Pneumonia

REVIEW

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The role of corticosteroids in severe viral pneumonia: lessons from COVID-19 and influenza

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Abstract

Background Corticosteroids have long been used as immunomodulatory agents in viral respiratory infections, but their role in influenza and COVID-19 remains controversial. While both diseases share overlapping pathogenic mechanisms involving hyperinflammation and immune dysregulation, clinical evidence suggests divergent outcomes in response to corticosteroid therapy.

Objective This review critically examines the evidence regarding corticosteroid use in influenza and COVID-19, focusing on their impact on mortality, disease progression, and secondary infections.

Methods A narrative review was conducted including randomized controlled trials, meta-analyses, and major observational studies published between 2000 and 2025. Data were analyzed comparatively for influenza (seasonal and pandemic strains) and SARS-CoV-2 infection.

Results In influenza, most studies associate corticosteroid administration—particularly at high doses or prolonged courses—with increased mortality, delayed viral clearance, and higher rates of secondary bacterial pneumonia. Conversely, in COVID-19, randomized trials such as RECOVERY demonstrated that low-to-moderate doses of dexamethasone significantly reduce mortality in patients requiring oxygen or mechanical ventilation, without clear benefit in mild disease. These opposing outcomes highlight the importance of timing, dosing, and patient selection, reflecting distinct immunopathological trajectories between the two infections.

Conclusions Corticosteroid therapy exerts context-dependent effects in viral pneumonia. While detrimental in most cases of influenza, it is beneficial in severe COVID-19 when guided by systemic inflammation. Future strategies should focus on personalized and real-time immune monitoring to tailor immunomodulatory interventions to each patient's inflammatory and virological status.

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Introduction

Corticosteroids, long utilized in critical care, have been frequently administered to critically ill patients, particularly those developing acute respiratory distress syndrome (ARDS) or severe septic shock [1–3]. In severe community-acquired pneumonia (CAP), the use of corticosteroids is theoretically supported by the anti-inflammatory and immunomodulatory properties of glucocorticoids, which may counteract the uncontrolled local and systemic inflammation—often described as a "cytokine storm"—that characterizes severe lung injury. This exaggerated innate immune response involves intense trafficking of macrophages and neutrophils, along with the abundant release of highly cytotoxic mediators and proinflammatory cytokines in the lung parenchyma [4]. Corticosteroids, by inhibiting these proinflammatory mediators, are hypothesized to modulate and reprogram the immune response [5].

The role of corticosteroids in severe CAP has been extensively studied, particularly in bacterial etiologies. Evidence from randomized controlled trials supports their use in selected patients with severe disease and an exaggerated systemic inflammatory response, demonstrating benefits such as reduced time to clinical stability and shorter ICU stays [6–8]. However, when the etiology is viral—especially in influenza or SARS-CoV-2 pneumonia—the role of corticosteroids becomes more complex and pathogen-specific.

Corticosteroids in severe influenza pneumonia

Influenza virus infections, particularly novel or pandemic strains such as H1N1, H7N9, and H5N1, can cause substantial influenza-related critical illness and mortality [7]. Severe manifestations typically include viral pneumonitis and ARDS [7]. Despite standard care options, including neuraminidase inhibitors and admission to intensive care units (ICUs) for supportive treatment, morbidity and mortality remain high [7]. In this context, the efficacy and safety of adjunctive corticosteroid therapy in severe influenza pneumonia remain highly debated, largely due to the lack of well-conducted randomized controlled trials (RCTs). Most available evidence derives from observational studies, which are inherently susceptible to bias. A recent RCT including severe CAP has been published, 658 patients were included and 536 received a fixed 7-days hydrocortisone treatment. Influenza CAP was diagnosed in 81 patients, and 66 received hydrocortisone. No benefit was detected in terms of mortality and secondary outcomes in the hydrocortisone group. However, the low number of included patients with influenza CAP included it does not allow for concrete conclusions to be drawn in this etiological subgroup [8].

During the 2009 A(H1N1)pdm09 pandemic, corticosteroids were widely used, with reported administration rates ranging from 32.7% in a Spanish cohort [7] to 57.3% in a European ICU registry [9]. Commonly administered corticosteroids included methylprednisolone, hydrocortisone, and prednisone, typically given for a median duration of about seven days [7–10].

Association with mortality

Numerous observational studies and meta-analyses have examined the relationship between corticosteroid use and patient outcomes, frequently revealing a concerning association with increased mortality (Table 1).

