, the different dosages (6 mg/day of dexamethasone in a patient with approximately 70 kg versus 2 mg/kg/day of methylprednisolone) make it impossible to state whether the difference observed was due to the mechanism of action of each drug or due to the dosage used. Furthermore, the small sample size (86 hospitalized patients) misleads the detection of clinical effects, which was not performed based on intention to treat[32].

In this scenario, dexamethasone has emerged as a more effective and safer drug for critically ill COVID-19 patients, particularly because of its potent anti-inflammatory action and weak mineralocorticoid effects compared with other corticoids[33,34]. In July 2020, the preliminary results of the Randomized Evaluation of COVID-19 Therapy Study (RECOVERY trial) were published[35]. It was an open-label study that compared the effects of using low doses of dexamethasone (6 mg orally or parenterally) once a day for ten days. The

Table 1 — Summarized data from randomized clinical trials testing corticosteroids in the COVID-19 treatment.

Study	Nr. of patients and treatments	Corticosteroid dose	Study type	Enrolled patients	Results
RECOVERY Collaborative Group et al (2021)[35]	A total of 2104 patients were assigned to receive dexamethasone and 4321 to receive usual care.	6 mg once daily for up to 10 days.	Controlled open-label trial	Hospitalized patients with clinically suspected or laboratory-confirmed SARS-CoV-2 infection	In patients hospitalized with COVID-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support
Tomazini et al (2020)[36]	Of the enrolled patients, 151 were randomly assigned to receive dexamethasone and 148 to the control group.	20 mg of dexamethasone intravenously daily for 5 days, 10 mg of dexamethasone daily for 5 days or until ICU discharge, plus standard care (n =151) or standard care alone (n = 148).	Multicenter, randomized, open-label, clinical trial	Patients were enrolled who were at least 18 years old, had confirmed or suspected COVID-19 infection (eMethods in Supplement 3), and were receiving mechanical ventilation within 48 hours of meeting criteria for moderate to severe ARDS with partial pressure of arterial blood oxygen to fraction of inspired oxygen (Pao2:Fio2) ratio of 200 or less.	Among patients with COVID-19 and moderate or severe ARDS, use of intravenous dexamethasone plus standard care compared with standard care alone resulted in a statistically significant increase in the number of ventilator-free days (days alive and free of mechanical ventilation) over 28 days.
Ranjbar et al (2021)[32]	A total of 46 patients were assigned to receive dexamethasone and 47 to methylprednisolone.	Methylprednisolone, 2 mg/kg/day, for 10 days; Dexamethasone, 6 mg/day, for 10 days.	Prospective triple-blinded randomized controlled trial	Patients over 18 years that were hospitalized in the main teaching hospital of Shiraz University of Medical Sciences with SARS-CoV-2 infection, which was confirmed by real-time PCR.	In hospitalized hypoxic COVID-19 patients, methylprednisolone demonstrated better results compared to dexamethasone
Dequin et al (2020)[30]	A total of 76 patients received low-dose of hydrocortisone and 73 received placebo.	200 mg/d of hydrocortisone until day 7 and then 100 mg/d for 4 days and 50 mg/d for 3 days, for a total of 14 days.	Multicenter randomized double-blind sequential trial	Patients aged at least 18 years admitted to 1 of the 9 participating French ICUs for acute respiratory failure with a biologically confirmed (reverse transcriptase–polymerase chain reaction) or suspected (suggestive chest computed tomography scan result in the absence of any other cause of pneumonia) COVID-19	Low-dose hydrocortisone, compared with placebo, did not significantly reduce treatment failure (defined as death or persistent respiratory support) at day 21. However, the study was stopped early and likely was underpowered to find a statistically and clinically important difference in the primary outcome
Angus et al (2020)[29]	A total of 137 patients received hydrocortisone on 50 mg or 100 mg every 6 hours, 146 received 50 mg of hydrocortisone every 6 hours when shock was clinically evident, and 101 did not receive hydrocortisone.	Hydrocortisone, 50 mg or 100 mg every 6 hours, a shock-dependent course (50 mg every 6 hours when shock was clinically evident), or no hydrocortisone, for 7 days.	Bayesian randomized clinical trial	Patients aged 18 years or older with presumed or confirmed SARS-CoV-2 infection who were admitted to an intensive care unit (ICU) for provision of respiratory or cardiovascular organ support were classified as severe and eligible for enrollment in the COVID-19 corticosteroid domain	Treatment with a 7-day fixed-dose course of hydrocortisone or shock-dependent dosing of hydrocortisone, compared with no hydrocortisone, resulted in 93% and 80% probabilities of superiority, respectively, regarding the odds of improvement in organ support–free days within 21 days. However, the trial was stopped early, and no treatment strategy met prespecified criteria for statistical superiority, precluding definitive conclusions.

