

Efficacy of glucocorticoids versus placebo on mortality in patients with community-acquired pneumonia: systematic review

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Abstract

The use of glucocorticoids (GCS) in acute respiratory distress syndrome is well documented; however, their use in community-acquired pneumonia (CAP) is controversial, and their impact on mortality is not well defined. The objective is evaluating the efficacy of GCS use compared to placebo in patients with CAP through a systematic review. A systematic review of the literature was conducted in databases such as PubMed, Scopus, and Web of Science for randomized clinical trials published between 2019 and 2024. Articles were classified according to the level of evidence by the Oxford Center for Evidence-Based Medicine. In the results, seven original articles were included, all of which were randomized clinical trials. The studies included a total of 2847 participants, evaluating outcomes such as mortality, days of mechanical ventilation use, length of hospital stay, need for vasopressor use, development of shock, and ARDS. The use of hydrocortisone showed a significant benefit in reducing mortality at 28 days and the need for mechanical ventilation and vasopressors. In contrast, the use of dexamethasone and methylprednisolone did not show significant differences compared to placebo.

Keywords: Corticosteroids. Pneumonia. Mortality. Placebo. Systematic review.

Introduction

Community-acquired pneumonia (CAP) is defined as acute lung infection involving the alveoli that occurs in a patient with no recent exposure to healthcare¹. In Latin America (Argentina, Brazil, Chile, Colombia, Mexico, and Venezuela), an incidence ranging from 32.6 to 80.4/10,000 person-years is reported in a population over 50 years of age².

CAP-related mortality remains a major concern, especially for the elderly and in patients admitted to the intensive care unit (ICU)³. Since the first identification in Wuhan, China, in December 2019, more than 20 million COVID-19 cases and 750,000 deaths had

been reported worldwide as of August 2020. One class of agents that has received considerable attention is corticosteroids or also called glucocorticoids (GCS)⁴.

Randomized clinical trials over several decades have compared the safety and efficacy of different corticosteroids (hydrocortisone, methylprednisolone, and dexamethasone) in the treatment of patients with CAP and have shown a trend of better results with corticosteroid administration. Despite the encouraging results, the use of these drugs remains controversial as current guidelines present different recommendations⁵.

Overall, discrepancies regarding the benefit of corticosteroids on mortality in patients with CAP are perhaps

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due to the heterogeneity found within the populations studied. Corticosteroids may only work in select groups of patients, such as those with a high systemic inflammatory response⁶.

Therefore, it is important to continue investigating its effects through the analysis of randomized clinical trials, outside the spectrum of acute respiratory distress syndrome type 2 and septic shock, to evaluate its possible implications for outcomes such as mortality, days of hospital stay, need for use of mechanical ventilation, admission to the ICU, and prevention of the development of septic shock and ARDS.

Objective

The objective of this study was to assess the efficacy of GCS use compared to placebo in patients with CAP through a systematic review of clinical trials.

Methods

This systematic review was integrated by searching PubMed, Scopus and Web of Science for randomized trial published between 2019 and 2024, up to October 6, 2024, with the adaptation of the descriptors (DeCS/MeSH) (Corticosteroids OR steroids OR GCS OR Prednisone OR methylprednisolone) AND (Pneumonia OR respiratory infection OR CAP OR lung infection) AND (Mortality OR survival OR clinical outcomes) AND (Placebo OR control) AND (severe OR critical) AND (adults OR ≥ 18 years) AND (randomized controlled trials OR RCT). Mediante el seguimiento de las directrices del modelo PRISMA 2020⁷.

Inclusion criteria

Clinical trials were selected that met the following characteristics: (1) patients over 18 years of age diagnosed with moderate-to-severe CAP, (2) presence of use of 1 or more GCS (including hydrocortisone, prednisone, dexamethasone, and methylprednisolone) compared to placebo or another steroid, (3) studies published in English, and (4) studies reporting clinical outcomes (mortality, days of mechanical ventilation use, days of hospital stay, need for vasopressor use, development of shock, and ARDS).

Exclusion criteria

Articles were excluded where it will be observed: (1) duplicate populations, (2) studies that do not report

numbers or that do not allow data extraction, (3) patients with mild pneumonia, (4) patients with underlying lung disease (COPD, asthma, cystic fibrosis, tuberculosis, etc.), (5) hospitalizations before 90 days, (6) patients with septic shock, (7) known malignancy, and (8) presence of respiratory distress syndrome.

