Use of corticosteroids in COVID-19 patients vs. acute respiratory distress syndrome of other etiologies: Are there any differences?

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INTRODUCTION

The disease resulting from infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), widely known as coronavirus disease 2019 (COVID-19), has been classified as a global pandemic. It is characterized by respiratory compromise, which may include multisystemic involvement due to endothelial damage as well as activation of multiple thrombo-inflammatory mechanisms, leading to various serious clinical stages such as multiple organ failure and death due to Acute Respiratory Distress Syndrome (ARDS). In addition, the increased demand for health services, including the need for intensive care units and advanced vital resources such as mechanical ventilation or extracorporeal membrane oxygenation and trained personnel, poses serious challenges in choosing a suitable treatment.

In the absence of a standard treatment, the clinical approach to those affected has focused on pharmacological management, particularly the use of antivirals and immunomodulators. According to the phases of the immunological response, the use of glucocorticoids has become widespread given its effect on the control of the inflammatory cascade from its origin (blockade of phospholipase cascade) to its wide pharmacological availability and low cost. To date, the results have been controversial. At the beginning of the pandemic, these drugs were not recommended for use in COVID-19 patients. Nonetheless, current preliminary results of a clinical trial in the RECOVERY group show a decrease in mortality in patients receiving dexamethasone, raising the possibility of the systematic use of glucocorticoids for COVID-19 disease. The purpose of this review is to perform a rapid assessment of the evidence for and against the use of...
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glucocorticoids to prevent progression to ARDS and related mortality in both COVID-19 and ARDS mediated by other pathologies.

METHODS

A systematic review was carried out in the "PubMed," "EMBASE," and "Cochrane" databases with the following MESH terms: Articles published in the English and Spanish languages were included. For articles related to COVID-19, the deadline was July 31, 2020, and the start date was December 2019. For the meta-analysis related to ARDS from other causes, the start date was 2017, and the search and review time was two months. To assess the effect on COVID-19 patients, only original studies and meta-analyses published to date for other ARDS etiologies were included. Each search yielded 235 and 34 publications, respectively. Studies with samples smaller than ten patients; studies that evaluated the use of glucocorticoids in patients with rheumatological disease, autoimmune disease, and transplant or neoplasm recipients; reviews focused on neonates; lung maturation studies; and one meta-analysis on ARDS and septic shock were excluded. Finally, 14 original articles and 4 meta-analyses were obtained for review (Figure 1).

RESULTS

The main findings are summarized in the table. In general, a comparative analysis of the findings on the use of glucocorticoids for the treatment of COVID-19 and other causes of ARDS revealed great heterogeneity among treatment types using prednisone, methylprednisolone, dexamethasone, and hydrocortisone. Treatment schedules ranged from low doses to pulses of steroids in both groups, and for COVID-19, dexamethasone and methylprednisolone were used more frequently than for ARDS of other causes, where the most used were methylprednisolone and dexamethasone. Only the RECOVERY study specified the application protocol (table 1). Furthermore, it was evidenced that the effectiveness in reducing mortality, recovery from ARDS, or reduction in hospitalization time remained inconclusive, with high heterogeneity in the findings. Two observational studies in China (1326 patients),10,11 described a greater use of glucocorticoids in seriously ill patients with an increase in mortality; even a meta-analysis by Lu et al. (May, 2020) and the WHO provisional guidelines of January 28, 2020 advised against its use.12

DISCUSSION

Despite the heterogeneity in the findings described above, an understanding of the pathophysiology and evolution of COVID-19 disease, mainly the syndrome of innate release of cytokines mediated by the immune system (macrophages and proinflammatory granulocytes) through the production of TNF-α and IL-6 was achieved; in addition to recognition of the phases of SARS-CoV-2 infection, which initiates a response mainly mediated by "natural killer" cells and cytotoxic T lymphocytes to the secretion of type I interferon by infected cells.5 Subsequently, a series of deleterious mechanisms are activated, leading to lung tissue infiltration and damage progressing to ARDS, and endothelial impairment. With the foregoing, the use of corticosteroids alone or concomitantly with...
other immunomodulatory therapies for the management of severe forms of COVID-19 has been reconsidered and recommended, to reduce mortality in patients who have already developed lung damage.\(^\text{13}\)

The most recent systematic reviews and meta-analyses (Table 1), besides corroborating previous findings, demonstrate a decrease in the duration of mechanical ventilation compared with the usual management, without evidence of a significant increase in side effects. Only lower clearance of the virus was observed, but low certainty in the findings remained, given the heterogeneity of the studies.

