RAPID RECOMMENDATIONS

A living WHO guideline on drugs for covid-19

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ABSTRACT

UPDATE

This is a living guideline. It replaces earlier versions (4 September 2020, 20 November 2020, 17 December 2020, 31 March 2021, 6 July 2021, and 23 September 2021). The previous versions can be found as data supplements. New recommendations will be updated as published to this guideline.

CLINICAL QUESTION

What is the role of drugs in the treatment of patients with covid-19?

CONTEXT

The evidence base for therapeutics for covid-19 is increasing with numerous randomized controlled trials (RCTs) underway. This update includes recommendations on convalescent plasma, informed by pooled data from 16 RCTs with 16,236 patients.

NEW RECOMMENDATIONS

The Guideline Development Group (GDG) made a strong recommendation against the use of convalescent plasma in patients with non-severe illness, and a recommendation against its use in patients with severe and critical illness, except in the context of an RCT.

UNDERSTANDING THE NEW RECOMMENDATIONS

When moving from evidence to recommendations, the GDG considered a combination of evidence assessing relative benefits and harms, values and preferences, and feasibility issues. The GDG recognised there was no clear benefit for critical outcomes such as mortality and mechanical ventilation for patients with non-severe, severe, or critical illness, and significant resource requirements in terms of cost and time for administration. Thus, the strong recommendation against use reflects the GDG’s view that plasma administration, especially for patients with non-severe illness where there is a low baseline risk of mortality and other important clinical outcomes, is not justified. The GDG believed that, although convalescent plasma should not be used in any severity subgroups as part of routine care, there was sufficient uncertainty in patients with severe and critical illness to warrant continuation of RCTs.

PRIOR RECOMMENDATIONS

• Recommended for patients with severe and critical covid-19—a strong recommendation for systemic corticosteroids; a strong recommendation for interleukin-6 receptor blockers (tocilizumab or sarilumab); a conditional recommendation for casirivimab and imdevimab, for those having seronegative status.

• Recommended for patients with non-severe covid-19—a conditional recommendation for casirivimab and imdevimab, for those at highest risk of severe disease.

• Not recommended for patients with non-severe covid-19—a conditional recommendation against systemic corticosteroids.

• Not recommended, regardless of covid-19 disease severity—a conditional recommendation against remdesivir, a strong recommendation against hydroxychloroquine; a strong recommendation against lopinavir/ritonavir; a recommendation against ivermectin, except in the context of a clinical trial.

ABOUT THIS GUIDELINE

This living guideline, from the World Health Organization (WHO), incorporates new recommendations on therapies for covid-19 and provides updates on existing recommendations. The GDG typically evaluates a therapy when WHO judges sufficient evidence is available to make a recommendation. While the GDG takes an individual-patient perspective in making recommendations, it also considers resource implications, acceptability, feasibility, equity, and human rights. This guideline was developed according to standards and methods for trustworthy guidelines. MAGIC Evidence Ecosystem Foundation provides methodological support, including the coordination of living systematic reviews with network meta-analysis to inform the recommendations.
This is the seventh version (update 6) of the living guideline (BMJ 2020;370:m3379). It was published on 7 December 2021. When citing this article, please consider adding the update number and date of access for clarity. Guidelines for the use of drugs to prevent (rather than treat) covid-19 are published separately on the WHO website and in The BMJ.

This living guideline responds to emerging evidence from randomised controlled trials (RCTs) on existing and new drug treatments for covid-19. Vaccines are linked to limiting hospitalisations, but it is unclear how long protection following vaccination or natural infection will last, or how this might alter with the emergence of new variants. Therefore, the potential for drugs to treat people infected with covid-19 remains of interest and is the focus of this guideline.

