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Additional material is published online only. To view please visit the journal online

Cite this as: *BMJ* 2020;370:m3379
http://dx.doi.org/10.1136/bmj.m3379

RAPID RECOMMENDATIONS

A living WHO guideline on drugs for covid-19

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ABSTRACT

CLINICAL QUESTION

What is the role of drug interventions in the treatment and prevention of covid-19?

RECOMMENDATIONS

The first version on this living guidance focuses on corticosteroids. It contains a strong recommendation for systemic corticosteroids in patients with severe and critical covid-19, and a weak or conditional recommendation against systemic corticosteroids in patients with non-severe covid-19. Corticosteroids are inexpensive and are on the World Health Organisation list of essential medicines.

HOW

this guideline was created This guideline reflects an innovative collaboration between the WHO and the MAGIC Evidence Ecosystem Foundation, driven by an urgent need for global collaboration to provide trustworthy and living covid-19 guidance. A standing international panel of content experts, patients, clinicians, and methodologists, free from relevant conflicts of interest, produce recommendations for clinical practice. The panel follows standards, methods, processes, and platforms for trustworthy guideline development using the GRADE approach. We apply an individual patient perspective while considering contextual factors (that is, resources, feasibility, acceptability, equity) for countries and healthcare systems.

THE EVIDENCE

A living systematic review and network meta-analysis, supported by a prospective meta-analysis, with data from eight randomised trials (7184 participants) found that systemic corticosteroids probably reduce 28 day mortality in patients with critical covid-19 (moderate certainty evidence; 87 fewer deaths per 1000 patients (95% confidence interval 124 fewer to 41 fewer)), and also in those with severe disease (moderate certainty evidence; 67 fewer deaths per 1000 patients (100 fewer to 27 fewer)). In contrast, systemic corticosteroids may increase the risk of death in patients without severe covid-19 (low certainty evidence; absolute effect estimate 39 more per 1000 patients, (12 fewer to 107 more)). Systemic corticosteroids probably reduce the need for invasive mechanical ventilation, and harms are likely to be minor (indirect evidence).

UNDERSTANDING THE RECOMMENDATIONS

The panel made a strong recommendation for use of corticosteroids in severe and critical covid-19 because there is a lower risk of death among people treated with systemic corticosteroids (moderate certainty evidence), and they believe that all or almost all fully informed patients with severe and critical covid-19 would choose this treatment. In contrast, the panel concluded that patients with non-severe covid-19 would decline this treatment because they would be unlikely to benefit and may be harmed. 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 lifesaving therapy.

UPDATES

This is a living guideline. Work is under way to evaluate other interventions. New recommendations will be published as updates to this guideline.

READERS NOTE

This is version 1 of the living guideline, published on 4 September (*BMJ* 2020;370:m3379) version 1. Updates will be labelled as version 2, 3 etc. When citing this article, please cite the version number.

SUBMITTED

August 28

ACCEPTED

August 31

As of 1 September 2020, 25 327 098 people worldwide have been diagnosed with covid-19, according to the international World Health Organization (WHO) dashboard.[1] 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 resource and low resource countries alike.

The covid-19 pandemic—and its related infodemic, given the explosion of research combined with misinformation and hoaxes—has demonstrated a need for trustworthy, accessible, and regularly updated (living) guidance to place emerging findings into context and give clear recommendations for clinical practice. This living guideline responds to emerging evidence on existing and new drug treatments for covid-19 from trials. An overview of registered and ongoing trials is available from the Infectious Diseases Data Observatory (see table of

ongoing trials for corticosteroids in appendix 1 on bmj.com).[2] The living network meta-analysis associated with this guideline will incorporate new trial data as the evidence base increases and allow for analysis of comparative effectiveness of multiple covid-19 treatments.[3] This network meta-analysis and other related publications are included in box 1. We will also use additional relevant evidence on long term safety, prognosis, and patient values and preferences related to covid-19 treatments to inform the living guidance.