In other ARDS etiologies, marginal benefits of drug therapies have been shown over time. In the four meta-analyses that condensed 17 clinical trials and more than 1,500 patients, the results are equally heterogeneous; cases of reduction in mortality or duration of mechanical ventilation are specific cases that do not allow recommendations to be made for systematic application. In one of the meta-analyses, there is even evidence of a decrease in mortality at day 28 for all patients,\(^\text{14}\) a finding that so far is the main argument for the use of dexamethasone in COVID-19\(^\text{8}\); however, this finding is not demonstrated in other settings. The findings of side effects of steroids in ARDS are similar, mainly the risk of superinfection, which is not shown to be persistently increased in all patients.

Within the pathophysiology of COVID-19 disease, the progression to severe forms does not depend only on the infectious agent but also on the interaction with the host’s immune system, in which the human leukocyte antigen (HLA) plays a central role. HLA represents one of the most polymorphic systems that participate in the immune response, and its various polymorphisms have been associated with worse outcomes both in COVID-19\(^\text{6}\) and in other viral infections, such as Influenza AH1N1.\(^\text{15}\)

Therefore, we consider that glucocorticoid therapy for patients with COVID-19 should not be based solely on pulmonary involvement. Hence, the indication should be individualized according to the patient’s immune response and immunophenotype, particularly in those with a proinflammatory state that can decline over the course of the disease, based on laboratory markers that have been associated with a worse outcome and a deleterious immune response, such as IL-6 and tumor necrosis factor alpha.

CONCLUSION

It is hypothesized that the demonstrated benefits of steroids in modulating the inflammatory response, slowing the progression to ARDS and associated mortality, both for COVID-19 and for ARDS due to other causes, will be enhanced if the type of immune response can be identified. Administration of a treatment aimed at the specific pathophysiological mechanism will also allow reduction of the possible adverse results associated with the use of these drugs. We understand that the limited access and costs associated with the collection and processing of immunological profiles or HLA subtypes compared with the benefits of the application of glucocorticoids limit the possibility of carrying out a targeted treatment according to the immunophenotype, but we believe that this is as area of potential research and development to optimize individualized therapies.

LIMITATIONS

The main limitations of the study were related to time, phrases and languages that could be analyzed, which restricted the criteria for article inclusion in the meta-analysis, because there are many other references of great importance in languages such as Italian and Mandarin. Likewise, the time interval covered by the review is an important limitation because the production time in COVID-19 is in constant growth, and it is not possible to keep reviews like this one completely up-to-date. It is important to note that the objective was always to carry out a systematic review of the literature with a subjective comparison and analysis, and the application of a statistical analysis (meta-analysis) was not within the objectives and design of the study.

ADDENDUM

After the search window for inclusion of articles in the systematic review, a meta-analysis published on September 2, 2020 was found that evaluated the usefulness of steroids to reduce mortality in COVID-19. This included seven studies with 1703 patients, of which 678 patients received dexamethasone, hydrocortisone, or methylprednisolone, and 1025 patients received a placebo. The conclusion is that patients who receive glucocorticoids systematically presented a reduction in mortality at day 28, compared with the placebo.\(^\text{16}\)