More than 5070 trials on covid-19 interventions have been registered or are ongoing (see section on emerging evidence1). Although most of these studies are small and of variable methodological quality, some large, international platform trials are better equipped to provide robust evidence. Such trials can also adapt their design, recruitment strategies, and selection of interventions based on new insights. Examples include RECOVERY, WHO SOLIDARITY, REMAP-CAP, and ACTIV, which recruit large numbers of patients in many countries.1-5 An overview of ongoing trials is available from the Infectious Diseases Data Observatory, through their living systematic review of covid-19 clinical trial registrations1 and the World Health Organization (WHO) website (https://www.covid-nma.com/dataviz/).

However, existing and evolving evidence demonstrates remaining uncertainties concerning treatment effects for all outcomes of importance to patients. There is also a need for better evidence on prognosis and values and preferences of patients with covid-19. Several living network meta-analyses associated with this guideline incorporate emerging trial data and allow for analysis of comparative effectiveness of multiple covid-19 treatments.6-7 Box 1 includes these network meta-analyses and other related publications. We also use additional relevant evidence on safety, prognosis, and patient values and preferences related to covid-19 treatments to inform the living guidance.

What triggered this version of the guideline?
This seventh version of the WHO living guideline was triggered by the availability of sufficient RCT results to inform recommendations for the use of convalescent plasma in two groups of patients: those with non-severe covid-19, and those with severe and critical illness. It is informed by 16 RCTs and based on a living network meta-analysis on antibodies and cellular therapies for covid-19.7

How to use this guideline
This is a living guideline. The recommendations and evidence included here will be updated, and new recommendations will be added for other drugs for covid-19. The infographic provides a summary of the recommendations 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 1: Linked resources in this BMJ Rapid Recommendations cluster

Versions of this guideline
- MAGICapp (https://app.magicapp.org/#/guideline/nBkOeE)
  - Expanded version of the guideline, including methods, processes, and results with multilayered recommendations, evidence summaries, and decision aids for use on all devices

Linked research

Box 2: How this living guideline was created (see MAGICapp for full details https://app.magicapp.org/#/guideline/nBkOeE)

Standards, methods, and processes for living and trustworthy guidance

Selection and support of the GDG
For the most recent recommendations addressing convalescent plasma, WHO convened a Guideline Development Group (GDG) with 22 individuals, of whom 20 were content experts (clinicians, methodologists, scientists) and two were patients who previously had covid-19. The methods chair (methodological expertise) and a clinical chair (content expertise) guided the GDG discussions. GDG members were invited by WHO, with the aim of achieving gender, geography, expertise, and patient representation balance as well as relevant technical and clinical expertise. No relevant conflict of interest was identified for any GDG member or other contributors to the guideline development process. The GDG aimed to create a recommendation based on consensus with a provision for voting that proved unnecessary for this recommendation.

Guideline perspective, outcomes, and values and preferences
The target audience for this guidance consists of clinicians, patients, and healthcare decision makers. The GDG defined covid-19 by clinical severity (Box 3). The GDG 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, and to recognise system challenges in implementing recommendations.

There were insufficient published data to provide the GDG with an evidence-based description of patient experiences, or values and preferences regarding treatment decisions for covid-19 drug treatments.

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The GDG therefore relied on their own judgments of what well informed patients would value after carefully balancing the benefits, harms, and burdens of treatment. These judgments on values and preferences were also informed through the experiences of former patients with covid-19, represented in the GDG. The GDG agreed that the following values and preferences would be representative of those of typical well-informed patients:

- Most patients would be reluctant to use a treatment for which the evidence left high uncertainty regarding effects on the outcomes they consider important. This was particularly so when evidence suggested treatment effects, if they exist, are small and the possibility of important harm remains.
- In an alternative situation with larger benefits and less uncertainty regarding both benefits and harms, more patients would be inclined to choose the treatment.