Box 1: Linked resources in this *BMJ* Rapid Recommendations cluster

- Lamontagne F, Agoritsas T, Macdonald H, et al. A living WHO guideline on drugs for covid-19. *BMJ* 2020;370:m3379
- Siemieniuk RAC, Bartoszko JJ, Ge L, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. *BMJ* 2020;370:m2980, doi:10.1136/bmj.m2980
- World Health Organization. Corticosteroids for COVID-19. Living guidance 2 September 2020. https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1
- The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA* 2020 doi:10.1001/jama.2020.17023
  - Additional prospective meta-analysis supporting the guidance
- MAGICapp (https://app.magicapp.org/#/guideline/EZYw5n)
  - Expanded version of the methods, processes, and results with multilayered recommendations, evidence summaries, and decision aids for use on all devices

How to use this guideline?

This is a living guideline, so the recommendations included here will be updated, and new recommendations will be added on other therapies for covid-19. The infographic provides a summary of the recommendations and supporting evidence and includes links to the MAGICapp for more details on the evidence and rationale for the recommendation, as well as patient decision aids. Box 2 outlines key methodological aspects of the guideline process.

Box 2: How this living guideline was created

This guideline was developed by WHO and the MAGIC Evidence Ecosystem Foundation (MAGIC), with support from *The BMJ*. It is driven by an urgent need for global collaboration to provide trustworthy and living guidance, rapidly informing policy and practice worldwide during an outbreak of an emerging infectious disease, such as this covid-19 pandemic. WHO has partnered with MAGIC for their methodologic support in the development and dissemination of living guidance for covid-19 drug treatments, in the form of *BMJ* Rapid Recommendations, to provide patients, clinicians, and policy makers with up to date, evidence based, and user friendly guidance.

Standards, methods, and processes for living and trustworthy guidance

The panel produced the recommendations following standards for trustworthy guideline development using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach, in compliance with the *WHO Handbook for Guideline Development 2nd edition*,[4] the Institute of Medicine, and the Guideline International Network (G-I-N).[5] Details are provided in MAGICapp (https://app.magicapp.org/#/guideline/EZYw5n).

Selection and support of the panel

An international, guideline development panel was composed of 23 individuals, of whom 21 were content experts (clinicians, methodologists, scientists) and two were patients who survived covid-19. The Methods Chair (methodological expertise) and a Clinical Chair (content expertise) guided the panel discussions. 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. Following consultation with the 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, and patient representation. No relevant conflict of interest was identified for any panel member. As recommended by 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.

Guideline perspective, outcomes, and values and preferences

The target audience for this guidance consists primarily of clinicians, but secondarily of patients and healthcare decision makers. The panel considered an individual patient perspective but also took account of contextual factors (such as resources, feasibility, acceptability, equity) to accommodate global re-use and adaptation for countries and healthcare systems. 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 that they should therefore attempt to consider the values and preferences of the average patient.

During a pandemic, access to healthcare may vary over time and between different countries. The panel defined covid-19 by clinical severity, and mutually exclusive definitions are provided in box 3.

Values and preferences of the average patient were considered, ahead of the first meeting, by panel members, including two covid-19 survivors. Asked to consider a list of outcomes deemed relevant to covid-19 research, panel members considered the importance of each outcome and whether they agreed with a hierarchy ranging from "critically important" to "not very important." Panel members were reminded to consider the perspective of the patients and 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 would be conversations with patient panel members as the discussion proceeded. Another would be their own experience in shared decision making with patients and families.

