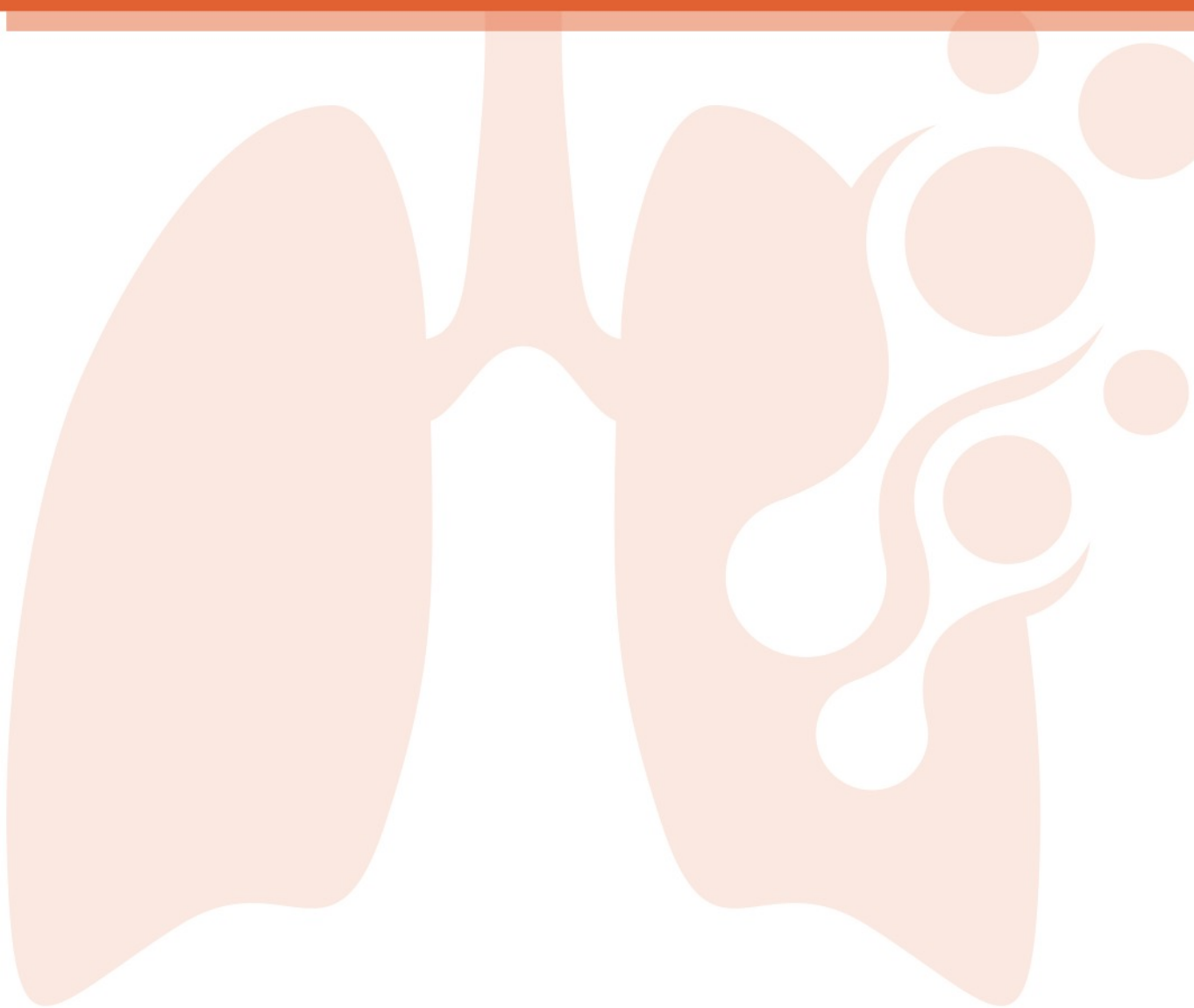
Corticosteroids for COVID-19

LIVING GUIDANCE
2 SEPTEMBER 2020

World Health Organization



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Abbreviations

ARDS	acute respiratory distress syndrome
CAP	community-acquired pneumonia
CI	confidence interval
GI	gastrointestinal
GRADE	Grading of Recommendations Assessment, Development and Evaluation
MAGIC	Magic Evidence Ecosystem Foundation
PMA	prospective meta-analysis
RCT	randomized controlled trial
RR	relative risk/risk ratio
SEA	serious adverse event
WHO	World Health Organization

Summary

Clinical question: What is the role of systemic corticosteroids in the treatment of patients with COVID-19?

Target audience: The target audience consists primarily of clinicians, and, secondarily, health care decision-makers.

Current practice: Corticosteroids have received worldwide attention as a potentially effective treatment for COVID-19. This guideline was triggered on 22 June 2020 by the publication of the preliminary report of the RECOVERY trial *(1, 2)*, which has now been published as a peer-reviewed paper. Corticosteroids are listed in the World Health Organization (WHO) model list of essential medicines, readily available globally at a low cost, and of considerable interest to all stakeholder groups.

How this guideline was created: This guideline reflects an innovation from the WHO, driven by an urgent need for global collaboration to provide trustworthy and living COVID-19 guidance informing policy and practice worldwide during an outbreak of an emerging infectious disease, such as this pandemic. For this purpose, WHO has partnered with the non-profit Magic Evidence Ecosystem Foundation (MAGIC) for methodologic support, to develop and disseminate living guidance for COVID-19 drug treatments. WHO also partnered with investigators of seven trials on corticosteroids to conduct a prospective meta-analysis of randomized trials for corticosteroid therapy for COVID-19 (PMA), in order to rapidly provide additional evidence to build on RECOVERY data and inform guidance development. Drawing on these data, an international panel of content experts, patients, clinicians and methodologists (no conflicts of interest declared for any of the participants) produced recommendations following standards for trustworthy guideline development using the GRADE approach. We considered an individual patient perspective and contextual factors (i.e. resources, feasibility, acceptability, equity) for countries and health care systems.