H1N1:

- A large multicenter Spanish cohort study (2009–2014, 1846 patients) found that crude ICU mortality was higher among patients receiving corticosteroids (27.5% vs. 18.8%). After rigorous propensity score (PS) matching to control for confounders, corticosteroid use remained associated with increased ICU mortality (Hazard Ratio [HR] 1.32; 95% CI 1.08–1.60) [7].
- A French registry analysis of 208 ARDS patients with H1N1pdm09 pneumonia found steroid therapy was associated with increased mortality both in crude analysis (33.7% vs. 16.8%) and after PS-adjusted Cox regression (adjusted HR 2.82; 95% CI 1.5–5.4),

Table 1 Summary of clinical outcomes from principal studies of steroid in influenza pneumonia

Reference	Population	Exposure	Primary outcome / Key finding
Moreno et al. [7]	1846 ICU patients	Corticosteroid use	Increased ICU Mortality (HR 1.32, 95% CI 1.08–1.60)
Brun-Buisson et al. [10]	208 ARDS patients	Early corticosteroid use	Increased Hospital Mortality (aHR 2.82, 95% CI 1.5–5.4, $P = 0.002$) & more acquired pneumonia
Kim et al. [11]	245 ICU patients	Corticosteroid use	Increased 90-day Mortality (aOR 2.20, 95% CI 1.03–4.71) & higher superinfection rate
Tsai et al. [12]	241 ARDS patients	Early corticosteroid use	Increased Hospital Mortality (aOR 5.02, 95% CI 2.39–10.54). Dose and timing dependent effect
Yang et al. [13]	19 Studies	Corticosteroid treatment	Increased Mortality (aHR 1.77, 95% CI 1.40–2.23); Increased Nosocomial Infection (OR 3.16, 95% CI 2.09–4.78); Prolonged IMV/ICU Stay
Delaney et al. [9]	607 ICU patients	Corticosteroid use	Association with mortality disappeared after adjusting for time-dependent confounding (OR 0.96)

ICU: intensive care unit; IMV: invasive mechanical ventilation

particularly when administered early (within three days of mechanical ventilation) [11].

- A South Korean cohort of 245 critically ill patients reported that adjunctive steroid treatment was significantly associated with higher 90-day mortality (58% vs. 27%) [12]. Multivariate and PS-adjusted analyses confirmed steroid therapy as an independent predictor of mortality (adjusted OR 2.20; 95% CI 1.03–4.71) [12].
- A recent Taiwanese multicenter study (2020) focusing on influenza-associated ARDS requiring invasive mechanical ventilation found that early corticosteroid treatment (≥ 200 mg hydrocortisone equivalent within three days) was significantly associated with higher hospital mortality (adjusted OR 5.02; 95% CI 2.39–10.54), with a clear dose–response trend [14].

H5N1 and H7N9: Studies of other severe strains, including H5N1 and H7N9, have similarly reported higher mortality among corticosteroid-treated patients [15, 16].

Among hematopoietic cell transplant (HCT) recipients with seasonal influenza limited to upper respiratory tract disease, high-dose corticosteroids (> 1 mg/kg/day) were associated with prolonged viral shedding but not with worse clinical outcomes such as progression to lower respiratory disease (LRD), hypoxemia, or death [13]. Interestingly, low-to-moderate doses appeared to trend toward a protective effect against LRD, suggesting that corticosteroid impact may vary depending on patient population (immunocompromised vs. general critical illness).

Observational studies face substantial challenges in adjusting for baseline and time-dependent confounders. For instance, a Canadian ICU study of 607 H1N1pdm09 patients demonstrated that while crude mortality was higher in the steroid group (25.5% vs. 16.4%), the association disappeared after accounting for time-dependent variables via marginal structural modeling. Nevertheless, steroid use conferred no clinical benefit [10].

Association with complications and resource utilization

Beyond mortality, corticosteroid use is consistently linked to increased complications and healthcare resource utilization.