Research question

The PICO system used was patients with moderate-to-severe CAP, with the intervention of GCS use compared to placebo and its results in mortality. The research question was; What is the effect of GCS use compared to placebo on mortality and complications?

Data extraction

A standardized form was designed for the extraction of relevant data from the selected studies. Data extracted included participant characteristics, interventions, clinical outcomes, and mortality outcomes. Data extraction was performed by two independent review authors, and any discrepancies were resolved by consensus.

Risks of bias

We assessed the quality of the included studies using the Cochrane tool for assessing risk of bias in randomized clinical trials. Aspects such as randomization, concealment of assignment, blinding, data integrity, and declaration of conflicts of interest were considered.

Results

From the search in PubMed, Scopus, and Web of science, with the search matrix presented in the methodology, 573 articles were collected, of which 242 articles were preliminarily subtracted by automation methods by date and type of article, which later through the reading of the title and abstract ten randomized clinical trials were selected for 100% reading. Of these, once read, seven articles were selected from the initial 10, 3 being excluded due to the presence of duplicates and the initial presence of the population with ARDS (Fig. 1).

This review included seven randomized clinical trials totaling 2847 patients with CAP, in which the presence of clinical outcomes such as mortality, days of hospital

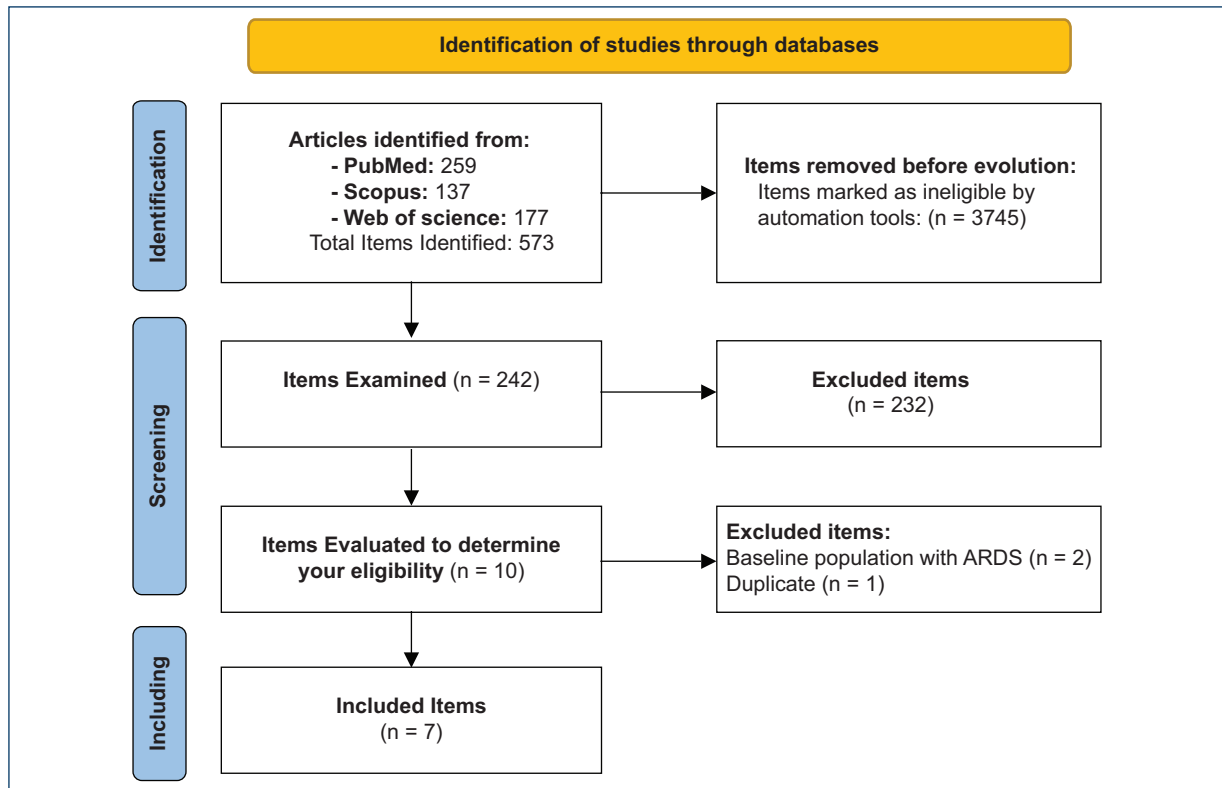


Figure 1. PRISMA diagram. In which the initial identification is shown by the search matrix, then the elimination by automation methods, year, and type of article. In the screening, articles were selected and eliminated by reading titles and abstracts of these selected 3 were excluded for not meeting the research criteria, where finally seven articles were selected to be included in this review.

stays, admission to the ICU, need for invasive or non-invasive mechanical ventilation, use of vasopressors, as well as development of ARDS and septic shock (Table 1).