The evidence: The guideline panel was informed by combining two meta-analyses which pooled data from eight randomized trials (7184 participants) of systemic corticosteroids for COVID-19. The panel discussions were also informed by two other meta-analyses, which were already published and pooled data about the safety of systemic corticosteroids in distinct but relevant patient populations. The resulting evidence summary suggested that systemic corticosteroids probably reduce 28-day mortality in patients with critical COVID-19 (moderate certainty evidence; seven studies,1703 patients; relative risk [RR] 0.80, 95% CI 0.70–0.91; absolute effect estimate 87 fewer deaths per 1000 patients, 95% CI 124 fewer to 41 fewer), and also in those with severe disease (moderate certainty evidence; one study, 3883 patients; RR 0.80, 95% CI 0.70–0.92; absolute effect estimate 67 fewer deaths per 1000 patients, 95% CI 100 fewer to 27 fewer). In contrast, systemic corticosteroids may increase the risk of death when administered to patients with non-severe COVID-19 (low certainty evidence; one study, 1535 patients; RR 1.22, 95% CI 0.93–1.61; absolute effect estimate 39 more per 1000 patients, 95% CI 12 fewer to 107 more). In addition, systemic corticosteroids probably reduce the need for invasive mechanical ventilation (moderate certainty of evidence; two studies, 5481 patients; RR 0.74, 95% CI 0.59–0.93). In contrast, harms, in the context of the mortality reduction in severe disease, are minor.

Recommendations: The panel made two recommendations: a strong recommendation for systemic (i.e. intravenous or oral) corticosteroid therapy (e.g. 6 mg of dexamethasone orally or intravenously daily or 50 mg of hydrocortisone intravenously every 8 hours) for 7 to 10 days in patients with severe and critical COVID-19, and a conditional recommendation not to use corticosteroid therapy in patients with non-severe COVID-19.

Understanding the recommendation: Given the moderate certainty evidence of an important reduction in the risk of death, the panel concluded that all or almost all fully informed patients with severe or critical COVID-19 would choose treatment with systemic corticosteroids. Moreover, the panel believed that other perspectives (i.e. costs, equity, feasibility of implementation), and patient values and preferences would not alter decisions. In contrast, the panel concluded that fully informed patients with non-severe COVID-19 would mostly not choose to receive this treatment given that current data indicated they would not likely derive benefit and may derive harm. Moreover, taking both a public health and a patient perspective, the panel warned that indiscriminate use of any therapy for COVID-19 would potentially rapidly deplete global resources and deprive patients who may benefit from it most as potentially life-saving therapy.

Background

As of 1 September2020, 25 327 098people worldwide have been diagnosed with COVID-19, according to the international World Health Organization (WHO) dashboard *(3)*. The pandemic has claimed 848 255 lives, and a resurgence in the number of new cases and continued growth is some countries has threatened high- and low-resource countries alike. Although recent evidence suggested that remdesivir may be effective in reducing the time to clinical improvement in patients with severe COVID-19 *(4)*, the magnitude of reduction in time to clinical improvement and the impact of this antiviral agent on mortality and other important outcomes remains uncertain *(5)*. Where the host immune response may drive the pathophysiology of disease, there has been substantial uncertainty regarding the role of corticosteroids in improving clinical outcomes and reducing mortality in patients with COVID-19.

This clinical practice guideline was triggered by the dissemination of the preliminary report of the RECOVERY trial on 22 June 2020, which suggested that dexamethasone 6 mg given once daily for up to 10 days versus usual care reduced 28-day mortality (482/2104 [22.9%] of patients allocated dexamethasone versus 1110/4321 [25.7%] of patients allocated to usual care; age-adjusted rate ratio [RR] 0.83; 95% confidence interval [CI] 0.75–0.93; $P < 0.001$) *(1)*.

Methods

This guideline reflects an innovation from the WHO, driven by an urgent need for global collaboration to provide trustworthy and living COVID-19 guidance informing policy and practice worldwide rapidly during an outbreak of an emerging infectious disease, such as this pandemic. For this purpose, WHO has partnered with the non-profit Magic Evidence Ecosystem Foundation (MAGIC) to provide methodologic support in the development and dissemination of living guidance for COVID-19 drug treatments.

The international, guideline development panel was composed of 23 individuals, of whom 21 were content experts (clinicians, methodologists, scientists) and 2 were patients who survived COVID-19. No conflict of interest was identified for any panel member. Following consultation with a Methods Chair and MAGIC, invitations were sent out to candidate panel members by the WHO with the aim of achieving balance within the panel in terms of gender, geography, expertise, patient representation. Patients had received basic training to familiarize themselves with the process of creating trustworthy guidelines and actively participated in all the discussions. Their votes had the same weight as other panel members. The panel produced the recommendation following standards for trustworthy guideline development using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach in full compliance with the *WHO Handbook for guideline development 2nd edition (6)*. The Methods Chair (methodological expertise) and a Clinical Chair (content expertise) guided the discussions but did not influence the final recommendations. Similarly, four resource persons with methodologic expertise assisted the Methods Chair, and 15 observers (12 from WHO, 3 from MAGIC) attended the panel

meetings but did not directly participate in discussions. As per the *WHO Handbook*, the panel aimed to create a recommendation based on consensus, but elected, at the beginning of the first panel meeting, to call a vote if a consensus could not be reached. Before discussions started, the panel determined that a simple majority would provide the direction of the recommendation and that 80% would be required to make a strong recommendation. The panel considered an individual patient perspective. The panel also considered contextual factors (e.g. resources, feasibility, acceptability, equity) for countries and health care systems. The target audience consists primarily of clinicians, but secondarily of patients and health care decision-makers.