- Infections: Meta-analyses have shown a significantly higher risk of nosocomial infections (OR 3.16; 95% CI 2.09–4.78) [17, 18]. The European H1N1 registry found that early corticosteroid therapy doubled the risk of hospital-acquired pneumonia (OR 2.2) [9]. Invasive fungal infections, particularly mucormycosis and aspergillosis, have been recognized as complications associated with viral pneumonia, immune dysfunction, and corticosteroid therapy [9, 12, 19].
- Viral Clearance: Corticosteroid-induced immunosuppression may lead to prolonged viral shedding, delayed clearance, and increased risk of secondary infection and death [20, 21]. In HCT patients, high-dose steroids were associated with delayed viral clearance [13].
- Resource Utilization: Corticosteroid therapy has been associated with fewer ventilator-free days at 28 days (12.5 ± 10.7 vs. 15.7 ± 10.1) [9] and longer ICU stays [11, 21, 22]. Meta-analyses confirm extended mechanical ventilation duration among corticosteroid recipients [17, 18].

Corticosteroids in specific contexts

Chronic Obstructive Pulmonary Disease (COPD): A retrospective analysis of acute decompensated COPD (AECOPD) hospitalizations in Switzerland (2012–2017) found no evidence of worse outcomes among patients with concurrent or confirmed influenza compared to those without. Most AECOPD patients likely received corticosteroids as standard care, suggesting this practice is safe in this subset, possibly because airway obstruction and inflammation—major determinants of disease severity—are effectively reduced by steroids [23].

Drug–Drug Interactions (Oseltamivir): Oseltamivir remains the cornerstone antiviral for severe influenza pneumonia, reducing hospitalization duration and improving outcomes when administered within 48 h of symptom onset [24, 25]. Co-administration of dexamethasone with oseltamivir slightly reduced systemic exposure to oseltamivir carboxylate in healthy volunteers, though this effect was deemed clinically insignificant [26].

Limitations and future directions

Most existing evidence derives from retrospective or prospective observational studies, which are prone to substantial methodological weaknesses—particularly confounding by indication, dosage, timing, and comorbidities [27]. Clinicians often reserve corticosteroids for the most critically ill patients, potentially biasing outcomes against the intervention. Although advanced statistical techniques such as propensity score matching and marginal structural modeling attempt to address these biases, unmeasured confounders remain problematic [10].

Current WHO guidelines advise against routine systemic corticosteroid use in severe or progressive influenza illness, except in specific circumstances such as septic shock requiring vasopressors or suspected adrenal insufficiency [28].

Given the inconsistent findings and low-quality evidence, there is broad consensus on the urgent need for randomized, double-blind, placebo-controlled trials to clarify the efficacy and safety of corticosteroids in severe influenza pneumonia. The ongoing FLUDEX trial in Spain aims to evaluate low-dose dexamethasone (6 mg/day for 7 days) combined with oseltamivir in hospitalized patients with severe influenza [29]. The results of such trials will be critical to refining clinical guidelines regarding timing, dose, and duration of corticosteroid therapy in this population.

Conclusion

Overwhelming observational evidence and meta-analyses indicate that adjunctive corticosteroid therapy in critically ill patients with influenza pneumonia—particularly when administered early or at high doses for ARDS—is associated with increased mortality and infectious complications. While corticosteroids have a strong biological rationale for modulating hyperinflammation, current clinical data do not support their routine use as adjunctive therapy in influenza pneumonia. Clinicians should exercise extreme caution with this intervention, recognizing its potential for harm, pending confirmation from high-quality randomized controlled trials.

Corticosteroids in severe SARS-CoV-2 pneumonia

The outbreak of the COVID-19 pandemic had a major impact worldwide. Most cases were mild or asymptomatic, but up to 10% of patients required hospitalization and oxygen therapy, and many of them presented with severe ARDS and needed respiratory support and ICU admission [30, 31]. The development of ARDS was characterized by an unusual severity and an atypical response to the standard treatment [32]. During the first half of 2020, while health systems around the world were overwhelmed, researchers and healthcare professionals were trying to gather information to understand the pathophysiology of that unknown virus.

The abrupt onset of ARDS and findings such as high levels of circulating cytokines and inflammatory biomarkers, lymphopenia, and mononuclear infiltration of lungs or lymph nodes suggested a macrophage activation syndrome-like condition as the key in COVID-19-induced organ dysfunction [33, 34]. Subsequent investigations ruled out this hypothesis, as interleukin-6 levels were much lower in COVID-19 patients than in other critical illnesses such as bacterial sepsis [35, 36]. Latest evidence suggests a defect in host immunity, with a profound depletion in the number of effector immune cells and severe functional defects in T cell and monocyte function [36] which leads to a poor control of viral replication [37], overregulation of the pro- and anti-inflammatory response, endothelial dysfunction, and organ failure.