Table 1 — Summarized data from randomized clinical trials testing corticosteroids in the COVID-19 treatment (cont.).

Study	Nr. of patients and treatments	Corticosteroid dose	Study type	Enrolled patients	Results
The COVID STEROID 2 Trial Group (2021)[37]	A total of 491 patients received 12mg of dexamethasone, and 480 received 6mg of dexamethasone	12 mg or 6 mg of dexamethasone was suspended in sodium chloride 0.9% and administered as a masked bolus injection (total volume of 5 mL) intravenously once daily for up to 10 days	Randomized trial	Eligible patients were aged 18 years or older, hospitalized with confirmed SARS-CoV-2 infection, and required (1) supplementary oxygen at a flow rate of at least 10 L/min (independent of delivery system), (2) noninvasive ventilation or continuous positive airway pressure for hypoxemia, or (3) invasive mechanical ventilation	Among patients with COVID-19 and severe hypoxemia, 12 mg/d of dexamethasone compared with 6 mg/d of dexamethasone did not result in statistically significantly more days alive without life support at 28 days. However, the trial may have been underpowered to identify a significant difference

primary outcome was the mortality rate on day 28 after randomization. Overall, 482 patients (22.9%) in the dexamethasone group and 1.110 patients (25.7%) in the usual care group died within 28 days of randomization (age-adjusted rate ratio, 0.83; 95% CI 0.75–0.93; p = 0.001)35.However, the mortality rate in the RECOVERY trial was lower compared to the usual care group only among those under mechanical ventilation (29.3% vs. 41.4%; rate of 0.64; 95% CI 0.51–0.81) and among those under supplemental oxygenation (23.3% vs. 26.2%; rate ratio 0.82; 95% CI 0.72–0.94). In contrast, among those who did not receive any respiratory support at the randomization, there was no consistent benefit (17.8% vs. 14.0%; ratio 1.19; 95% CI, 0.91–1.55)[35].

The COVID-19 Dexamethasone randomized clinical trial (CoDEX trial) also found positive results[36]. It was observed that intravenous dexamethasone (in the same dosage of DEXA-ARDS trial) plus standard care, compared to standard care alone, in patients with moderate to severe ARDS due to COVID-19, resulted in a statistically significant increase in the number of ventilator-free days (difference, 2.26; 95% CI, 0.2–4.38; p = 0.04) over 28 days[36]. Notably, the proportion of adverse events did not differ significantly between the dexamethasone group and control group, as also observed in the DEXA-ARDS trial, a critical aspect regarding the safety of this drug[36].

When comparing different dosages of dexamethasone, the COVID STEROID 2 Randomized Trial found that 12 mg versus 6 mg was not statistically different in the number of days alive without life support at 28 days in patients with COVID-19 and severe hypoxemia[37]. Thus, although serious adverse reactions, including septic shock and invasive fungal infections, did not differ between groups, higher doses of dexamethasone did not result in better outcomes[37].

Potential harms of corticotherapy

The RECOVERY trial demonstrated that the most significant benefit in reducing mortality rate using dexamethasone might be restricted to COVID-19 patients receiving respiratory support[35]. This finding, in line with previous assessments[38], served as a warning against the extrapolation of the effect of dexamethasone in COVID-19 patients without respiratory support requirements.

Since the beginning of the COVID-19 pandemic, several scientific publications have alerted the health community about fungal infections in patients with severe forms of this disease, particularly those who require intensive care for prolonged periods. However, interest in discussing this topic has taken on a new dimension with the growth of cases in India, still in early 2021[39-42].