To create the recommendations, the panel relied on evidence synthesized in a living network meta-analysis led by MAGIC *(5)* which is iteratively tracking the development of evidence from randomized controlled trials (RCTs), a prospective meta-analysis (PMA) of RCTs conducted by the the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group *(7)*; and two meta-analyses which were already published and pooled data about the safety of systemic corticosteroids in distinct but relevant patient populations *(8, 9).* The lead investigators of the living network meta-analysis and the PMA independently rated the overall certainty of the evidence as moderate, although the main reasons for downgrading were different. The panel ultimately relied on the GRADE assessment presented by the independent group composed of the Methods Chair and supporting methodologists who attended the meeting, but did not influence the creation of the recommendation.

Values and preferences

The panel took an individual patient perspective to values and preferences. Ahead of the first meeting, panel members, including two COVID-19 survivors, were asked to consider a list of outcomes deemed relevant to COVID-19 research. They were asked to consider the importance of each outcome and whether they agreed with a hierarchy ranging from “critically important” to “not very important”. In doing so, each member was asked to consider the perspective of the patients and was instructed to make their recommendation on the basis not on their own values and preferences, but rather on those of COVID-19 patients around the world. One source of their information in this regard was conversations with patient panel members as the discussion proceeded. Another was their own experience in shared decision-making with patients and families. During all discussions, which occurred via email and during both meetings, the Methods Chair actively reminded the panel that guidelines were designed to inform the care of the average patient and, therefore, that they should attempt to consider the values and preferences of the average patient. Given the burden of the pandemic for health care systems globally, the panel also placed a high value on resource allocation (i.e. from a public health perspective). In such a perspective, attention is paid to opportunity cost, or lack thereof, associated with the widespread provision of therapies for COVID-19.

The panel ranked the outcomes and attributed a high value to even a very small reduction in mortality. In addition, the panel also placed a high value on even a small reduction in the need for mechanical ventilation, which places a large physical burden on patients and an emotional burden on patients and families. A second reason the panel placed a high value on a small reduction in mechanical ventilation concerns health resource issues: the availability of mechanical ventilation stands out as an important vulnerability during the COVID-19 pandemic. Note, mechanical ventilation requires a stable source of oxygen and trained workforce, which are also important vulnerabilities during COVID-19, especially in resource-limited settings.

The evidence

On 17 July 2020, the panel reviewed evidence from eight RCTs (7184 patients) evaluating systemic corticosteroids versus usual care in COVID-19. RECOVERY, the largest of the seven trials, from which mortality data were available by subgroup (severe and non-severe), evaluated the effects of dexamethasone 6 mg given once daily (oral or intravenous) for up to 10 days in 6425 hospitalized patients in the United Kingdom (2104 were randomized to dexamethasone and 4321 were randomized to usual care). At the time of randomization, 16% were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation; 60% were receiving oxygen only (with or without non-invasive ventilation); and 24% were receiving neither *(2)*. The data from seven other smaller trials included 63 non-critically ill patients and approximately 700 critically ill patients (definitions of critical illness varied across studies). For the latter, patients were enrolled up to 9 June 2020, and approximately four-fifths were invasively mechanically ventilated; approximately half were randomized to receive corticosteroid therapy, and half randomized to no corticosteroid therapy. Corticosteroid regimens included: methylprednisolone 40 mg every 12 hours for 3 days and then 20 mg every 12 hours for 3 days (GLUCOVID) *(10)*; dexamethasone 20 mg daily for 5 days followed by 10 mg daily for 5 days (two trials, DEXA-COVID, CoDEX) *(11)*; hydrocortisone 200 mg daily for 4 to 7 days followed by 100 mg daily for 2 to 4 days and then 50 mg daily for 2 to 3 days (one trial, CAPE-COVID) *(12)*; hydrocortisone 200 mg daily for 7 days (one trial, REMAP-CAP) *(13)*; methylprednisolone 40 mg every 12 hours for 5 days (one trial, Steroids-SARI) *(5, 7)*. Seven of the trials were conducted in individual countries (Brazil, China, Denmark, France, Spain) whilst REMAP-CAP was an international study (recruiting in 14 European countries, Australia, Canada, New Zealand, Saudi Arabia and the United Kingdom). All trials reported mortality 28 days after randomization, except for one trial at 21 days and another at 30 days. Because the mortality data from one trial (GLUCOVID, n=63) were not reported by subgroup, the panel reviewed only the data pertaining to the outcome of mechanical ventilation from this trial *(10)*. An additional trial, which randomized hospitalized patients with suspected SARS-CoV-2 infection, published on 12 August 2020 (MetCOVID) *(14),* was included as a supplement in the PMA publication, as it was registered after the searches of trial registries were performed. The supplement showed that inclusion would not change results other than reduce inconsistency.

Subgroup effect for mortality

While all other trials evaluated systemic corticosteroids exclusively in critically ill patients, the RECOVERY trial enrolled hospitalized patients with COVID-19. The panel considered the results of a subgroup analysis of the RECOVERY trial suggesting that the relative effects of systemic corticosteroids varied as a function of the level of respiratory support received at randomization. On the basis of the peer-reviewed criteria for credible subgroup effects *(15)*, the panel determined that the subgroup effect was sufficiently credible to warrant separate recommendations for severe and non-severe COVID-19.

However, acknowledging that during a pandemic, access to health care may vary considerably over time as well as between different countries, the panel decided against defining patient populations concerned by the recommendations on the basis of access to health interventions (i.e. hospitalization and respiratory support). Thus, the panel attributed the effect modification in the RECOVERY trial to illness severity.