**Sources of evidence**

To create recommendations, the GDG relied on evidence synthesised in two living network meta-analyses coordinated by MAGIC. To derive absolute effects for drug treatments for patients with non-severe illness, we used the median of the control arm of the RCTs that contributed to the evidence. For patients with severe and critical illness, the GDG identified the control arm of the WHO SOLIDARITY trial, performed across a wide variety of countries and geographical regions, as representing the most relevant source of evidence for baseline risk estimates for mortality and mechanical ventilation. Systemic corticosteroids now represent standard of care in patients with severe and critical covid-19 (see strong recommendation issued by WHO September 2020). Therefore, the baseline risk estimates in the evidence summaries for convalescent plasma and interleukin-6 receptor blockers were adjusted for treatment effects of corticosteroids for the outcome of mortality and mechanical ventilation. For other outcomes, we used the median of the control arm of the RCTs that contributed to the evidence. Baseline risks, and thus absolute effects, may vary significantly geographically and over time. Thus, users of this guideline may prefer estimating absolute effects by using local event rates.

**Who do the recommendations apply to?**

This guideline applies to all patients with covid-19. Recommendations may differ based on the severity of covid-19. The guideline applies to all patients with covid-19.

**The guidance**

**Convalescent plasma**

Treatment with convalescent plasma involves the transfer of endogenously produced neutralising antibodies present within the plasma from previously infected and recovered patients into patients with active infection. The concentrations (titre) of neutralising antibodies present within convalescent plasma are highly variable between donors, and various methodologies are available to measure antibody levels.

**Evidence underpinning the recommendations is outlined in box 4.**

**Box 4: Convalescent plasma trial data**

The living network meta-analysis evidence summary was informed by 16 trials that enrolled 16,236 patients across non-severe, severe, and critical illness subgroups. All trials were registered, and 80% were published in peer reviewed journals; 20% were preprints. Of the participants, 99% were enrolled from inpatient settings, and 15% of them were admitted to the intensive care unit (ICU). None of the included studies enrolled children or pregnant women.

Antibody titre, method of measuring titres, and the volume of convalescent plasma administered all varied widely across included studies. In some trials, the antibody titre reported for donor eligibility was higher than the reported antibody titre in the donor plasma because of differences in techniques used for the two assessments (for example, total IgG for donor eligibility with subsequent assessment of the specific neutralising antibody titre). Patients with non-severe illness

The living network meta-analyses pooled data from four RCTs with 1602 patients with non-severe illness. Pooled data showed no important impact on mortality (odds ratio [OR] 0.83 [95% confidence interval [CI] 0.43 to 1.46]), with an absolute difference of 1 fewer death per 1000 patients (95% CI 2 fewer to 1 more) (high certainty evidence). Data showed probably no impact on mechanical ventilation (OR 0.71 [0.18 to 1.77]), with an absolute difference of 2 fewer patients needing mechanical ventilation per 1000 patients (95% CI 5 fewer to 5 more). Evidence certainty was rated down to moderate because of concerns regarding serious risk of bias in included studies. There was no data evaluating the risk of hospitalisation with convalescent plasma; therefore, the impact was deemed very uncertain.

**Patients with severe illness**

Pooled data showed convalescent plasma possibly has a small or no effect on mortality (14,366 patients, 10 RCTs; OR 0.92, 95% CI 0.70 to 1.12), with an absolute difference of 9 fewer deaths per 1000 patients (95% CI 35 fewer to 13 more). Evidence certainty was rated down to low because of concerns with indirectness, risk of bias and imprecision. No important impact was seen on mechanical ventilation (623 patients, 5 RCTs; OR 0.92, 95% CI 0.46 to 1.68; 6 fewer per 1000, 95% CI 45 fewer to 50 more), time to symptom resolution (472 patients, 3 RCTs; mean difference [MD] 0 fewer days, 95% CI 1.04 fewer to 3.6 more), length of hospital stay (1,015 patients, 7 RCTs; MD 0.7 fewer days, 95% CI 2.3 fewer to 1.0 more) or ventilator-free days (2859 patients, 3 RCTs; MD 0.7 fewer days, 95% CI 1.8 fewer to 0.4 more) (all low certainty evidence). Patients with any illness severity