Three comorbidities were highlighted: aspergillosis, mucormycosis, and candidemia. Aspergillosis is an infectious disease caused by fungi of the genus *Aspergillus*, a ubiquitous filamentous fungus frequently found in the environment and with dispersion favored by construction and renovation in general. The main form of acquisition is the inhalation route, transmitted to susceptible hosts, particularly allergic, immunosuppressed (such as neutropenic), or patients with pulmonary cavitary sequelae of tuberculosis through inhalation of conidia (spores) dispersed in the air. Most individuals do not develop *Aspergillus* diseases, despite the daily inhalation of conidia[43,44].

In the case of COVID-19, the association was such that it has been named CAPA (COVID-19 associated pulmonary aspergillosis) and has complicated cases of patients with severe forms of the disease. This scenario is worrisome, as there is a known impact on the mortality of patients affected by severe COVID-19 (52% in patients with CAPA versus 39% in non-CAPA; p = 0.027)[45]. Evidence shows a considerable prevalence of CAPA in critically ill patients with COVID-19 (15%),

where the method of choice for diagnosis appears to significantly impact diagnostic success. Given the severity of the infection and the impact on mortality, directing the best diagnostic method (lower airway sample) and initiating appropriate treatment empirically can help modify the outcome of higher risk of death in this population[45].

Mucormycosis is a rare and severe invasive fungal infection caused by fungi of the order Mucorales. Several species of fungi may be involved in the development of mycosis, and they may vary in terms of virulence, the form of acquisition, and sensitivity to antifungal agents[46-48]. This disease mainly affects patients with diabetes, particularly the decompensated. Immunocompromised patients can also develop mucormycosis, particularly the neutropenic due to hematological neoplasms or hematopoietic stem cell transplants, and those using immunosuppressive medications such insolid organ transplants or with autoimmune diseases[46-48].

Bloodstream infections caused by fungi of the genus Candida have high morbidity and mortality rates, particularly in patients requiring intensive care for prolonged periods, undergoing invasive medical procedures, and/or immunosuppressed[49-51]. Among the risk factors for developing candidemia in patients with COVID-19 are dysbiosis induced by broad-spectrum antibiotics, colonization by Candida spp., use of a central venous catheter, hypoxia or prolonged hypotension, leading to changes in the gastrointestinal barrier, renal failure and hemodialysis, and use of immunosuppressive drugs such as corticosteroids[49-51].

Although these three morbidities have been associated with severe cases of COVID-19, mainly in patients using immunosuppressive drugs, such as corticosteroids, it is essential to note that, in these studies, patients who developed severe forms of COVID-19 often had other conditions that increase the risk for the development of fungal infections: diabetes, chronic lung diseases, advanced age, and often are in a scenario of prolonged hospital stay.

OTHER IMMUNOMODULATORY OPTIONS

Many treatments have been used and approved only in the later stages of the disease when patients are more severe. However, some medications, such as monoclonal neutralizing antibodies (in a single or multimodal regimen), are being widely evaluated for treating COVID-19. They have effectively reduced mortality, hospitalization, length of hospital stay, duration of symptoms, and viral load in different severities of COVID-19[52-56].

However, the benefits described for monoclonal antibodies were similar to those for corticosteroids, such as dexamethasone and methylprednisolone, especially in patients hospitalized with severe COVID-19[32]. For instance, there is also a study indicating the benefit of inhaled budesonide in patients with mild forms of the disease[57]. The findings suggest the evaluation of use, especially at the beginning of the disease, as it is widely available and relatively safe regarding complications[57].

Given the severity and aggressiveness of the pandemic, the possibility of choosing drugs with a good pathophysiological rationale, cheaper and widely available, such as corticosteroids, and with results similar to those of monoclonal antibodies, especially in terms of public health, seems preferable.

CONCLUSION

Corticosteroids have been raised as the most effective treatment for critically ill COVID-19 patients. Most evidence shows that dexamethasone, compared with usual care or placebo, represents the best choice regarding safety and effectiveness. However, we highlight that high doses or long-term use of corticosteroids might be harmful, leading to harmful effects, such as secondary infections, endocrine impairment, and uncontrolled glucose levels. Thus, according to the available evidence, corticosteroid use in COVID-19 treatment should be cautiously reserved for moderate to severe patients, especially those requiring respiratory support.

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