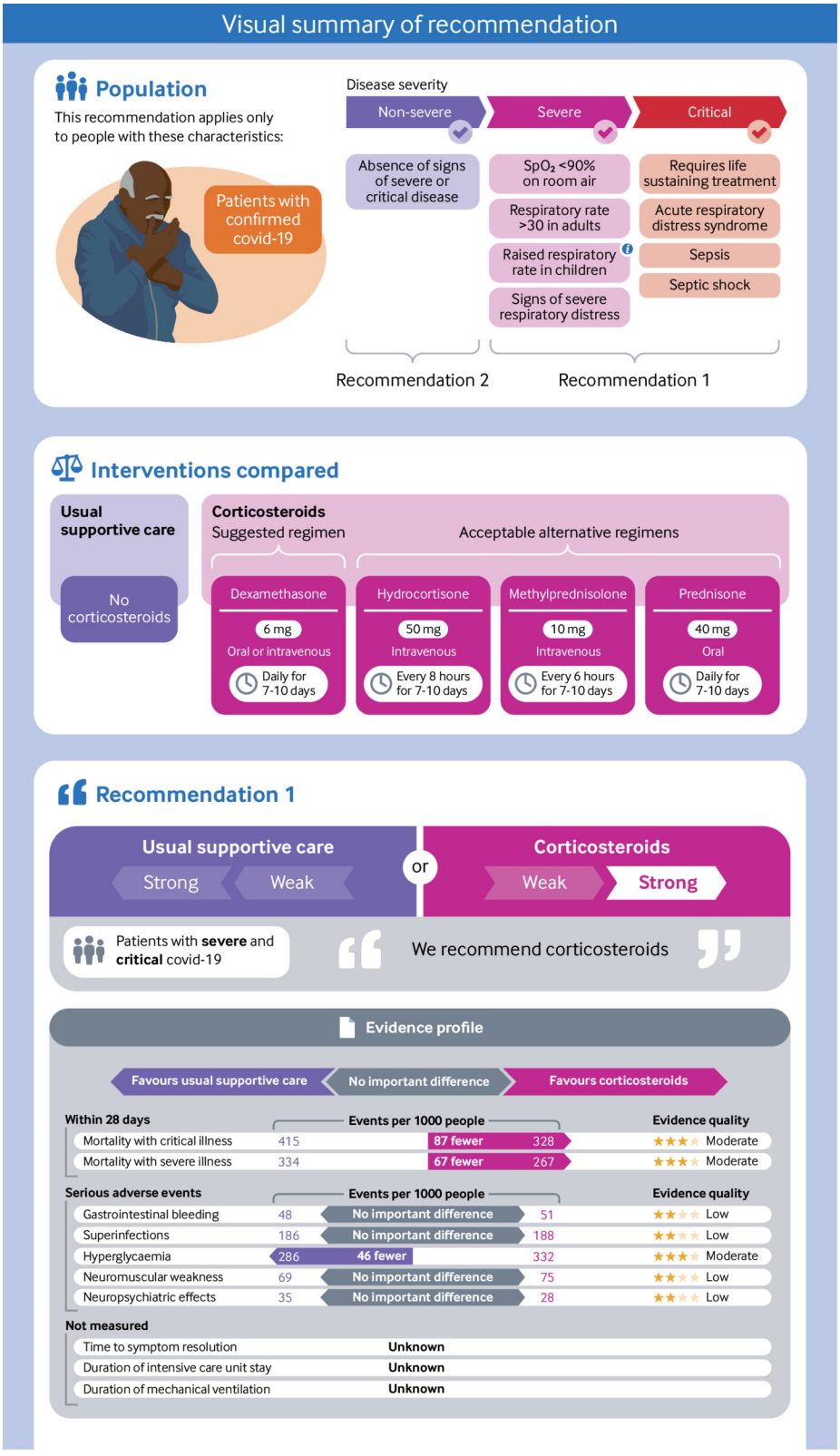
Sources of evidence

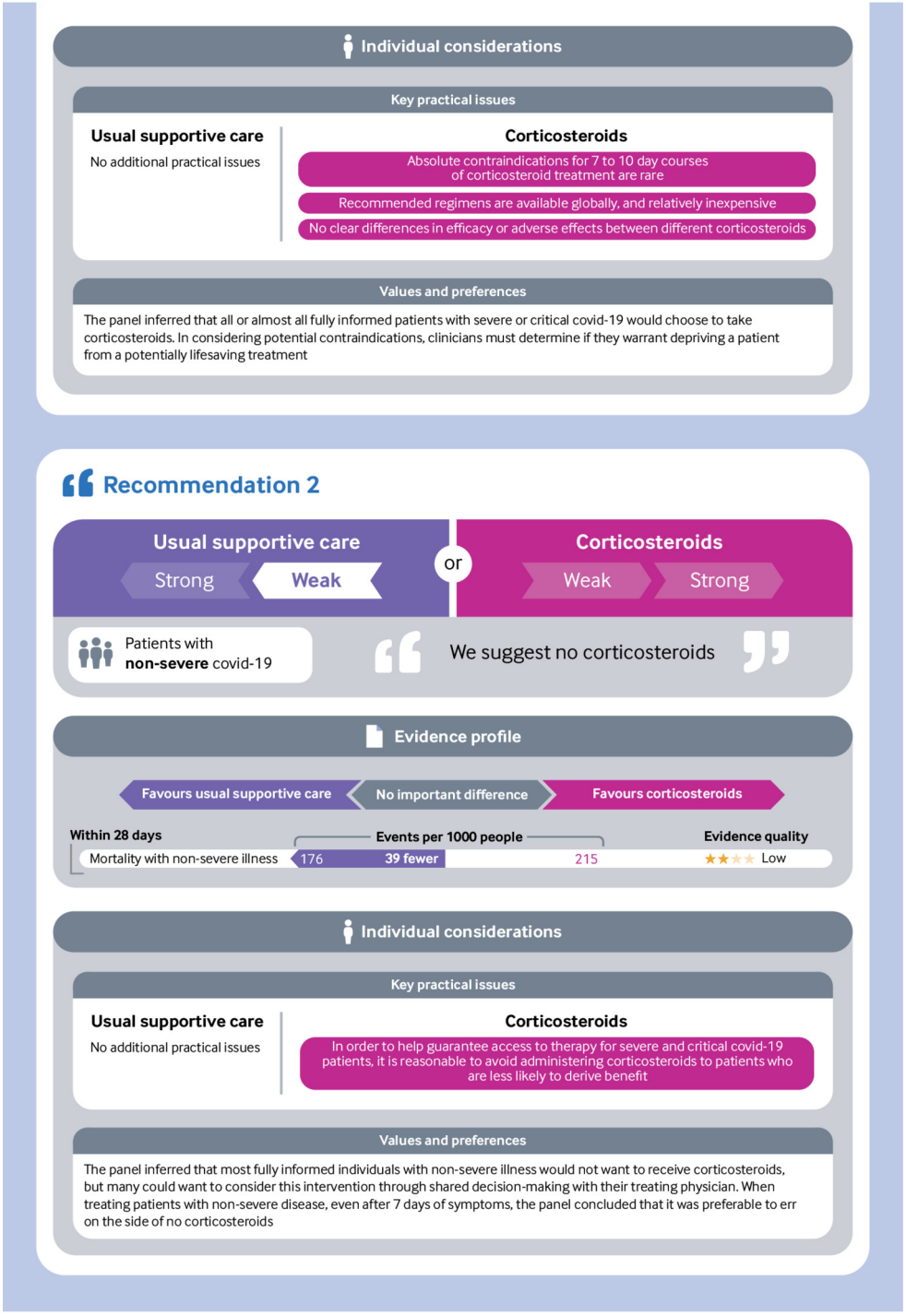
To create recommendations, the panel relied on evidence synthesised in a living network meta-analysis led by MAGIC,[3] on a prospective meta-analysis of RCTs evaluating corticosteroids for critically ill COVID-19 patients commissioned by the WHO,[6] as well as systematic reviews of the safety of similar regimens of systemic corticosteroids in distinct but relevant patient populations.[7 8] While the investigators responsible for meta-analyses rate the certainty of the evidence, this is re-assessed independently by the guideline panel.

Derivation of absolute effects for drug treatments

Using the pooled relative risk from the meta-analyses and the best available current evidence of prognosis in patients with covid-19 (such as 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. Taking corticosteroids as an 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 for corticosteroids apply across baseline event rates.





thebmj See an interactive version of this graphic online http://bit.ly/BMJrrccs

The standing guideline panel applied the WHO severity definitions based on clinical indicators[9] in order to align with other WHO guidance.[10] These definitions avoid reliance on access to health care to define patient subgroups. Box 3 is adapted from WHO covid-19 disease severity categorisation. This guideline is presented by drug and by patient population: the evidence related to the effect of each drug may lead the panel to adapt the specific population one drug would apply to.