In addition, on February 25, 2021, the RECOVERY group updated its results where the use of dexta-
| Type of Study | Title | Corresponding Author | Journal | DOI | Selection Criteria | Number of Cases | Used Drug |
|---------------|-------|----------------------|---------|-----|--------------------|-----------------|----------|
| Meta-analysis | Effectiveness and safety of glucocorticoids to treat COVID-19: a rapid review and meta-analysis | Chenyan Zhou | Annals of Translational Medicine | 10.21037/atm-20-3307 | ACE - Cohort Study | 23 Studies 1 ACE 22 Cohorts | For the COVID-19 studies, methylprednisolone was used |
| Meta-analysis | Antiviral agents, glucocorticoids, antibiotics, and intravenous immunoglobulin usage in 1142 patients with coronavirus disease 2019: a systematic review and meta-analysis | Wenfang Li | Polish Archives of Internal Medicine | 10.20452/pamw.15543 | ACE - Cohort Study | 6 Studies 1 ACE 5 Observational | 1 methylprednisolone study, the rest were unspecified |
| Meta-analysis | Drug treatments for covid-19: Living systematic review and network meta-analysis | Reed AC Siemieniuk | BMJ: British Medical Journal | 10.1136/bmj.m2980 | ACE | 23 ACEs | methylprednisolone dexamethasone |
| Systematic review | Role of corticosteroid in the management of COVID-19: A systemic review and a Clinician's perspective | Awadhesh Kumar Singh | Diabetes & Metabolic Syndrome | 10.1016/j.dsx.2020.06.054 | ACE - Observational | 1 ACE 5 Observational | 1 methylprednisolone 1 dexamethasone (RECOVERY) Other unknown |
| Systematic review | Treatment options in people with COVID19: Selecting the best armamentarium against the novel virus | Deep Dutta | JPMA The Journal of the Pakistan Medical Association | 10.5455/JPMA.22 | Not specified | 289 studies - does not specify which studies were for corticosteroids | methylprednisolone |
| Clinical Trial | Dexamethasone in Hospitalized Patients with Covid-19 – Preliminary Report | RECOVERY Collaborative Group | The New England Journal of Medicine | 10.1056/NEJMoa2021436 | Open ACE - irpatient | 2104 Treatment Group 4321 Control Group | Oral or IV dexamethasone |
| Literature review | A critical evaluation of glucocorticoids in the management of severe COVID-19 | Cinzia Solinas | Cytokine & Growth Factor Reviews. | 10.1016/j.cytogfr.2020.06.012 | Literature review | 7 Treatment Guidelines | methylprednisolone dexamethasone |
| Cohort | Impact of glucocorticoid treatment in SARS-COV-2 infection mortality: A retrospective controlled cohort | Ana Fernández Cruz | Antimicrobial Agents and Chemotherapy. | 10.1128/AAC.01168-20 | According to the management received upon hospital admission | 463 patients - 396 receive treatment 67 control group | methylprednisolone |
| Cohort | Historically controlled comparison of glucocorticoids with or without tocilizumab versus supportive care only in patients with COVID-19-associated cytokine storm syndrome results of the CHIC study | Sofia Ramiro | Annals of the Rheumatic Diseases | 10.1136/annrheumdis-2020-218479 | Patients with cytokine release syndrome in COVID-19 | 86 Treatment Group and 86 Control Group | methylprednisolone (pulsed) |
| Type of Study | Title | Corresponding Author | Journal | DOI | Selection Criteria | Number of Cases | Used Drug |
|---------------|-------|-----------------------|---------|-----|-------------------|----------------|-----------|
| Meta-analysis | Do glucocorticoids decrease mortality in acute respiratory distress syndrome? A meta-analysis | Ritesh Agarwal | Respirology : Official Journal of the Asian Pacific Society of Respirology; Internal Medicine | 10.1111/j.1440-1843.2007.01060.x | ECAs (1980–2006) | 6 ACEs - number of patients not specified | 5 methylprednisolone 1 hydrocortisone |
| Impact of corticosteroids on mortality in patients with acute respiratory distress syndrome: A systematic review and meta-analysis | Nobuyuki Horta | Respiratory Medicine | 10.2169/16820.4015 | 4 ACEs 1 ACE - secondary analysis 6 cohorts 949 patients in total (461 treated – 488 control) Added: 8 ACEs - 4 methylprednisolone and 4 with hydrocortisone | 322 patients treated with methylprednisolone (118 early treatment < 72 h – 204; initial treatment on days 5 – 7) 297 with hydrocortisone |
| Prolonged glucocorticoid treatment is associated with improved ARDS outcomes: analysis of individual patients’ data from four randomized trials and trial-level meta-analysis of the updated literature | G. Umberto Meduri | Intensive Care Medicine | 10.1007/s00134-015-4095-4 | ACEs using methylprednisolone | 8 ACEs - 4 methylprednisolone and 4 with hydrocortisone |
| Pharmacological agents for adults with acute respiratory distress syndrome | Sharon R Lewis | The Cochrane Database of Systematic Reviews | 10.1002/14651858.CD004477.pub3 | ACE (2000–2018) | Steroids - 7 studies (643 patients) | hydrocortisone methylprednisolone budesonide |