However, the panel acknowledged the existence of variable definitions for severity and use of respiratory support interventions. The WHO clinical guidance for COVID-19 published on 27 May 2020 (version 3) defined severity of COVID-19 by clinical indicators, but modified the oxygen saturation threshold from 94% to 90% *(16)*, in order to align with previous WHO guidance *(17).* Table 1 is adapted from WHO COVID-19 disease severity categorization.

Table 1. Mutually exclusive categories of illness severity

Critical COVID-19	Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock or other conditions that would normally require the provision of life-sustaining therapies, such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.
Severe COVID-19	Defined by any of: • oxygen saturation < 90% on room air. • respiratory rate > 30 breaths per minute in adults and children > 5 years old; ≥ 60 in children less than 2 months; ≥ 50 in children 2–11 months; and ≥ 40 in children 1–5 years old. • signs of severe respiratory distress (i.e. accessory muscle use, inability to complete full sentences; and in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs).
Non-severe COVID-19	Defined as absence of any signs of severe or critical COVID-19.

Caution: The panel noted that the oxygen saturation threshold of 90% to define severe COVID-19 was arbitrary and should be interpreted cautiously when used for determining which patients should be offered systemic corticosteroids. For example, clinicians must use their judgement to determine whether a low oxygen saturation is a sign of severity or is normal for a given patient suffering from chronic lung disease. Similarly, a saturation above 90–94% on room air may be abnormal if the clinician suspects that this number is on a downward trend. Generally, if there is any doubt, the panel suggested erring on the side of considering the illness as severe.

Using the pooled relative risk from the meta-analyses and the pooled control event rates for each subgroup from included trials, we calculated the absolute effect estimates that were presented to the guideline panel members in the form of GRADE evidence summaries. Of note, baseline risks, and thus absolute effects, may vary significantly geographically and over time.

As such, users of this guideline may prefer estimating absolute effects by using local event rates. For example, if the baseline event rate in one area is much lower, the expected benefit from steroids will also be lower in absolute terms. Notwithstanding, the panel attributed a high value to even a small reduction in mortality and concluded that the recommendations apply across baseline event rates.

From the PMA, in patients with COVID-19, based on data from 1703 critically ill patients (as defined above) in seven trials, systemic corticosteroids compared with no corticosteroid therapy probably reduce the risk of 28-day mortality (moderate certainty evidence; RR 0.80, 95% CI 0.70–0.91; absolute effect estimate 87 fewer deaths per 1000 patients, 95% CI 124 fewer to 41 fewer). In patients with severe COVID-19 who are not critically ill, based on data from 3883 patients in one study, systemic corticosteroids also probably reduce the risk of death (moderate certainty evidence; RR 0.80, 95% CI 0.70–0.92; absolute effect estimate 67 fewer deaths per 1000 patients, 95% CI 100 fewer to 27 fewer). In contrast, in patients with non-severe COVID-19, based on data from 1535 patients in one study, systemic corticosteroids may increase the risk of 28-day mortality (low certainty evidence; RR 1.22, 95% CI 0.93–1.61; absolute effect estimate 39 more per 1000 patients, 95% CI 12 fewer to 107 more).

Other outcomes are described in the summary of findings (Appendix 2 Table A2.1). Systemic corticosteroids probably reduce the need for invasive mechanical ventilation (moderate certainty of evidence, two studies, 5481 patients, RR 0.74, 95% CI 0.59–0.93). With respect to harms, certainty ratings refer to the confidence in the effects of steroids on individual outcomes, which can be characterized as trivial, small or moderate in magnitude and, in this case, are low to moderate. However, overall, the panel has high certainty that the adverse effects when considered together are sufficiently limited in importance and frequency that patients with severe COVID-19 will consider the mortality reduction more important.

Understanding the recommendations

Recommendation 1:

We recommend systemic corticosteroids rather than no systemic corticosteroids for the treatment of patients with severe and critical COVID-19 (strong recommendation, based on moderate certainty evidence).

This recommendation was achieved after a vote, which concerned the strength of the recommendation in favour of systemic corticosteroids. Of the 23 voting panel members, 19 (83%) voted in favour of a strong recommendation, and 4 (17%) voted in favour of a conditional recommendation. The reasons for the four cautionary votes, which were shared by some panel members who voted in favour of a strong recommendation, are summarized below.

Applicability

Panel members who voted for a conditional recommendation argued that many patients who were potentially eligible for the RECOVERY trial were excluded from participating in the evaluation of corticosteroids by their treating clinicians and that without detailed information on the characteristics of excluded patients, this precluded, in their opinion, a strong recommendation. Other panel members felt that such a proportion of excluded patients was the norm rather than the exception in pragmatic trials and that, while detailed information on the reasons for excluding patients were not collected, the main reasons for refusing to offer participation in the trial were likely related to safety concerns of stopping corticosteroids in patients with a clear indication for corticosteroids (confirmed as per personal communication from the RECOVERY Principal Investigator). Panel members noted that there are few absolute contraindications to a 7–10 day course of corticosteroid therapy, that recommendations are intended for the average patient population, and that it is understood that even strong recommendations should not be applied to patients in whom the intervention is contraindicated as determined by the treating clinician.

Eventually, the panel concluded that this recommendation applies to patients with severe and critical COVID-19 regardless of hospitalization status. The underlying assumption is that these patients would be treated in hospitals and receive respiratory support in the form of oxygen; non-invasive or invasive ventilation if these options were available. Following GRADE guidance, in making a strong recommendation, the panel has inferred that all or almost all fully informed patients with severe COVID-19 would choose to take systemic corticosteroids. It is understood that even in the context of a strong recommendation, the intervention may be contraindicated for certain patients. Absolute contraindications for 7–10 day courses of systemic corticosteroid therapy are rare. In considering potential contraindications, clinicians must determine if they warrant depriving a patient of a potentially life-saving therapy.