Analysis of the data revealed that the use of hydrocortisone showed a significant benefit in reducing mortality at 28 days compared to placebo. In one specific study, mortality was observed to be 6.2% in the hydrocortisone-treated group (200 mg IV every 24 h for 7 days) versus 11.9% in the placebo group, with an absolute difference of -5.6% (95% CI -9.6 – -1.7 ; $p = 0.006$). In turn, of the 442 patients who did not require mechanical ventilation at the beginning, 18% of the hydrocortisone group were intubated, while 29.5% of the control group were intubated with an OR of 0.59; 95% CI (0.40-0.86) and of the 703 patients who did not receive vasopressors, the cumulative incidence of initial vasopressor was 15.3% in the hydrocortisone group while 25% in the placebo group with OR 0.59 with 95% CI (0.43-0.82)⁸.

In terms of days of hospital stay, the results were mixed. Some studies suggested a trend towards a reduction in length of stay in the GCS group. In the Wittermans et al., the dexamethasone group had a mean hospital stay of (4.5 days, 95% CI 4.0-5.0 days) while in the placebo group, it was (5.0 [95% CI 4.6-5.4 days). The OR at discharge was (1.14 [95% CI: 0.93-1.39]) for all patients, in turn the study Tang et al. The use of methylprednisolone in-hospital stay was 17 days in participants in the methylprednisolone group and 13 days in the control group OR 1.3 95% CI (0.844-2.022) $p = 0.235$. No significant differences were found in both study groups^{9,10}.

The incidence of ARDS and the need for vasopressors due to septic shock was also evaluated. Methylprednisolone in the Meduri et al. did not show a significant reduction in the incidence of these adverse events in the GCS group compared to placebo, the need for vasopressor uses, and development of shock in the methylprednisolone group was present in 5% (n = 13) while in the placebo group, 4% (n = 3) with