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**Table 1 – continued**

| Cohort | Clinical efficacy of glucocorticoid on the treatment of patients with COVID-19 pneumonia: A single-center experience | Yan Hu | Biomedical & Pharmacotherapy | 10.1016/j.biopha.2020.110529 | Presence of lung consolidations - COVID-19 pneumonia | 308 patients | methylprednisolone (97.7%) prednisone (17.4%) |
|-------------|-------------------------------------------------|--------|-----------------------------|-----------------------------|-----------------------------|-------------|-----------------------------|
| Observational | Eficacia de los pulsos de corticoides en pacientes con síndrome de liberación de citocinas inducido por infección por SARS-CoV-2 | José Luis Callejas Rubio | Medicina Clinica | 10.1016/j.medi.2020.04.018 | Patients with cytokine release syndrome in COVID-19 | 92 patients | methylprednisolone |
| Observational | Análisis de los aspectos clínicos, tratamiento y pronóstico de 136 pacientes con COVID-19 | Yongping Chen | Journal of Clinical Pharmacy and Therapeutics | 10.1111/jcpt.13170 | Not applicable | 136 patients | methylprednisolone |
| Case Series | Short-term dexamethasone in SARS-CoV-2 patients | Vijay Selvaraj | Rhode Island Medical journal | PMID: 32570995 | Disease Severity (1980–2006) | 21 patients | IV pexamethasone |

**Abbreviations:** ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; ACE = ; CMV = ; WMD = ; CRP = C-reactive protein; OTI = ; SLC =
| Mortality                        | Hospital stay | Results | Signs and Symptoms | Treatment Complications |
|--------------------------------|---------------|---------|--------------------|-------------------------|
| The drug does not reduce mortality (RR: 2.00, 95% CI 0.69) | Prolonging WMD = 2.4 days, 95% CI = 1.4 – 3.4, 12 = 0.0% (5872 patients) | Duration of lung inflammation WMD = -1 day, C = 1 95% CI = -2.91 – 0.91 (4709 patients) | Reduction in fever WMD = -3.23 days, 95% CI = -3.56 to -2.90 | No significant findings for lung inflammation or mortality in SARS and MERS | Yes | Extension of hospital stay Risk of co-infections. |
| Increased risk: OR: 2.43; 95% CI = 1.44 – 4.10; p = 0.001; 12 = 61.9% | Not specified | Not specified | Not specified | No | No |

| Mortality                        | Hospital stay | Results | Signs and Symptoms | Treatment Complications |
|--------------------------------|---------------|---------|--------------------|-------------------------|
| Reduces mortality: (RR: 0.88, 95% CI = 0.80 – 0.97) | Not analyzed for glucocorticoids | Reduces the need for CMV RR: 0.74 95% CI = 0.59 – 0.93 30 fewer patients per 1000 (95% CI = 0.80 – 0.97) | Not analyzed for glucocorticoids | No | No |
| Not explored | Not explored | Not explored | Not explored | Yes |

| Mortality                        | Hospital stay | Results | Signs and Symptoms | Treatment Complications |
|--------------------------------|---------------|---------|--------------------|-------------------------|
| Hydroxychloroquine, Remdesivir, and Lopinavir / Ritonavir can decrease the duration of symptoms. | No | Not analyzed for glucocorticoids | Not analyzed for glucocorticoids | No |

| Mortality                        | Hospital stay | Results | Signs and Symptoms | Treatment Complications |
|--------------------------------|---------------|---------|--------------------|-------------------------|
| Longer virus detection time in those who receive corticosteroid 15 vs 8 days p = 0.013 | Not reported | Not reported | Yes |

**Study Limitations**

- The analysis was not exclusive to COVID-19; studies of SARS and MERS were included. Classification of the recommendations for COVID-19 as "VERY LOW" according to GRADE.
- Selection criteria for receiving therapies were not specified in retrospective studies.
- The glucocorticoid analysis only included observational studies with high heterogeneity.
- Among the multiple treatment options, corticosteroids show a harmful effect in patients with COVID-19.
- Glucocorticoids probably reduce mortality and the need of CMV in COVID-19 patients compared with the usual standard of care. Observational studies do not allow inference of a definite beneficial effect of glucocorticoids; RECOVERY shows a favorable result, but more studies are required.

**Conclusions**

- They do not recommend the routine use of systemic glucocorticoids in COVID-19 patients.