The applicability of the recommendation is less clear for populations that were under-represented in the considered trials, such as children, patients with tuberculosis, and those who are immunocompromised. Notwithstanding, clinicians will also consider the risk of depriving these patients of potentially life-saving therapy. In contrast, the panel concluded that the recommendation should definitely be applied to certain patients who were not included in the trials, such as patients with severe and critical COVID-19 who could not be hospitalized or receive oxygen because of resource limitations.

The recommendation does not apply to the following uses of corticosteroids: transdermal or inhaled administration, high-dose or long-term regimens, or prophylaxis.

Balance of benefits and harms

Panel members who voted for a conditional recommendation argued that the trials evaluating systemic corticosteroids for COVID-19 reported limited information regarding potential harm. Between the two panel meetings, indirect evidence regarding the potential harmful effects of systemic corticosteroids from studies in sepsis, ARDS and community-acquired pneumonia (CAP) was added to the summary of findings table *(8, 9)*. While generally of low certainty, these data were reassuring and suggested that corticosteroids are not associated with an increased risk of adverse events, beyond likely increasing the incidence of hyperglycaemia (moderate certainty evidence; absolute effect estimate 46 more per 1000 patients, 95% CI 23 more to 72 more) and hypernatraemia (moderate certainty evidence; 26 more per 1000 patients, 95% CI 13 more to 41 more). Panel members also noted that, given the expected effect of systemic corticosteroids on mortality, most patients would not refuse this intervention to avoid adverse events believed to be markedly less important to most patients than death. In contrast with new agents proposed for COVID-19, clinicians have a vast experience of systemic corticosteroids and the panel was reassured by their overall safety profile. Moreover, the panel was confident that clinicians using these guidelines would be aware of additional potential side-effects and contraindications to systemic corticosteroid therapy, which may vary geographically in function of endemic microbiological flora. Notwithstanding, clinicians should exercise caution in use of corticosteroids in patients with diabetes or underlying immunocompromise.

Ultimately, the panel made its recommendation on the basis of the moderate certainty evidence of a 28-day mortality reduction of 8.7% in the critically ill and 6.7% in patients with severe COVID-19 who were not critically ill, respectively.

Resource implications, feasibility, equity and human rights

In this guideline, the panel took an individual patient perspective, but also placed a high value on resource allocation. In such a perspective, attention is paid to the opportunity cost associated with the widespread provision of therapies for COVID-19. In contrast to other candidate treatments for COVID-19 that, generally, are expensive, often unlicensed, difficult to obtain and require advanced medical infrastructure, systemic corticosteroids are low cost, easy to administer, and readily available globally *(18)*. Dexamethasone and prednisolone are among the most commonly listed medicines in national essential medicines lists; listed by 95% of countries. Dexamethasone was first listed by WHO as an essential medicine in 1977, while prednisolone was listed 2 years later *(19)*.

Accordingly, systemic corticosteroids are among a relatively small number of interventions for COVID-19 that have the potential to reduce inequities and improve equity in health. Those considerations influenced the strength of this recommendation.

Acceptability

The ease of administration, the relatively short duration of a course of systemic corticosteroid therapy, and the generally benign safety profile of systemic corticosteroids administered for up to 7–10 days led the panel to conclude that the acceptability of this intervention was high.

Recommendation 2:

We suggest not to use corticosteroids in the treatment of patients with non-severe COVID-19 (conditional recommendation, based on low certainty evidence).

This recommendation was achieved by consensus.

Applicability

This recommendation applies to patients with non-severe disease regardless of their hospitalization status. The panel noted that patients with non-severe COVID-19 would not normally require acute care in hospital or respiratory support, but that in some jurisdictions, these patients may be hospitalized for isolation purposes only, in which case they should not be treated with systemic corticosteroids. The panel concluded that systemic corticosteroids should not be stopped for patients with non-severe COVID-19 who are already treated with systemic corticosteroids for other reasons (e.g. patients with chronic obstructive pulmonary disease need not discontinue a course of systemic oral corticosteroids; or other chronic autoimmune diseases). If the clinical condition of patients with non-severe COVID-19 worsens (i.e. increase in respiratory rate, signs of respiratory distress or hypoxaemia) they should receive systemic corticosteroids (see recommendation 1).

Balance of benefits and harms

The panel made its recommendation on the basis of low certainty evidence suggesting a potential increase of 3.9% in 28-day mortality among patients with COVID-19 who are not severely ill. The certainty of the evidence for this specific subgroup was downgraded due to serious imprecision (i.e. the evidence does not allow to rule out a mortality reduction) and risk of bias due to lack of blinding. In making a conditional recommendation against the indiscriminate use of systemic corticosteroids, the panel inferred that most fully informed individuals with non-severe illness would not want to receive systemic corticosteroids, but many could want to consider this intervention through shared decision-making with their treating physician *(6).*

Note: WHO recommends antenatal corticosteroid therapy for pregnant women at risk of preterm birth from 24 to 34 weeks' gestation when there is no clinical evidence of maternal infection, and adequate childbirth and newborn care is available. However, in cases where the woman presents with mild or moderate COVID-19, the clinical benefits of antenatal corticosteroid might outweigh the risks of potential harm to the mother. In this situation, the balance of benefits and harms for the woman and the preterm newborn should be discussed with the woman to ensure an informed decision, as this assessment may vary depending on the woman's clinical condition, her wishes and that of her family, and available health care resources.

Resource implications, feasibility, equity and human rights

The panel also considered that in order to help guarantee access to systemic corticosteroids for patients with severe and critical COVID-19, it is reasonable to avoid administering this intervention to patients who, given the current evidence, would not appear to derive any benefit from this intervention.