Across disease severities, pooled data showed treatment is probably not associated with important increases in risks of transfusion-associated acute lung injury (TRALI) (1365 patients, 4 RCTs; risk difference [RD] 0.03 to 0.13 fewer, 95% CI 0.00 to 0.27 fewer).
fewer per 1000 (95% CI 5 fewer to 6 more)); transfusion-associated circulatory overload (TACO) (1442 patients, 4 RCTs; RD 5 more per 1000 (3 fewer to 12 more); or allergic reactions (15 243 patients, 8 RCTs; OR 3.25 (1.27 to 9.30); 7 more per 1000 (1 more to 24 more)) (all moderate certainty evidence).

- **Subgroup analysis**

  - We pre-specified three subgroup analyses of interest: age (younger adults <70 years old versus older adults >70 years); severity of illness at time of treatment initiation (non-severe vs severe and critical); and treatment dose (higher donor titre vs lower donor titre plasma). The majority of subgroups did not have sufficient data across outcomes of interest to pursue subgroup analyses. Of those that did, we found no significant subgroup effects for severity of illness (P = 0.80) or age (P = 0.84) on mortality, and for severity of illness (P = 0.17) on mechanical ventilation.
Recommendation 1: We recommend against administering convalescent plasma for the treatment of patients with non-severe covid-19 (strong recommendation)

Understanding the recommendation

A combination of the evidence, values and preferences, and feasibility contributed to the strong recommendation against convalescent plasma in patients with non-severe covid-19. The GDG noted that, although it is not demonstrated in the evidence summary, there is always a potential for harms with blood product transfusion. Most importantly, given there was no benefit demonstrated in any of the critical or important outcomes for non-severe covid-19, the GDG did not see any justification for the resources (including time and cost) that would be associated with administration of convalescent plasma.

The included RCTs enrolled non-pregnant women and men. The GDG had no reason to think that children or pregnant women with covid-19 would respond any differently to treatment with convalescent plasma, and the GDG therefore inferred that children and pregnant women should not receive the intervention either.

Balance of benefit and harm—In patients with non-severe disease, convalescent plasma does not have an important impact on mortality. Convalescent plasma probably does not affect mechanical ventilation. There were no data evaluating the risk of hospitalisation with convalescent plasma, and so the impact is very uncertain. Convalescent plasma probably does not result in important increases in risks of transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), or allergic reactions.

The certainty for mortality was high, whereas it was moderate for mechanical ventilation because of serious risk of bias. Certainty was rated as moderate for TRALI and TACO due to serious risk of bias, and for allergic reactions due to concerns regarding risk of bias and imprecision.

Values and preferences—Applying the agreed values and preferences, the GDG inferred that almost all well informed patients with non-severe covid-19 would choose against receiving convalescent plasma.

Resource implications, feasibility, equity, and human rights—The GDG noted that convalescent plasma use is associated with significant resource requirements including identification of potential donors, testing of donors to ensure adequate titres of anti-SARS-CoV-2 antibodies, collection of donor plasma, storage of plasma, transportation of plasma to recipient location, and administration of plasma. These resources and feasibility issues are compounded for those with non-severe disease, who are most often outpatients. Also, this process is costly and time consuming. Given the number of patients with non-severe disease and the low event rate in this subgroup of patients, mobilising the use of convalescent plasma on a large scale would be of questionable feasibility.

Acceptability—Although blood transfusion is acceptable to most, there is a subset of the population who will not accept allogenic blood transfusion. There are also regulatory challenges in most jurisdictions related to blood product transfusion.

Practical issues—Issues include, though are not limited to, the identification and recruitment of potential donors, collection of plasma, storage and distribution of plasma, and infusion of convalescent plasma into recipients.