**Table 1**

| Use of corticosteroids in COVID-19 patients vs. acute respiratory distress syndrome of other etiologies | Barrera-López et al. | 2021 / ART. 30 | Qatar Medical Journal | VOL. 2021 / ART. 30 | 6 | Qatar Medical Journal |

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Table 1 – continued

| Treatment | Mortality Reduction | Requirement of CMV | Discharge Day 28 | Combination Management | Selection and Evaluation of Quality | Possible Salvage Therapy | Mortality Comparison |
|-----------|---------------------|--------------------|------------------|------------------------|-------------------------------------|--------------------------|---------------------|
| Not explored | Not explored | Only recommended for severe cytokine storm disease | Not explored | Not reported | Yes | Increase the virus clearance time | It does not specify the method of selection and evaluation of the quality of the articles; rather, it focuses on multiple drugs. Preliminary report. Patients with CMV were younger at the time of randomization. | They consider the possibility of combined management between immunomodulators and antivirals. The use of dexamethasone is associated with lower mortality at day 28 among patients with COVID-19 who require in-hospital management. The possibility of using glucocorticoids is raised based on the possible immunomodulatory effects and pathophysiology of COVID-19 despite the lack of evidence of benefit in the face of the public health emergency. |
| Mild to moderate reduction of 12 vs 13 days | Reduction in the requirement of CMV RR = 0.77 (95% CI = 0.62–0.95) | Highest possibility of discharge on day 28 | No | No | No | No | Literature review focused on the management guidelines and pathophysiology of COVID-19. |
| Not explored | Not explored | Not analyzed | Not explored | Not reported | No | No | |
| 41.8% reduction in mortality (13.9% vs 23.9%, OR = 0.51 [95% CI = 0.27–0.96], p = 0.044) – NNT 10 | Lower mortality in ARDS 26.2 vs 60%, OR = 0.23 [95% CI = 0.08–0.71], p = 0.014 | Not specified after treatment | Not reported | No | No | |
| | | | | | | Higher proportion of patients with hematologic disease, presence of confusion and less use of other immunomodulators (hydroxychloroquine and tocilizumab) in the control group; lower levels of inflammatory markers. Less use of steroids in patients with diabetes. | Lower mortality in steroid-treated patients; no differences in mortality between usual doses and steroid pulses. |
Table 1 – continued

| Mortality                              | Hospital stay                                      | Severity Progression | Signs and Symptoms | Treatment Complications | Study Limitations | Conclusions                                                                 |
|----------------------------------------|---------------------------------------------------|----------------------|--------------------|-------------------------|-------------------|----------------------------------------------------------------------------|
| 65% mortality reduction OR: 0.35 (95% CI: 0.19 – 0.65) | Reduction in hospitalization time OR: -6.65 (95% CI: 10.93 to -2.37) | 71% reduction in CMV requirement OR: 0.29 (95% CI = 0.14 – 0.65) | Not explored         | 79% greater probability of correcting the SLC at day 7 of follow-up (OR = 1.8; 95% CI = 1.2 – 2.7) | Yes                | Higher proportion of diabetic patients in the control group. Greater use of Tocilizumab in the treatment group; all patients in the treatment group received some type of anticoagulation. |
| No difference in healing 73 (84.9%) vs 58 (69.3%) p = 0.065 or discharge 13 (15.1%) vs 3 (16.7%) | No differences at discharge | Not described | No differences in the duration of fever p = 0.19 and the time of return to a normal temperature p = 0.68 | No differences in the duration of fever No differences in the resolution time of the pulmonary findings by CT 11 (9–14) vs 11 (8–15) p = 0.87 | Yes | No differences between the presence of hypokalemia and hyperglycemia The steroid treatment group had worse risk markers, especially lymphopenia and elevated CRP. |
| Decrease in mortality combined with Tocilizumab (OR = 0.02, 95% CI = 0.0004 – 0.835, p = 0.04) | Not explored | Need for CMV OR: 0.28 (95% CI = 0.019 – 4.19) p = 0.356 | Not explored | Marked decrease in CRP | No | Limited to exclusive management of SLC; they pose less progression to death and OTI with the use of steroids but this is not reflected in the results. |

108/136 (79.4%) patients receive methylprednisolone with greater use in critically ill patients where the doses were also higher. In the discussion, a controlled use is proposed given the risk of immunosuppression adjusted to \( \alpha = \frac{L_{25} + J_{15:R_{16}}}{L_{25} + J_{15:R_{16}}} \). A deleterious effect is evidenced in patients receiving steroids with increased mortality in severely ill patients 59.8% vs 39.7%, p = 0.0005 and greater deterioration (progression) of the disease. Without disease progression 144 (17.7%) vs progression in severity 107 (47.4%) < 0.0001.
Table 1 – continued