Practicalities/implementation considerations

Systemic corticosteroids may be administered both orally and intravenously. Of note, while the bioavailability of dexamethasone is very high (i.e. similar concentrations are achieved in plasma after oral and intravenous intake), critically ill patients may be unable to absorb any nutrients or medications due to intestinal dysfunction. Clinicians therefore may consider administering systemic corticosteroids intravenously rather than orally if intestinal dysfunction is suspected. While more patients received corticosteroids in the form of dexamethasone 6 mg daily for up to 10 days, the total duration of regimens evaluated in the seven trials varied between 5 and 14 days, and treatment was generally discontinued at hospital discharge (i.e. the duration of treatment could be less than the duration stipulated in the protocols).

The once daily dexamethasone formulation may increase adherence. A dose of 6 mg of dexamethasone is equivalent (in terms of glucocorticoid effect) to 150 mg of hydrocortisone (e.g. 50 mg every 8 hours), or 40 mg of prednisone, or 32 mg of methylprednisolone (e.g. 8 mg every 6 hours or 16 mg every 12 hours). It would be prudent to monitor glucose levels in patients with severe and critical COVID-19, regardless of whether the patient is known to have diabetes.

The timing of therapy from onset of symptoms was discussed by the panel. The RECOVERY investigators reported a subgroup analysis suggesting that the initiation of therapy 7 days or more after symptom onset may be more beneficial than treatment initiated within 7 days of treatment onset. A post hoc subgroup analysis within the PMA did not support this hypothesis. While some panel members believed that postponing systemic corticosteroids until after viral replication is contained by the immune system may be reasonable, many noted that, in practice, it is often impossible to ascertain symptom onset and that signs of severity frequently appear late (i.e. denote a co-linearity between severity and timing). The panel concluded that, given the evidence, it was preferable to err on the side of administering corticosteroids when treating patients with severe or critical COVID-19 (even if within 7 days of symptoms onset) and to err on the side of not giving corticosteroids when treating patients with non-severe disease (even if after 7 days of symptoms onset).

Other endemic infections that may worsen with corticosteroids should be considered. For example, for *Strongyloides stercoralis* hyperinfection associated with corticosteroid therapy, diagnosis or empiric treatment may be considered in endemic areas if steroids are used.

Ongoing uncertainties and opportunities for future research

- Long-term effect of systemic corticosteroids on mortality and functional outcomes in COVID-19 survivors are unknown and will be the subject of future analyses of the evidence considered by the panel.
- The clinical effects of systemic corticosteroids in patients with non-severe COVID-19 (i.e. pneumonia without hypoxaemia) remain unclear and may be studied further.
- As additional therapies emerge for COVID-19, notably novel immunomodulators, it will become increasingly important to ascertain how these interact with systemic corticosteroids. All investigational therapies for severe and critical COVID-19 (including remdesivir) should be compared with systemic corticosteroids or evaluated in combination with systemic corticosteroids vs. systemic corticosteroids alone.
- Other uncertainties include:
    - The impact of systemic corticosteroids on immunity and the risk of a subsequent infection, which may impact the risk of death after 28 days.
    - Steroid preparation, dosing and optimal timing of drug initiation.

- Generalizability of study results to populations that were under-represented in the trials considered by the panel (e.g. children, immunocompromised patients, patients with tuberculosis).
- Generalizability in resource-limited settings (i.e. low- and middle-income countries).
- Effect on viral replication.

Dissemination

These guidelines will be published on the WHO website, in the *British Medical Journal* as part of the rapid recommendation series, and available for global re-use and adaptation in other platforms, including the MAGIC authoring and publication platform (MAGICapp) These guidelines will also be disseminated by the WHOACADEMY app, OpenWHO.org clinical care channel, and included into the updates of WHO Clinical care for severe acute respiratory infection toolkit: COVID-19 adaptation and WHO COVID-19 clinical care bundles.

Updates to this article

This guidance will be released in coordination with the release of the publication of the prospective meta-analysis and three other large clinical trials on corticosteroids. As new evidence is published, the WHO Secretariat for Therapeutics and COVID-19 will assess the new evidence and make a judgment on the extent that it is expected to alter the recommendation. Updated recommendations will appear on the WHO website and be disseminated as above.

Appendix 1: Summary

Guideline perspective and key considerations in resource-limited settings

In this guideline we take an individual patient perspective but also place a high value on resource allocation. In such a perspective, attention is paid to the opportunity cost associated with the widespread provision of therapies for COVID-19. The fact that systemic corticosteroids are a low-cost intervention, are easy to administer and readily available globally influenced the strength of this recommendation.

Description of population and interventions

This recommendation applies to all patients with COVID-19.

Description of interventions

Systemic corticosteroids (intravenous or oral) added to usual care versus usual care alone.

Description of outcomes

1. Mortality.
2. Need for invasive mechanical ventilation.
3. Serious adverse events leading to drug discontinuation.
4. Duration of hospitalization.
5. Time to symptom resolution.
6. Duration of intensive care unit stay.
7. Duration of mechanical ventilation.

Recommendation 1

We recommend systemic corticosteroids rather than no corticosteroids for the treatment of patients with severe and critical COVID-19 (strong recommendation).

Recommendation 2

We suggest not to use systemic corticosteroids in the treatment of patients with non-severe COVID-19 (conditional recommendation).