Recommendation 2: We recommend against administering convalescent plasma for the treatment of patients with severe or critical covid-19 except in the context of a clinical trial

Understanding the recommendation

Given the low certainty evidence suggesting a small or no effect on mortality, mechanical ventilation, or time to symptom improvement, with possible associated harms (although not demonstrated in the evidence summary, there is always a potential for harms with blood product transfusion), the GDG agreed further research addressing these patient-important outcomes would be valuable. A recommendation to use a drug only in the setting of clinical trials is appropriate when there is low certainty evidence and future research has potential to reduce uncertainty about the effects of the intervention and for doing so at a reasonable cost.

Balance of benefit and harm—In patients with severe or critical covid-19, convalescent plasma may not result in an important impact on mortality, mechanical ventilation, time to symptom improvement, length of hospital stay, or ventilator-free days. Convalescent plasma probably does not result in important increases in risks of transfusion-associated acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), or allergic reactions. However, there is always potential for harms with blood product transfusion.

The certainty for mortality was low due to concerns with indirectness, risk of bias, and imprecision. The GDG rated down certainty to low for mechanical ventilation, length of hospital stay, and ventilator-free days because of serious risk of bias and serious imprecision, and rated certainty to low for time to symptom improvement due to serious imprecision. As in patients with non-severe covid-19, certainty was rated as moderate for TRALI and TACO due to serious risk of bias, and moderate for allergic reactions due to concerns regarding risk of bias and imprecision.

Values and preferences—Applying the agreed values and preferences, the GDG inferred that almost all well informed patients would choose against receiving convalescent plasma.

Resource implications, feasibility, equity and human rights, acceptability, and practical issues—Resource implications and feasibility issues were largely similar to those noted for patients with non-severe covid-19. Although convalescent plasma may be easier to administer to hospitalised patients with severe or critical covid-19, it still represents a resource-demanding intervention with several practical challenges to limit its feasibility and applicability.

Specific uncertainties, emerging evidence, and future research on convalescent plasma

- Effects in severe and critical illness (low to moderate certainty evidence for most patient-important outcomes)
- Long term mortality and functional outcomes in covid-19 survivors
- Safety and efficacy in children and pregnant women
- Effects of high titre convalescent plasma on mortality and other patient-important outcomes
- Effects in patients with seronegative antibody status.

Casirivimab-imdevimab (neutralising monoclonal antibodies) (Update 6 published 24 September 2021)

For patients with non-severe illness, data were derived from four RCTs with 4722 patients with non-severe illness, coming from a
larger adaptive randomised master trial. For patients with severe and critical illness, one large trial (RECOVERY) enrolling 9785 patients, most of whom received corticosteroids, informed the estimates. See MAGICapp for detailed description of the mechanism of action, the evidence, and subgroup analyses underpinning the recommendation (https://app.magicapp.org/#/guide-line/nBkO1E/section/LG5NRE).

Overview
Casirivimab and imdevimab are two fully human antibodies (REGN10933 and REGN10987) that bind to the SARS-CoV-2 spike protein and have demonstrated anti-viral activity in animal models. It has been postulated that administration of a combination of casirivimab and imdevimab might have differential effects in patients who have produced their own anti-SARS-CoV-2 spike protein antibodies (hereafter seropositive) compared with those who have not (hereafter seronegative); it was hypothesised that effects might be larger for, or restricted to, seronegative individuals who have not yet mounted an effective natural antibody response.

Recommendation 1: Among patients with non-severe covid-19, we suggest treatment with casirivimab-imdevimab, conditional to those at highest risk of hospitalisation (conditional/weak recommendation)

Understanding the recommendation
A combination of the evidence, values and preferences, and feasibility contribute to the conditional recommendation for the use of casirivimab-imdevimab only in patients with non-severe covid-19 at highest risk of hospitalisation. Although there is moderate certainty evidence of a substantial relative risk reduction in hospitalisation, only a minority of patients who are at highest risk are likely to achieve important benefit. In routine care of those with non-severe covid-19, there exists a lack of tools to accurately identify those at highest risk of hospitalisation. This limitation, combined with the limited availability of the drug and need for parental administration for a group of patients who are typically cared for in the community, present challenges for care that healthcare systems need to address.