| Mortality | Hospital stay | Sevency Progression | Signs and Symptoms | Other Findings | Reported | Explanation |
|-----------|---------------|---------------------|--------------------|----------------|----------|-------------|
| No one died | Discharge of 71.4% of patients Average stay 7.8 days | No patient required escalation in the management of the disease or presented deterioration | 77.98% reduction in peak CRP levels \((129.52 \pm 72.05)\) to \((40.73 \pm 49.28)\) | Not reported | Yes | 1 Patient with hyperglycemia |
| Mortality | Hospital stay | Sevency Progression | Signs and Symptoms | Other Findings | Reported | Explanation |
| No reduction in early ARDS (<14 days) OR 0.57 (95% CI 0.25–1.32) with NNT of 10 rel 818 harm / 5 benefit. | Not explored | Not explored | — | Not explored | No | No |
| No reduction in late ARDS (>14 days) OR 0.58 (95% CI 0.22–1.53) with NNT of 15 rel 6 harm / 21 benefit. | Not explored | Not explored | — | Not explored | No | No |
| Shorter time to reach extubation, OR: 2.59 (95% CI 1.95–3.43), p = 0.001. Those who received early management (36 vs 49%, risk ratio 0.76, 95% CI 0.59–0.98, I² = 17%, p = 0.035). With the addition of ACE’s hydrocortisone reduction in mortality 37 (20%) 45 (33%) OR 0.48 (0.29–0.81), p = 0.006. | No increase in nosocomial infection OR: 2.24 (95% CI 1.21–4.13, p = 0.01) (I² = 7, p = 0.30) | Reduction in CRP and interleukin levels in those who received glucocorticoid. | No increase in nosocomial infection in the treatment group. There is an increase in return to CMV at day 28 (24 (16%) vs 4 (6%) OR: 4.04 (1.31–12.43), p = 0.015) without SOFA and age adjustments. | Two studies show an increased risk of lung infection OR: 2.24 (95% CI 1.21–4.13, p = 0.01) (I² = 7, p = 0.30) | Yes | Two studies show an increased risk of lung infection OR: 2.24 (95% CI 1.21–4.13, p = 0.01) (I² = 7, p = 0.30) |

Current evidence does not support the use of corticosteroids in the treatment of ARDS in both early and late stages.

Based on existing studies, the favorable impact of the use of corticosteroids on mortality in patients with ARDS cannot be confirmed.

A short pulse of steroids is well tolerated and can mitigate proinflammatory states and improve patient outcomes.

By day 28: General hospital mortality 20 vs. 33% (\(p = 0.006\)). Those who received early management (36 vs 49%, risk ratio 0.76, 95% CI 0.59–0.98, \(I^2 = 17\%, p = 0.035\)). With the addition of ACE’s hydrocortisone reduction in mortality 37 (20%) 45 (33%) OR 0.48 (0.29–0.81), \(p = 0.006\).
| Mortality          | Hospital stay | Results                                                                 | Signs and Symptoms | Treatment Complications | Study Limitations | Conclusions |
|-------------------|---------------|--------------------------------------------------------------------------|--------------------|-------------------------|-------------------|-------------|
| Possible reduction at 90 days in all-cause mortality in 86 out of 1000 patients (with up to 161 fewer or 19 more deaths). RR: 0.77; 95% CI 0.57 – 1.05; I² = 27%; low-certainty evidence. | Four studies evaluated 28-day follow-up without the need for a ventilator in 494 patients. The CMV-free time increased 4.09 days, 95% CI 1.74 – 6.44; I² = 36%; low-certainty evidence. | 4 studies (368 patients) found a median decrease in CMV time of 5 (IQR 3 – 8) vs median of 9.5 (IQR 6 – 9.5 days). p = 0.002. Others of greater weight failed to show a reduction MD 4.30 days; 95% CI – 9.72 – 1.12; I² = 93%; 277 patients; very low-certainty evidence. | Not explored | No | No |
| Four studies evaluated 28-day follow-up without the need for a ventilator in 494 patients. The CMV-free time increased 4.09 days, 95% CI 1.74 – 6.44; I² = 36%; low-certainty evidence. | | | | | | |

There is insufficient evidence to determine with certainty whether any drug was effective in reducing mortality or decreasing CMV time in patients with ARDS. It was found that steroids could increase the number of days without mechanical ventilation. Most of the findings are of low or very low certainty; therefore, there is little confidence in the findings.
methasone was associated with a lower mortality on day 28 among patients who required the use of invasive mechanical ventilation or supplemental oxygen, which was not the case for patients with noninvasive mechanical ventilation. These new results continue to reinforce our recommendation that the benefits of steroids can be enhanced by applying targeted therapy to specific immunophenotypes.

Disclosure of interest
The authors have no potential competing interest to report.

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