Table 1. Studies included in the review

Title, author, and level of evidence	Population	Intervention	Results
<p>Title: Adjunctive treatment with oral dexamethasone in non-uci patient hospitalised with community acquired pneumonia: randomised clinical trial Author: Wittermans Esther Level of evidence: 2b</p>	<p>Total population 401 patients were randomized; dexamethasone group (n = 203) and placebo (n = 198)</p>	<p>Receive 6 mg of dexamethasone or placebo once daily for 4 days</p>	<p>Primary outcome: hospital stay was shorter in the dexamethasone group (4.5 days, 95% CI 4.0-5.0 days) than in the placebo group (5.0 (95% CI 4.6-5.4 days). The OR at discharge was (1.14 [95% CI 0.93-1.39]) for all patients, while 1.19 (95% CI 0.92-1.54) was 1.19 (95% CI 0.92-1.54) in the mild pneumonia group and 1.06 (95% CI 0.76-1.48) in the severe pneumonia group Secondary result: ICU admission had a lower ratio in the dexamethasone group (n = 5) compared to placebo (n = 14), with an OR 0.64 95% CI (0.22-1.87) p = 0.41. Respiratory failure is the most common cause of admission to the ICU There were no differences in mortality at 30 days between the two groups (dexamethasone group [n = 3], while in the placebo group [n = 5] with an OR of 0.62, 95% CI (0.15-2.29), p = 0.49</p>
<p>Title: Early use of corticosteroid may prolong SARS-CoV-2 shedding in non-intensive care unit patients with COVID-19 pneumonia: a multicenter, single-blind, randomized control trial Author: Xiao Tang Level of evidence: 2b</p>	<p>Total population of 86 patients were randomized; methylprednisolone group (n = 43) and placebo (n = 43)</p>	<p>The methylprednisolone group received 1 mg/kg body weight per day diluted in 100 mL of 0.9% saline administered once daily for 7 days, while in the control group only 100 mL of 0.9% saline solution was administered</p>	<p>Primary outcome: clinical deterioration within 14 days after randomization was 4 participants in the methylprednisolone group, while 2 in the control group with OR 1 95% CI (0.134-7.442), p = 1 Secondary outcomes: admission to the ICU was 2 participants in the methylprednisolone group and 2 in the control group with OR 1 95% CI (0.134-7.442) p = 1 Mortality was 0 participants in the methylprednisolone group and 1 in the control group OR 0.977 95% CI (0.93-1.02) p = 0.314 In-hospital length of stay was 17 participants in the methylprednisolone group and 13 in the control group OR 1.3 IC 95% (0.844-2.022) p = 0.235</p>
<p>Title: Effect of EARLY administration of dexamethasone in patients with COVID-19 pneumonia without acute hypoxemic respiratory failure and risk of development of acute respiratory distress syndrome: (EARLY-DEX COVID-19 trial) Author: Franco-Moreno Anabel Level of evidence: 2b</p>	<p>Total population of 126 patients; dexamethasone group (n = 58) and control group (n = 68)</p>	<p>Receive dexamethasone 6 mg intravenously 1 time daily for 7 days, while the group controlled only the standard management established by COVID-19 management guidelines</p>	<p>Primary outcome: patients in the control group developed ARDS in 14.7% while 17.2% in the dexamethasone group developed SRDA, with no significant differences, p = 0.8 Secondary outcomes: use of non-invasive or invasive mechanical ventilation occurred in 2.9% (n = 2) of the control group, while in 9.6% (n = 4) of the intervention group, with no significant differences, p = 0.71 Admission to the ICU occurred in 0% of patients in the control group and in 1.6% (n = 1) of patients in the experimental group, with no significant differences, p = 0.45 Days of hospital stay were 6.6 days in the control group, while in the experimental group 6.4 days with no significant differences, p = 0.89</p>

(Continues)

Table 1. Studies included in the review (*continued*)

Title, author, and level of evidence	Population	Intervention	Results
Title: Adjunct prednisone in community-acquired pneumonia: 180-day outcome of multicenter, double-blind, randomized. Placebo-controlled trial (STEP trial) Author: Blum Claudine A. Level of evidence: 2b	Total population of 727 patients; prednisone group (n = 361) and Control group (n = 366)	To receive 50 mg of prednisone every 24 h for 7 days versus placebo to assess mortality at 180 days	Primary outcome: no significant differences were found in all-cause mortality at 180 days with OR 1.15 (95 CI [0.68-1.95]) p = 0.601 Secondary outcomes: the presence of pneumonia recurrence in the prednisone group with significant differences OR 2.57 (95% CI [1.29-5.12]) p = 0.007
Title: Effect of intravenous pulses of methylprednisolone 250 mg versus dexamethason 6 mg in hospital adults with severe COVID-19 pneumonia: an open-label randomized trial Author: Corral-Gudino Luis Level of evidence: 2b	Total population of 128 patients; dexamethasone group (n = 64) and methylprednisolone group (n = 64)	Receive dexamethasone 6 mg intravenously 1 time a day for 10 days or methylprednisolone 250 mg 1 time a day for 3 days	Primary outcome: mortality at 28 days occurred in 5% (n = 3) of the methylprednisolone group, as well as in the dexamethasone group with an OR of 1 95% CI (0.2-5.1) p = 0.984 Secondary outcomes: admission to the ICU occurred in 16% (n = 10) of the methylprednisolone group, while the dexamethasone group occurred in 15% (n = 9) with an OR of 1.1 95% CI (0.4-3.0) p = 0.833 Use of non-invasive mechanical ventilation was present in 5% (n = 3), while in the dexamethasone group it was present in 3% (n = 2) with an OR of 1.5 95% (0.2-9.3) p = 0.661 The need for orotracheal intubation occurred in 13% (n = 8) of the methylprednisolone group, while in 12% (n = 7) of the dexamethasone group with an OR of 1.1 95% CI (0.4-3.0) p = 0.809
Title: Hydrocortisone in severe community-acquired pneumonia Author: Dequin PF Level of evidence: 2b	Total population of 795 patients, the hydrocortisone group was made up of 400 patients while the control group was made up of 395	Receive hydrocortisone 200 mg 1 time daily for 4-7 days, followed by tapering for a total of 8-14 days or receive placebo	Primary outcome: mortality at 28 days occurred in 25 of 400 patients (6.2% with 95% CI 3.9-8.6) in the hydrocortisone group and in 47 of 395 patients (11.9%; 95% CI 8.7-15.1) in the placebo group with an absolute difference of -5.6%, CI -9.6--1.7; p = 0.006 Secondary result: mortality at 90 days occurred in 9.3% of patients in the hydrocortisone group, while in the control group it occurred in 14.7% with an absolute percentage difference of -5.4 with 95% CI -9.9--0.8 Of the 442 patients who did not require mechanical ventilation at the beginning, 18% of the hydrocortisone group were intubated, while 29.5% of the control group had an OR of 0.59; 95% CI (0.40-0.86) Of the 703 patients who did not receive vasopressors, the cumulative incidence of initial vasopressor was 15.3% in the hydrocortisone group while 25% in the placebo group with OR 0.59 with 95% CI (0.43-0.82)