Based on the cytokine storm hypothesis, most therapeutic efforts in the first months of 2020 were directed to block proinflammatory cytokines or inhibit the inflammatory signaling cascade using drugs such as corticosteroids. Corticosteroids, given their lipophilicity, cross the host cell membrane and bind to glucocorticoid receptors present in the cell cytoplasm, which initiates a series of immune cell responses that lead to a decrease in gene transcription of pro-inflammatory cytokines IL-1, IL-2, IL-6, IL-8, TNF and IFN-γ, increase the gene expression of the anti-inflammatory cytokine mediator IL-10, and inhibit neutrophil adhesion to endothelial cells and activation of macrophages [38, 39].

Corticosteroids have played a controversial role in viral pneumonia, and many studies have failed to demonstrate a benefit in other diseases closely related to COVID-19, such as severe acute respiratory syndrome (SARS-CoV-1) or Middle East respiratory syndrome (MERS), where corticosteroid treatment even decreased viral RNA clearance [40, 41]. With the difficulties added by the pandemic, most studies in COVID-19 did not define standard treatment protocols or homogeneous criteria for the selection of patients. Moreover, most of the studies focused on mortality and did not report data on analytical, microbiological, or respiratory evolution. First reports from China between January and March 2020 found no differences in the incidence of clinical deterioration, cure rate, ICU admission, hospitalization duration, and in-hospital mortality with the adjuvant corticosteroid treatment [42].

The RECOVERY trial marked a turning point in recommendations regarding the use of corticosteroids in critically ill COVID-19 patients [43]. This controlled, open-label trial was conducted in the United Kingdom from March 19 to June 8, 2020. 2,104 patients who were hospitalized with COVID-19 were randomized to receive dexamethasone 6 mg/d for 10 days, and 4,321 patients were randomized to receive usual care (8% of them received dexamethasone as part of their clinical care). Mortality at 28 days was significantly lower in the dexamethasone group (22.9% vs. 25.7%; rate ratio, 0.83; 95% CI, 0.75 to 0.93; $p < 0.001$). There was a trend showing the greatest benefit among patients undergoing invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81). Among the patients who were not receiving invasive mechanical ventilation at randomization, the number of patients who finally required invasive mechanical ventilation or died was lower in the dexamethasone group (risk ratio, 0.92; 95% CI, 0.84 to 1.01).

Due to these results, some ongoing studies were prematurely terminated, some of them with confusing [44] or unfavorable results [45, 46]. The use of systemic corticosteroids for patients with severe or critical COVID-19

Table 2 Summary of clinical outcomes from principal studies

Reference	Population	Exposure	Primary outcome / Key finding
Recovery Study [42]	6,425 patients (1,007 undergoing IMV)	Dexamethasone 10 days vs. usual care (8% dexamethasone)	Mortality at 28 days significantly lower in the dexamethasone group, greatest benefit among patients undergoing IMV
CODEX trial [44]	299 ICU patients	Dexamethasone 10 days vs. standard	Interrupted due to RECOVERY trial. More days alive and free from IMV in the dexamethasone group. No significant differences in all-cause mortality at 28 days or adverse events.
CAPE COVID trial [45]	149 ICU patients	Hydrocortisone 14 days vs. placebo	Interrupted due to RECOVERY trial. No differences in mortality or dependency on mechanical ventilation or high-flow oxygen on day 21
Søvik et al. [49]	155 patients undergoing IMV	Dexamethasone or methylprednisolone vs. standard	More superinfections and lower 90-day survival rates in dexamethasone group

ICU: intensive care unit; IMV: invasive mechanical ventilation

has become a standard of use [31, 47, 48]. Nowadays it is difficult to design new randomized studies to expand current knowledge about the selection of patients, the proper timing of initiation, the optimal dose and duration, or the effect of corticosteroids on immune response and viral load. Table 2 summarizes clinical outcomes from principal studies.

Some lessons can be drawn from the existing scientific evidence:

Not for all patients

In the RECOVERY trial, no differences in mortality were found among those patients who were receiving no respiratory support at randomization (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55) [43]. Similar results were found by an observational study through medical record analysis of 1,461 patients in a single hospital in the USA between March 1 and March 31, 2020. 42.1% received corticosteroids, but the risk of death was not reduced in patients on high-flow (HR 0.46, 95% CI 0.20–1.07; p = 0.07) or other oxygen therapy (HR 0.84, 95% CI 0.35–2.00; p = 0.69) [50].