The evidence: *The panel made its recommendation on the basis of the moderate certainty evidence of a mortality reduction of 8.7% and 6.7% in patients with COVID-19 who are critically or severely ill.*

Key practical issues for the use of systemic corticosteroids will visualize the following:

Medication route: systemic corticosteroids may be administered orally or intravenously.
Medication type: dexamethasone or other corticosteroids, such as hydrocortisone or prednisone may be used.
Medication routine: once daily regimens of dexamethasone 6 mg once daily is equivalent to 160 mg of hydrocortisone (e.g. 50 mg every 8 hours or 100 mg every 12 hours), 40 mg of prednisone, 32 mg of methylprednisolone (e.g. 8 mg every 6 hours or 16 mg every 12 hours).
Duration: up to 7–10 days.
Monitoring: monitor glucose levels, regardless of whether patient is known to have diabetes.
Adverse effects, interactions and antidote: the safety profile of systemic corticosteroids is favourable.
Costs and access: systemic corticosteroid therapy is a low-cost intervention that is easy to administer and readily available globally.

Values and preferences

The panel took an individual patient perspective to values and preferences but, given the burden of the pandemic for health care systems globally, also placed a high value on resource allocation and equity. The benefit of corticosteroids on mortality was deemed of critical importance to patients, with little or no anticipated variability in their preference to be offered treatment if severely ill from COVID-19.

Appendix 2: Table A2.1 Summary of findings

Steroids versus standard care Patients with COVID-19 (including subgroups for critical, severe and non-severe illness for the outcome of mortality)					
Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (quality of evidence)	**Plain text summary**
		Usual care	Corticosteroids		
Mortality in patients with critical illness 28 days	Relative risk 0.79 (95% CI 0.70–0.90) Data from 1703 patients in 7 studies Follow up: 28 days	415 per 1000	328 per 1000	**Moderate** Due to serious risk of bias (lack of blinding)	Systemic corticosteroids probably reduce the risk of 28-day mortality in patients with critical illness due to COVID-19
		Difference: **87 fewer per 1000 (95% CI 124 fewer – 41 fewer)**			
Mortality in patients with severe illness 28 days	Relative risk 0.80 (95% CI 0.70–0.92) Data from 3883 patients in 1 study Follow up: 28 days	334 per 1000	267 per 1000	**Moderate** Due to serious risk of bias (lack of blinding)	Systemic corticosteroids probably reduce the risk of 28-day mortality in patients with severe COVID-19
		Difference: **67 fewer per 1000 (95% CI 100 fewer – 27 fewer)**			
Mortality in patients with non-severe illness 28 days	Relative risk 1.22 (95% CI 0.93–1.61) Data from 1535 patients in 1 study Follow-up: 28 days	176 per 1000	215 per 1000	**Low** Due to serious risk of bias (lack of blinding) and imprecision	Systemic corticosteroids may increase the risk of 28-day mortality in patients with non-severe COVID-19
		Difference: 39 more per 1000 **(95% CI 12 fewer – 107 more)**			
Need for invasive mechanical ventilation	Relative risk 0.74 (95% CI 0.59–0.93)	116 per 1000	86 per 1000	**Moderate** Due to serious risk of bias	

28 days	Data from 5481 patients in 2 studies Follow up: 28 days	Difference: **30 fewer per 1000** **(95% CI 48 fewer – 8 fewer)**	(risk of bias due to lack of blinding)	Systemic corticosteroids probably reduce the risk of mortality
Duration of hospitalization	Data from 6425 patients in 1 study Follow up: not reported	13 Days (median) | 12 Days (median) Difference: **1 lower**	**Low** Due to serious risk of bias (lack of blinding) and imprecision (CI includes no benefit)	Steroids may result in an important reduction in the duration of hospitalizations
Time to symptom resolution	Not reported			
Duration of intensive care unit stay	Not reported			
Duration of mechanical ventilation	Not reported			
Serious adverse events (indirect evidence from ARDS, community-acquired pneumonia and sepsis populations)				
Gastrointestinal bleeding	Relative risk 1.06 (95% CI 0.85–1.33) (5403 patients, 30 studies)	48 per 1000 | 51 per 1000 Difference: **3 more per 1000** **(95% CI 7 fewer – 16 more)**	**Low** Due to serious indirectness and serious imprecision	Corticosteroids may not increase the risk of gastrointestinal bleeding

Super-infections	Relative risk 1.01 (95% CI 0.90–1.13) (6027 patients, 32 studies)	186 per 1000	188 per 1000 Difference: **2 more per 1000 (95% CI 19 fewer – 24 more)**	**Low** Due to serious indirectness and serious imprecision	Corticosteroids may not increase the risk of super-infections
Hyperglycaemia	Relative risk 1.16 (95% CI 1.08–1.25) (8938 patients, 24 studies)	286 per 1000	332 per 1000 Difference: **46 more per 1000 (95% CI 23 more – 72 more)**	**Moderate** Due to serious indirectness	Corticosteroids probably increase the risk of hyperglycaemia
Hypernatraemia	Relative risk 1.64 (95% CI 1.32–2.03) (5015 patients, 6 studies)	40 per 1000	66 per 1000 Difference: **26 more per 1000 (95% CI 13 more – 41 more)**	**Moderate** Due to serious indirectness	Corticosteroids probably increase the risk of hypernatraemia
Neuromuscular weakness	Relative risk 1.09 (95% CI 0.86–1.39) (6358 patients, 8 studies)	69 per 1000	75 per 1000 Difference: **6 more per 1000 (95% CI 10 fewer – 27 more)**	**Low** Due to serious indirectness and serious imprecision	Corticosteroids may not increase the risk of neuromuscular weakness
Neuropsychiatric effects	Relative risk 0.81 (95% CI 0.41–1.63) (1813 patients, 7 studies)	35 per 1000	28 per 1000 Difference: **7 fewer per 1000**	**Low** Due to serious indirectness and serious imprecision	Corticosteroids may not increase the risk of neuropsychiatric effects