Balance of benefit and harm—In non-severely ill patients, casirivimab-imdevimab probably reduces the risk of hospitalisation and duration of symptoms (both moderate certainty); however, the absolute benefit will be trivial or unimportant in absolute terms for all but those at highest risk, for whom the intervention should be reserved. The GDG identified a risk beyond 10% of being hospitalised for covid-19 to represent a threshold at which most people would want treatment with casirivimab-imdevimab. In the absence of credible tools to predict risk for hospitalisation in people with covid-19, typical characteristics of people at highest risk include lack of vaccination, older people, or those with immunodeficiencies and chronic diseases (such as diabetes). The lack of an empirically developed and validated risk prediction tool for establishing patients’ risk of hospitalisation represents the major source of indirectness for which the GDG rated down the certainty of the evidence. In addition, the GDG felt that there was some indirectness because of the possible emergence of variants in which effectiveness of the treatment may be reduced. Casirivimab-imdevimab is unlikely to have serious adverse effects (high certainty evidence), including allergic reactions (moderate certainty due to imprecision). We found no evidence of subgroup effects on age or time from onset of illness for any outcomes.

Values and preferences—The GDG inferred that almost all well informed patients at typical low risk of hospitalisation would decline casirivimab-imdevimab, and only those at higher risk (for example, unvaccinated, older, or immunosuppressed) would choose the treatment.

Resource implications, feasibility, equity, and human rights—Major feasibility challenges include limited production of casirivimab-imdevimab and, for outpatients, the requirement for parenteral administration.

Casirivimab-imdevimab is unlikely to be available for all individuals who would choose to receive treatment, supporting the recommendation to reserve them for those at highest risk of hospitalisation.

Regarding intravenous administration, it is likely that specialised clinics with adequate amounts of the antibodies and staff to ensure safe and effective administration of the intervention will be required. For the intervention to achieve substantial use, health systems will have to address these challenges.

The trials used different doses of the monoclonal antibody combination, and health systems will face the choice of which dose to use, and this can be informed by values and preferences. If one’s priority is to ensure giving as many people as possible the opportunity to benefit from treatment, one might use the lowest effective dose offered in the studies of non-severe patients, 1200 mg total dose (600 mg of each antibody). If one’s priority is on ensuring effectiveness in every individual who receives treatment, and minimising the risk of emergence of resistance, one might use a higher total intravenous dose of 2400 mg (1200 mg of each antibody).

Similar considerations apply to choosing between intravenous and subcutaneous administration, the former used in the four trials included in the living network meta-analyses, and the latter used in a recent trial; one may balance priorities of maximum effectiveness and faster ability to achieve maximum drug concentrations with intravenous therapy, with widespread accessibility with subcutaneous therapy. Volumes that can be administered subcutaneously are limited to the lowest dose, which is a total dose 1200 mg (600 mg of each antibody).

Applicability—The applicability of this recommendation to children is uncertain, as the randomised trials exclusively enrolled adults. The GDG had no reason to think that children with covid-19 would respond any differently to treatment with casirivimab-imdevimab. However, the risk of hospitalisation in children is extremely low, and the GDG inferred that, in the absence of immunosuppression or another significant risk factor, children should not receive the intervention. Lack of data precluded the GDG from making specific recommendations for other special populations, such as pregnant women.

Practical information—Regarding monitoring, although the available trials have not convincingly shown that casirivimab-imdevimab results in allergic reactions, the possibility remains. Administer through an intravenous line containing a sterile in-line or add-on 0.2 µm filter. Following infusion, patients should undergo monitoring for allergic reactions.