(Continues)

Table 1. Studies included in the review (*continued*)

Title, author, and level of evidence	Population	Intervention	Results
<p>Title: Low-dose methylprednisolone treatment in critically ill patients with severe community-acquired pneumonia Author: Meduri G. Umberto Level of evidence: 2b</p>	<p>Total population of 584 patients, the methylprednisolone group was made up of 297 patients while the control group was made up of 287</p>	<p>Receive an intravenous loading bolus of 40 mg methylprednisolone followed by 40 mg every 24 h for 7 days and a progressive reduction over the 20-day course of treatment</p>	<p>Primary outcome: mortality at 60 days from any cause occurred in 16% (n = 47) of the methylprednisolone group, while in 18% (n = 50) of the placebo group, with no significant differences with OR 0.89 95% CI (0.58-1.38) p = 0.61 Secondary result: the need for vasopressor and the development of shock in the methylprednisolone group was present in 5% (n = 13), while in the placebo group 4% (n = 3) with no significant differences, with OR 1.08, 95% CI (0.48-2.4), p = 1.00 Development of SRDA in the methylprednisolone group occurred in 4% (n = 10), while in the placebo group 3% (n = 8) with no significant differences, with OR 1.14, 95% CI (0.44-2.94), p = 1.00</p>

no significant differences with OR 1.08 95% CI (0.48-2.4) p = 1.00. While the development of SRDA in the methylprednisolone group was present in 4% (n = 10), while in the placebo group, 3% (n = 8) with no significant differences, with OR 1.14, 95% CI (0.44-2.94), p = 1.00¹¹. Dexamethasone, on the other hand, in the Moreno et al. study, the control group developed ARDS in 14.7%, while 17.2% of the dexamethasone group developed SRDA, with no significant differences, p = 0.8¹².

A heterogeneity analysis was performed between the included studies. The I² statistic was used to assess the variability between the results of the different trials. Heterogeneity was moderate, suggesting that although the studies presented consistent results overall, there were differences in the population studied and in treatment protocols that could influence the results.

Despite the positive findings associated with the use of hydrocortisone, several limitations should be considered. The methodological quality of the included studies was generally high, but variability in study designs and patient characteristics may have influenced the results. In addition, the lack of data on long-term effects and variability in GCS dosing between studies limit the generalizability of the findings.

Discussion

The findings suggest a possible benefit of hydrocortisone use in patients with severe CAP. Importantly, the heterogeneity of the inflammatory response in different

subgroups of patients with CAP may influence the response to GCS treatment, underscoring the need to identify biomarkers that can predict individual response.

Nie et al.¹³ conducted a meta-analysis that included RCTs that used corticosteroids as adjuvant treatment in populations with CAP from 1956 to 2011. Demonstrating that the use of corticosteroids was associated with better survival in patients with severe CAP, supported by Confalonieri et al.¹⁴ who conducted a meta-analysis which included trials with severe and non-severe CAP, observing a decrease in mortality in favor of steroids in patients with severe CAP.

Emerging evidence of GCS use in COVID-19 patients, such as the RECOVERY trial, has demonstrated efficacy in reducing mortality and the need for mechanical ventilation. These results are consistent with our finding that hydrocortisone can significantly improve clinical outcomes in patients with CAP. The mechanisms underlying these beneficial effects could be related to the inhibition of the production of proinflammatory cytokines and the stabilization of lysosomal membranes¹⁵.