Moreover, some studies have found an increased risk of death among patients who do not require respiratory support at the time of starting corticosteroid treatment. A prospective cohort study with 67,348 hospitalized acute COVID-19 patients at 438 hospitals was conducted during 2020–2021 in Japan. Intravenous pulse therapy with a daily dose of 500–1,000 mg of methylprednisolone was administered to 2,244 (3.3%) patients, out of which 1,814 did not receive invasive mechanical ventilation. The risk of in-hospital mortality increased among these patients (HR 3.38; 95% CI 3.02–3.79) [51]. Another single-center, randomized clinical trial conducted in Oklahoma, United States, between January 2021 and December 2021 found similar results. 107 patients were enrolled to receive low or high dose of steroids, 52 patients were randomized to the high-dose dexamethasone group (20 mg daily for five days, followed by 10 mg daily for five days). For participants without invasive mechanical ventilation, high-dose dexamethasone was associated with higher mortality due to severe ARDS and septic shock (three patients), severe ARDS without septic shock (two patients), and cardiac arrest possibly due to massive pulmonary embolism (one patient) [52].

Some authors have tried to identify an inflammatory profile that could benefit from corticosteroid treatment. An observational study conducted in New York between March 11, 2020, and April 13, 2020, found a significantly increased risk of mortality or mechanical ventilation among patients with C-reactive protein < 10 mg/dL who received glucocorticoids within 48 h of admission (OR, 2.64; 95% CI, 1.39–5.03) [53]. Conversely, Chen et al. achieved different results in a retrospective cohort study in Wuhan, China, between January 2020 and February 2020. A total of 428 critically ill patients with COVID-19 were included in the final analysis, 65.4% received corticosteroid therapy while hospitalized. 223 patients (52.1%) were classified as having a hypoinflammatory phenotype, mainly based on three variables: TNF-α, D-dimer, and neutrophil-to-lymphocyte ratio (NLR), with an optimal cutoff of 10.1 pg/mL, 2.0 mg/mL, 6.9, respectively. The association between corticosteroid therapy and 28-day mortality was insignificant in these patients (HR, 1.15; 95% CI, 0.45–2.94; P = 0.76) [53]. Similarly, other authors have defined phenotypes derived by clustering analysis and demonstrated that the use of corticosteroids in patients with the lowest inflammatory levels was not associated with ICU mortality or even was associated with worse 90-day survival [54–58].

Not in early stages

If corticosteroids are administered in the first days after the onset of symptoms, they can coincide with the peak of viral excretion and disrupt the control of viral replication [37, 46]. In the RECOVERY trial, patients with a longer duration of symptoms (more than 7 days) had a greater mortality benefit in response to treatment with dexamethasone [43]. Similar results were obtained by an observational study through medical record analysis of 1,461 patients in a single hospital in the USA. 42.1%

received corticosteroids, there was a mortality benefit in patients with more than 7 days of symptom onset to initiation of corticosteroids (HR 0.56, 95% CI 0.33–0.95; p = 0.03). Patients receiving the first dose of corticosteroids after more than 72 h of hospitalization had a lower risk of death compared to patients with the first dose at earlier time intervals (HR 0.56, 95% CI 0.38–0.82; p = 0.003) [50].

Higher doses are not better

Some clinical trials have found a benefit on decreased clinical worsening [59] or successful discontinuation from mechanical ventilation [60] with higher doses of dexamethasone (16–20 mg/day for five days followed by 8–10 mg/day for an additional five days), but no differences on survival were found [61]. Another open-labeled randomized controlled trial comparing methylprednisolone 250 mg/day and dexamethasone 20 mg/day over the first three days, followed by dexamethasone 20 mg/day on days 4–5, and 10 mg/day on days 6–10, also found no differences in clinical status, in-hospital mortality, length of hospitalization, and rate of ICU transfer [62]. Moreover, some authors have found a significantly increased risk of 28-day death with higher dose of corticosteroids in patients receiving no oxygen or simple oxygen only (19% vs. 12%; rate ratio 1·59 [95% CI 1·20–2·10]; p = 0·0012) [63], or even more adverse events, with an excess of non-COVID pneumonia (10% vs. 6%; absolute difference 3·7% [95% CI 0·7–6·6]) and hyperglycaemia requiring increased insulin dose (22% vs. 14%; absolute difference 7·4% [95% CI 3·2–11·5]) [63].