Box 3: WHO definitions of disease severity for covid-19 (see https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2020.1)

- *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 breaths/min in children ‹2 months old, ≥50 in children 2-11 months old, and ≥40 in children 1-5 years old
  - Signs of severe respiratory distress (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 judgment to determine whether a low oxygen saturation is a sign of severity or is normal for a given patient with chronic lung disease. Similarly, a saturation ›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.

Table 1 lists the information that has emerged since the panel created recommendations (for corticosteroids; 17 July 2020) but before the guideline went to press. Rapid responses on bmj.com will highlight evidence that have emerged since this version of the guideline was published. As new evidence emerges, WHO will make a judgment on the implications for existing recommendations and will update and publish guidance as the evidence itself is published.

What triggered this version of the guideline?

A preliminary report of the RECOVERY trial in June 2020 suggested that dexamethasone reduced mortality in covid-19 patients, with a subgroup analysis suggesting the benefit to be restricted to patients with severe and critical covid-19.[11] This evidence was complemented by new data from six randomised trials of corticosteroids reporting mortality data by subgroup in a prospective meta-analysis of randomised trials for corticosteroid therapy for covid-19.[6] The data were made immediately available for the guideline panel, allowing the WHO guidance to be peer reviewed and published simultaneously with the prospective meta-analysis and three of the individual trials.[12-14]

The guidance

On 17 July 2020 the panel reviewed evidence from eight RCTs (7184 patients) evaluating systemic corticosteroids versus usual care in treatment of covid-19,[6] of which seven reported mortality data by subgroup of illness severity. (Mortality data from one trial, GLUCOCOVID, were not incorporated in the Summary of Finding for mortality because the mortality outcome data was not available by subgroup). The panel did not consider transdermal or inhaled administration of corticosteroids, high dose or long-term regimens, or prophylaxis. Box 4 outlines the evidence. The panel did not reach consensus on recommendation 1, which required a vote. The second recommendation was made by consensus. More details on the underlying panel discussions can be found in the WHO guidance document (see box 1 for link).

Box 4: Outline of the evidence on systemic corticosteroids

While six trials evaluated systemic corticosteroids exclusively in critically ill patients, the RECOVERY trial enrolled hospitalised patients with covid-19 and reported mortality data by subgroup, whereas the smaller GLUCOCOVID trial, which also enrolled hospitalised patients, did not. 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 randomisation. 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.

- *Population*—There were data from 1703 critically ill patients in seven trials. RECOVERY, the largest of the seven trials randomised 6425 hospitalised patients in the United Kingdom (2104 were randomised to dexamethasone and 4321 were randomised to usual care). At the time of randomisation, 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.[11] The mortality data from six other smaller trials included approximately 700 critically ill patients (definitions of critical illness varied across studies) enrolled up to 9 June 2020, approximately 80% were invasively mechanically ventilated; approximately 50% were randomised to receive corticosteroid therapy, and 50% randomised to no corticosteroid therapy. RECOVERY was the only trial reporting mortality data for patients with severe and non-severe COVID-19 (3883 patients with severe and 1535 patients with non-severe covid-19). Because the mortality data from one trial (GLUCOCOVID, n=63) was not reported separately for severe and non-severe covid-19,[16] the panel reviewed only the data pertaining to the outcome of mechanical ventilation from this trial.
- *Interventions*—RECOVERY evaluated the effects of dexamethasone 6 mg given once daily (oral or intravenous) for up to 10 days. Other corticosteroid regimens included dexamethasone 20 mg daily for 5 days followed by 10 mg daily for 5 days (two trials, DEXA-COVID and CoDEX); hydrocortisone 200 mg daily for 4-7 days followed by 100 mg daily for 2-4 days and then 50 mg daily for 2-3 days (one trial, CAPE-COVID); hydrocortisone 200 mg daily for 7 days (one trial, REMAP-CAP); methylprednisolone 40 mg every 12 hours for 5 days (one trial, Steroids-SARI); and methylprednisolone 40 mg every 12 hours for 3 days and then 20 mg every 12 hours for 3 days (one trial, GLUCOCOVID).[3] Seven of the trials were conducted in individual countries (Brazil, China, Denmark, France, Spain), while REMAP-CAP was an international study (recruiting in 14 European countries, Australia, Canada, New Zealand, Saudi Arabia, and UK).
- *Outcomes*—All trials reported mortality 28 days after randomisation, except for one trial at 21 days and the another at 30 days.