		(95% CI 21 fewer – 22 more)			
Stroke	Relative risk 2.07 (95% CI 0.45–9.61) (1105 patients, 3 studies)	4 per 1000	8 per 1000 Difference: **4 more per 1000 (95% CI 2 fewer – 34 more)**	**Very low** Due to serious indirectness and very serious imprecision	Whether or not corticosteroids impact the risk of stroke is uncertain
Myocardial infarction	Relative risk 0.91 (95% CI 0.45–1.82) (1080 patients, 3 studies)	30 per 1000	27 per 1000 Difference: **3 fewer per 1000 (95% CI 17 fewer – 25 more)**	**Very low** Due to serious indirectness and very serious imprecision	Whether or not corticosteroids impact the risk of myocardial infarction is uncertain

Appendix 2: Table A2.2 Characteristics of trials included in the systematic review of effects of systemic corticosteroids for COVID-19

	DEXA-COVID19 (NCT04325061)	CoDEX (NCT04327401)	RECOVERY (NCT04381936)	CAPE-COVID (NCT02517489)	COVID STEROID (NCT04348305)	REMAP-CAP (NCT02735707)	Steroids-SARI (NCT04244591)	GLUCOCOVID	MetCOVID (NCT04343729)
Planned sample size (N)	200	350	N/A	290	1000	N/A	80	180	420
Eligibility criteria	Intubated, mechanically ventilated, moderate-severe ARDS per Berlin criteria, confirmed COVID-19	Intubated, mechanically ventilated, moderate-severe ARDS per Berlin criteria, onset of ARDS < 48 hrs before randomization, probable or confirmed COVID-19	Intubated, suspected or confirmed COVID-19 (for this meta-analysis)	Minimal severity: admitted to ICU or intermediate care unit, on oxygen (minimum 6 L/min), probable or confirmed COVID-19	Minimal severity: on oxygen (minimum 10 L/min), confirmed COVID-19	Admitted to ICU receiving high-flow nasal oxygen with FiO_2 at least 0.4 at 30 L/min or higher; non-invasive or invasive ventilatory support; or receiving vasopressors, probable or confirmed COVID-19	Admitted to ICU with PaO_2/FiO_2 < 200 mmHg on positive pressure ventilation (invasive or non-invasive), or high-flow nasal cannula higher than 45 L/min, confirmed COVID-19	Symptom duration of at least 7 days, radiological evidence of lung disease in chest X-ray or CT scan, moderate-to-severe disease with abnormal gas exchange: PaFi (PaO_2/FiO_2) < 300, or SAFI (SaO_2/FiO_2) < 400, or at least two criteria of the Brescia-COVID Respiratory Severity Scale; laboratory parameters suggesting a hyper-inflammatory state: serum C-reactive protein (CRP) > 15 mg/dL, D-dimer > 800 mg/dL, ferritin > 1000 mg/dL or IL-6 levels > 20 pg/mL	Hospitalized patients with clinical and/or radiological suspicion of COVID-19 (history of fever and any respiratory symptom, e.g. cough or dyspnoea and/or ground glass opacity or pulmonary consolidation on CT scan), aged 18 years or older at the time of inclusion, with $SpO_2 \leq 94\%$ at room air or in use of supplementary oxygen or under invasive mechanical ventilation
Corticosteroid intervention, and classification as low or high dose	High: Dexamethasone 20 mg IV daily x 5 days, then 10 mg IV daily x 5 days	High: Dexamethasone 20 mg IV daily x 5 days, then 10 mg IV daily x 5 days	Low: Dexamethasone 6 mg PO/IV daily	Low: Hydrocortisone IV continuous infusion x 8 or 14 days (200 mg daily x 4 or 7 days, 100 mg daily x 2 or 4 days, 50 mg daily x 2 or 3 days)	Low: Hydrocortisone 200 mg IV daily x 7 days (continuous or bolus in q6h dosing)	Low: Hydrocortisone 50 mg IV q6h daily x 7 days	High: Methylprednisolone 40 mg IV q12h x 5 days	High: Methylprednisolone 40 mg IV q12 x 3 days and then 20 mg q12h x 3 days	High: Methylprednisolone IV 0.5 mg/kg q12h x 5 days

Control intervention	Standard of care	Standard of care	Standard of care	Placebo	Placebo	Standard of care	Standard of care	Standard of care	Saline solution q12h x 5 days
Primary outcome	60-day mortality	Ventilator-free days	28-day mortality	21-day treatment failure (death or persistent dependency on mechanical ventilation or high-flow oxygen therapy)	Days alive without life support at day 28	Composite of hospital mortality and ICU organ support-free days to day 21	Lower lung injury score at 7 and 14 days	Composite endpoint that included in-hospital all-cause mortality, escalation to ICU admission, or progression of respiratory insufficiency that required non-invasive ventilation	28-day mortality
Mortality outcome	28 days	28 days	28 days	21 days	28 days	28 days	30 days	In-hospital	28 days
Definition of serious adverse events (SAEs)	Secondary infections: pneumonia, sepsis and similar; pulmonary embolism	Mortality; infections; insulin use	Cause-specific mortality; ventilation; renal dialysis; cardiac arrhythmia (in a subset); other SAEs believed to be related to study treatment	All SAEs excluding some listed in the protocol and excluding those expected adverse events which are related to the patient's disease or comorbidity	New episodes of septic shock (Sepsis-3 criteria); invasive fungal infection; clinically important GI bleeding; anaphylaxis	Per ICH GCP (events not already captured as a trial endpoint, e.g. mortality) and where the event may reasonably have occurred because of study participation	Secondary bacterial infections; barotrauma; severe hyperglycaemia; GI bleeding requiring transfusion; acquired weakness (these events were not categorized into SAE and non-SAE)	Hyperglycaemia	Sepsis or positive blood culture collected on day 7; insulin due to hyperglycaemia
Location	Spain	Brazil	United Kingdom	France	Denmark	Australia, New Zealand, United Kingdom, Canada, United States, European Union	China	Spain	Brazil

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