A longer duration is not better

Ssentongo et al. conducted a systematic review and meta-analysis of 27 eligible studies consisting of 13,404 hospitalized COVID-19 patients from December 2019 to 9 March 2022. Pooled analysis of 18 studies showed the greatest survival benefit for a treatment duration up to 6 days (RR, 0.54 [95% CI, 0.39–0.74]). Survival benefit was 0.65 (95% CI, 0.51–0.83) up to 7 days, and no additional survival benefit was observed beyond 7 days of treatment (RR, 0.64 [95% CI, 0.44–0.93]) [64].

Viral kinetics and RNA clearance

A prospective cohort study across 23 hospitals in Spain between March 16, 2020, and Feb 27, 2021, showed that viral nucleocapsid region 1 (N1) RNA load measured in the first 48 h following ICU admission was a predictor of 90-day all-cause mortality. Patients with the highest N1 RNA load had also the highest concentrations of C-reactive protein in plasma and the lowest concentrations of both anti-SARS-CoV-2 S IgG and IgM antibodies and their profile of biomarkers denoted the existence of a wide dysregulation of the host response to the infection, involving activation of inflammation, chemotaxis, neutrophil degranulation and antiviral response, immunosuppression, endothelial dysfunction, and tissue damage [37].

However, data about the effect of corticosteroids on SARS-CoV-2 clearance are inconclusive. A retrospective study in Wuhan, China, from January 14 to February 9, 2020, showed no significantly association with delay in COVID-19 pneumonia negative transformation of nucleic acid in 86/104 patients receiving glucocorticoid treatment (median duration, 18 days [IQR,15 – 23] vs. 20 days [IQR,18 – 23], p = 0.55) [65]. Similarly, a parallel, double-blind, placebo-controlled, randomized, phase IIb clinical trial in a single Brazilian center from April 18 to June 16, 2020, found no differences in virus clearance in respiratory secretion until day 7 in 194/393 patients randomized to receive intravenous methylprednisolone (0,5 mg/kg twice daily for 5 days) [49].

Van Passen et al. conducted a systematic literature search of randomized controlled trials and observational studies on adult patients from late December 2019 until August 20, 2020. In 9 studies, viral clearance (defined as two consecutive negative RT-PCR on nasopharyngeal swabs, or a cycle time value of 40 or more) was reported, data were too heterogeneous but viral shedding seemed to be delayed in the corticosteroid group (10–29 days vs. 8–24 days) [66]. Another prospective, multicenter, single-blind, randomized, clinical control trial conducted in China from February 14, 2020 to March 31, 2020, with 86 patients randomized, 43 of them to the methylprednisolone group (1 mg/kg/d for 7 days), found that the median time from randomization to virus shedding (defined as negative result of the nucleic acid tests from throat swabs for 2 consecutive times) was significantly longer in the methylprednisolone group (11 days vs. 8 days; hazard ratio, 1.782 [1.057–3.003]; p = 0.030) [67].

Reported incidence of adverse events

Søvik et al. reported data from a multicentre, observational, retrospective study conducted in Norway from March 1 st 2020 until January 31 st 2021. A total of 155 patients requiring invasive mechanical ventilation were included, 72 of them received dexamethasone 6 mg/d or equivalent dose of methylprednisolone (9 patients) for a median of 11 days (interquartile range 8–16). In 43% of patients a total of 90 superinfections were detected, 8 fungal infections, 3 Pneumocystis jirovecii pneumonia and 2 reactivations of HSV and CMV, more frequent in patients in the corticosteroid group (61% vs. 28%; p < 0.001) [68]. Moreno et al. also reported a higher development of ventilator associated pneumonia among patients with the highest inflammatory levels (phenotype "C") receiving corticosteroids (20.4% vs. 14.6%, p = 0.04) [55]. Mucormycosis cases among COVID-19 patients

receiving corticosteroids have also been described, mainly in patients with diabetes [69].