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).

Who does it apply to?

This recommendation applies to patients with severe and critical covid-19. The panel judged that all or almost all fully informed patients with severe covid-19 would choose to take systemic corticosteroids. The recommendation should apply to patients with severe and critical covid-19 even if they cannot be hospitalised or receive oxygen because of resource limitations.

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. In considering potential contraindications to short term systemic corticosteroids in such patients, clinicians must determine if they warrant depriving a patient of a potentially lifesaving therapy. Clinicians should exercise caution in use of corticosteroids in patients with diabetes or underlying immunocompromise. 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.

Balance of benefit and harm

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% reduction in patients with severe covid-19 who were not critically ill. Systemic corticosteroids compared with no corticosteroid therapy probably reduce the risk of 28 day mortality in critically ill patients with covid-19 (moderate certainty evidence; relative risk (RR) 0.80 (95% confidence interval 0.70 to 0.91); absolute effect estimate 87 fewer deaths per 1000 patients (95% CI 124 fewer to 41 fewer)). In patients with severe covid-19, systemic corticosteroids also probably reduce the risk of death (moderate certainty evidence; RR 0.80 (0.70 to 0.92); absolute effect estimate 67 fewer deaths per 1000 patients (100 fewer to 27 fewer)). The effects of systemic corticosteroids on other outcomes are described in the summary of findings (infographic and links to MAGICapp).

Overall, the panel has high certainty that the adverse effects when considered together are sufficiently limited in importance and frequency that corticosteroids administered in these doses for 7 to 10 days 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 (23 more to 72 more)) and hypernatremia (moderate certainty evidence; 26 more per 1000 patients (13 more to 41 more)). 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.

Values and preferences

The panel took an individual patient perspective to values and preferences but, given the burden of the pandemic for healthcare systems globally, also placed a high value on resource allocation and equity. The benefits 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.

Resource implications, feasibility, equity, and human rights

Systemic corticosteroids are low cost, easy to administer, and readily available globally.[17] Dexamethasone and prednisolone are among the most commonly listed medicines in national essential medicines lists; listed by 95% of countries. 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 (weak or conditional recommendation based on low certainty evidence).

Who does it apply to?

This recommendation applies to patients with non-severe disease regardless of their hospitalisation status. The panel noted that patients with non-severe covid-19 would not normally require acute care in hospital or respiratory support, but in some jurisdictions these patients may be hospitalised for isolation purposes only, in which case they should not be treated with systemic corticosteroids. Several specific circumstances were considered.

- Systemic corticosteroids should not be stopped for patients with non-severe covid-19 who are already treated with systemic corticosteroids for other reasons (such as patients with chronic obstructive pulmonary disease or chronic autoimmune disease).
- If the clinical condition of patients with non-severe covid-19 worsens (that is, increase in respiratory rate, signs of respiratory distress or hypoxaemia) they should receive systemic corticosteroids (see recommendation 1).
- Pregnancy: antenatal corticosteroid therapy may be administered 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. 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 healthcare resources.
- 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.

Balance of benefit and harm

Systemic corticosteroids may increase the risk of 28 day mortality (low certainty evidence; RR 1.22 (95% CI 0.93 to 1.61); absolute effect estimate 39 more per 1000 patients (95% CI 12 fewer to 107 more)). The certainty of the evidence for this specific subgroup was downgraded due to serious imprecision (that is, the evidence does not allow to rule out a mortality reduction) and risk of bias due to lack of blinding. The effects of systemic corticosteroids on other outcomes are described in the summary of findings (infographic and links to MAGICapp).