Several randomized controlled clinical trials have investigated the benefits of adjuvant corticosteroids on mortality in patients with severe CAP, but the results have been inconclusive. For example, trials, such as Extended Stereoid in Use in CAP and Santeon-CAP (Dexamethasone in CAP), describe that the use of methylprednisolone and dexamethasone did not improve mortality in severe CAP. However, the CAPE COD (CAP: Evaluation of corticosteroid) trial showed

that hydrocortisone reduces mortality in patients with CAP admitted to the ICU¹⁶.

In patients with ARDS, a survival benefit may be associated with early corticosteroid use. Nevertheless, these patients constitute a heterogeneous group of underlying diagnoses with significant disease severity, and no direct extrapolation can be made to patients with CAP¹⁷.

Pitre et al. conducted a systematic review and meta-analysis of the use of corticosteroids in bacterial CAP, with an identification of 18 RCTs evidencing a decrease in mortality in patients with severe CAP (RR 0.62 [95% CI: 0.45-0.85]), while these may have no effect on less severe CAP (RR 1.08 [95% CI: 0.83-1.42])¹⁸. It is necessary to evaluate whether corticosteroids have a lasting effect beyond 30 days as did the STEP trial study where 727 patients with CAP were evaluated, where randomizing patients to receive 50 mg of prednisone every 24 h for 7 days against placebo to assess mortality at 180 days, no significant differences were found with OR 1.15 (95 CI [0.68-1.95]) $p = 0.601$. When evaluating the secondary outcomes, the presence of pneumonia recurrence in the prednisone group was highlighted, with significant differences OR 2.57 (95% CI [1.29-5.12])¹⁹.

Emphasis should be placed on the limitations found in the different studies included in this systematic review, such as the fact that the studies included populations with very diverse clinical characteristics, such as disease severity, comorbidities, and age. Some studies had relatively small sample sizes, which may limit statistical power and increase the risk of type II errors. As well as the inclusion of different methodological designs, which can influence, the results obtained.

Different types of GCS (dexamethasone, prednisone, and methylprednisolone) and doses were used, making it difficult to identify an optimal regimen. The variety of GCS used, the severity of the patients, and the outcomes evaluated make direct comparison between studies difficult. This heterogeneity limits the ability to generalize findings and makes it difficult to identify an optimal treatment protocol for all patients with CAP.

Despite these limitations, studies suggest potential benefits of GCS use in certain subgroups of patients with CAP. These findings suggest that the benefits of GCS may be more pronounced in patients with more severe disease.

The comparison with studies on COVID-19 is interesting, but the differences between the two diseases

must be taken into account. While GCS have been shown to be beneficial in some patients with COVID-19, the mechanisms of action and response to treatment may differ in CAP. Importantly, NAC is caused by a wide variety of pathogens, while COVID-19 is caused by a specific virus.

The methodological quality of the studies included in our review is variable, which limits the generalizability of the results. Clinical heterogeneity of patients, in terms of disease severity, comorbidities, and causal pathogens, may also influence the interpretation of results. Despite these limitations, the findings of our review suggest that GCS may have a role in the management of severe CAP, especially in those patients with an exacerbated inflammatory response.

Conclusion

The use of hydrocortisone in patients with severe CAP showed a significant benefit in reducing mortality at 28 days and in the need for more invasive interventions such as mechanical ventilation and vasopressor use, which could indicate its usefulness in this specific group. In contrast, the other studies on the use of dexamethasone and methylprednisolone showed no significant differences in terms of mortality or clinical course, especially in the context of COVID-19 pneumonia, suggesting that their effectiveness could depend on patient-specific factors and the type of pneumonia.

The current evidence on the use of GCS in CAP is heterogeneous and does not allow definitive recommendations to be made for all patients. While some studies suggest benefits in patients with severe CAP, further studies are needed to identify the specific groups of patients in which they benefit from GCS use and to explore the possibility of a “therapeutic window” in which early initiation of treatment can maximize benefits and minimize risks to confirm these findings and determine the exact role of GCS in treatment of this disease. Clinicians should individualize the treatment of each patient, considering the severity of the disease, comorbidities, and potential adverse effects of GCS.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the Institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that artificial intelligence was used in this manuscript, specify Chat GPT y mybib.com for the writing of the Abstract and bibliographies.

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