Apart from these studies, serious adverse events are not more frequent in COVID-19 patients with corticosteroid treatment. In the RECOVERY trial, an excess of non-COVID pneumonia (10% vs. 6%; absolute difference 3·7% [95% CI 0·7–6·6]) and hyperglycaemia requiring increased insulin dose (22% vs. 14%; absolute difference 7·4% [95% CI 3·2–11·5]) was seen in the higher dose corticosteroids group [63]. In the REMAP-CAP trial, two (1.5%) serious adverse events were reported in the fixed-dose hydrocortisone group: severe neuromyopathy and fungemia [44]. In another multicenter, randomized, open-label, clinical trial conducted in Argentina, 100 patients were included and 49 received high-dose dexamethasone (16 mg/d for five days and 8 mg/d for additional five days), no differences in adverse events (infections, hyperglycaemia, muscle strength or delirium) were observed [60]. In general, the incidence of adverse events was low and similar in frequency [52] and no differences in adverse events (hyperglycemia, ventilator-associated pneumonia) were found [62, 67]. Moreover, an observational cohort study 1 year after admission conducted in Spain analyzed 76 patients, 32 received corticosteroids. Most specific symptoms related to COVID-19 were less frequent in the group that received corticosteroids, with statistically significant differences for headache, dysphagia, chest pain, and depression [70].

Conclusion

Corticosteroids are nowadays a standard of care in severe or critical COVID-19 pneumonia. Patients not receiving invasive mechanical ventilation or with a lowest inflammatory profile may no benefit from this treatment. Patients with a longer duration of symptoms (more than 7 days) or receiving the first dose of corticosteroids more than 72 h into hospitalization have a greatear mortality benefit. Studies in other viral pneumonia (influenza, MERS, SARS-COV-1) have failed to demonstrate a benefit on the use of corticosteroids. About why this should be different for SARS-CoV-2, several authors hypothesize that the peak of viral excretion occurs earlier in COVID-19 and that clinical worsening may be related to the deregulation of the pulmonary inflammatory response, with active viral replication playing a secondary role. As studies about RNA load and SARS-CoV-2 clearance are inconclusive, this hypothesis remains to be proven.

Other viruses

The utilization of systemic corticosteroids for viral pneumonia caused by pathogens other than COVID-19 or influenza remains highly debated and largely unsupported by definitive outcome data from rigorous randomized controlled trials. Glucocorticoids were widely employed as adjuvant therapy during severe coronavirus outbreaks, such as SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome) [71]. However, observational studies correlated steroid use with detrimental effects, including decreased cellular immunity (CD4, CD8, and CD3 reduction), increased secondary infections, prolonged viral shedding, and increased 30-day mortality [72, 73]. Regarding common pediatric respiratory viruses, acute viral bronchiolitis (often caused by Respiratory Syncytial Virus [RSV], Adenovirus, or Metapneumovirus) lacks evidence supporting the use of systemic or inhaled glucocorticoids alone for improving primary outcomes such as hospital admissions or length of stay in infants and young children [74]. In hospitalized adults with RSV-related illness, steroid treatment was associated with a statistically significant longer duration of wheezing and dyspnea, although ICU admission and mortality rates were not statistically different compared to untreated patients [75]. Caution regarding steroid use extends to severe infections caused by paramyxoviruses in immunocompromised patients [76]. Similarly, severe Adenovirus pneumonia complicated by Acute Respiratory Distress Syndrome (ARDS) in immunocompetent adults has seen reported use of pulse methylprednisolone therapy, but clinical deterioration and persistent high viral loads have also been observed despite this intervention [77].

Conclusion

The divergent effects of corticosteroids in influenza and SARS-CoV-2 pneumonia could hypothetically be explained by differences in viral pathogenesis and host immune dynamics. In influenza, viral replication peaks early, accompanied by a rapid and essential type I interferon response that limits viral spread. Corticosteroid administration during this phase blunts the antiviral immune response, could delay viral clearance, and predispose to secondary bacterial infections [78]. Conversely, severe SARS-CoV-2 pneumonia is characterized by a delayed interferon response followed by a prolonged hyperinflammatory phase marked by cytokine dysregulation, endothelial injury, and diffuse alveolar damage [79]. In this context, corticosteroids could mitigate the exaggerated immune response without significantly impairing viral control. Thus, while corticosteroids exacerbate disease severity in influenza by suppressing early antiviral defense, they improve outcomes in COVID-19 by attenuating late, dysregulated inflammation.

In any case, a personalized and real-time approach that evaluates both the inflammatory and immune status, together with the direct viral effects, is more likely to enable tailored immunomodulation according to each patient's needs at any given time.

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