Values and preferences

The weak or conditional recommendation was driven by likely variation in patient values and preferences. The panel judged that most individuals with non-severe illness would decline systemic

corticosteroids. However, many may want them after shared decision making with their treating physician.

Resource implications, feasibility, equity, and human rights

To help guarantee access to systemic corticosteroids for patients with severe and critical covid-19, it is reasonable to avoid their administration to patients who, given the current evidence, do not seem to derive any benefit from this intervention

Practical issues for corticosteroids

Route—Systemic corticosteroids may be administered both orally and intravenously. Of note, while the bioavailability of dexamethasone is very high (that is, 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.

Duration—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 five and 14 days, and treatment was generally discontinued at hospital discharge (that is, the duration of treatment could be less than the duration stipulated in the protocols).

Dose—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 (that is, 50 mg every 8 hours), 40 mg of prednisone, or 32 mg of methylprednisolone (8 mg every 6 hours or 16 mg every 12 hours).

Monitoring—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.

Timing—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 seven days or more after symptom onset may be more beneficial than treatment initiated within seven days of symptom onset. A post hoc subgroup analysis within the prospective meta-analysis 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 often appear late (that is, 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)."

Uncertainty

The following uncertainties remain.

- 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 (that is, 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 versus systemic corticosteroids alone.
- Other uncertainties include:
  - The impact of systemic corticosteroids on immunity and the risk of a subsequent infection, which may affect the risk of death after 28 days.
  - Steroid preparation, dosing, and optimal timing of drug initiation.
  - Generalisability of study results to populations that were underrepresented in the trials considered by the panel (such as children, immunocompromised patients, patients with tuberculosis).
  - Generalisability in resource-limited settings (that is, low and middle income countries).
  - Effect on viral replication.

How patients were involved in the creation of this article

The guideline panel included two patients who have had covid-19. Both emphasized the distress associated with suffering from COVID-19 and expressed that benefits associated with corticosteroids appeared to considerably outweigh relatively minor safety concerns.

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Competing interests: All guideline panel members have completed the WHO interest disclosure form. All authors have completed the *BMJ* Rapid Recommendations interest of disclosure form. The WHO, MAGIC and *The BMJ* judged that no panel member had any financial conflict of interest. Professional and academic interests are minimised as much as possible, while maintaining necessary expertise on the panel to make fully informed decisions. MAGIC and BMJ assessed declared interests from other co-authors of this publication and found no conflicts of interests.

Provenance and peer review: This publication was commissioned by *The BMJ* in partnership with WHO and the MAGIC Evidence Ecosystem Foundation, in the context of the *BMJ* Rapid Recommendations. Pre-publication internal and external peer-review managed by WHO, and internal review at *The BMJ*. Post-publication review on bmj.com on rapid responses and through MAGICapp.

We thank all the following collaborators who contributed to this endeavour, as detailed in the WHO guidance (see link in Box 1)

- World Health Organization (WHO) Secretariat for Therapeutics and COVID-19
- WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group
- External reviewers for WHO

We also thank

- BMJ editorial team with Navjoyt Ladher (editor BMJ Education), Will Stahl-Timmins (infographics designer) and Greg Cotton (technical editor) of this living guideline publication in *The BMJ*
- Brittany Maguire, Philippe Guerin and Sumayyah Rashan for providing up to date corticosteroid data from the Infectious Diseases Data Observatory (IDDO) living systematic review for covid-19 clinical trial registration (https://www.iddo.org/research-themes/covid-19/live-systematic-clinical-trial-review)

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Main infographic: Summary of recommendations and evidence

Appendix 1. Table of registered ongoing trials for corticosteroids

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

Table 1 | Updates to this living guideline: new evidence that has emerged after initial publication

Date	Trigger	Action
12 August 2020	Jeronimo CMP, Farias MEL, Val FFA, et al. Methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19 (metcovid): a randomised, double-blind, phase IIb, placebo-controlled trial. *Clin Infect Dis* 2020 2020;ciaa1177. doi:10.1093/cid/ciaa1177	This additional trial on corticosteroids was published after the panel created recommendations on July 17. The trial results pertaining to critically ill participants was considered by the panel and deemed not to change the recommendation.