Recommendation 2: Among patients with severe or critical covid-19, we suggest treatment with casirivimab-imdevimab, conditional to those with seronegative status (conditional/weak recommendation)

Understanding the recommendations
In patients with severe or critical illness, the conditional recommendation in favour reflects the likelihood that any benefits
are restricted to patients who have seronegative status. In order to translate the trial findings into clinical practice, assessment of serological status will need to become integrated into a clinical decision pathway before treatment is administered. This implies rapid identification of serological status at the time of presentation of severe or critical illness to guide use in this population. Several rapid and relatively inexpensive tests with adequate performance characteristics are available and should see increasing use in settings in which casirivimab-imdevimab is available for administration to these patients.

**Balance of benefits and harms**—A credible subgroup effect based on the RECOVERY trial data demonstrated that casirivimab-imdevimab probably reduces mortality and mechanical ventilation in patients who are seronegative. For mortality among patients who are seronegative, the absolute effects range from 39 fewer per 1000 (95% CI 62 fewer to 13 fewer) in the severely ill to 69 fewer (110 fewer to 23 fewer) in the critically ill. Evidence for mortality for the seronegative subgroup was rated as moderate due to imprecision (the confidence intervals include effects as small as 14 in 1000 that some patients may perceive as unimportant) and indirectness (variants may emerge in which casirivimab-imdevimab antibodies may have reduced effect).

In seronegative patients, the intervention possibly reduces the need for mechanical ventilation (absolute effect 42 fewer per 1000 (95% CI 74 fewer to 6 fewer)). The GDG noted risk of bias from lack of blinding as an additional concern, resulting in low certainty evidence.

In the overall population of patients with severe and critical covid-19, casirivimab-imdevimab may not have an impact on mortality, and the impact on mechanical ventilation and duration of hospitalisation is very uncertain. Evidence for mortality was of low certainty because of imprecision and high likelihood that casirivimab-imdevimab has, in the seronegative and seropositive patients included in the overall group, very different effects. In this population, the evidence regarding the impact of the intervention on need for mechanical ventilation and duration of hospitalisation was, given additional concerns with risk of bias, very low certainty. Aside from the credible subgroup effect for serological status, we found no evidence of subgroup effects on age, time from onset of illness, and severity in patients with severe and critical covid-19.

**Values and preferences**—The GDG inferred that most, if not all, well informed patients with severe or critical covid-19 and seronegative status would choose to receive casirivimab-imdevimab. Other patients—those who are seropositive or whose status is uncertain—are likely to decline the intervention.

**Resource implications, feasibility, equity, and human rights**—Given the cost and availability of casirivimab-imdevimab, and the challenges associated with serological testing, the obstacles to ensuring access to low-to-middle income countries may prove formidable. Thus, the GDG’s suggestion that patients who are seronegative receive the intervention may exacerbate health inequity. On the other hand, given the demonstrated benefits for patients, the recommendations should provide a stimulus to engage all possible mechanisms to improve global access to the intervention and associated testing. Individual countries may formulate their guidelines, considering available resources and prioritise treatment options accordingly.

Dosing of casirivimab-imdevimab differed in trials for non-severe covid-19; a single intravenous dose of 8000 mg was used in the RECOVERY trial for severe and critical covid-19. Clinical trials and pharmacokinetic studies in non-severe covid-19 have provided supporting data for similar effects on decreasing the need for hospitalisation with total doses of 1200 mg, 2400 mg, 4000 mg, and 8000 mg. Thus, using doses lower than used in the RECOVERY trial (8000 mg total dose) for treatment of severely and critically ill patients may achieve the same benefit; on the other hand, it is theoretically plausible but untested that pharmacokinetic differences in severe and critical patients, when compared with non-severe, may reduce drug exposure. This would increase the risk of suboptimal drug exposure in some individuals, which in turn could increase the risk of therapeutic failure and the emergence of viral resistance. In the absence of clinical data on treatment of severe and critical covid-19 patients with doses lower than 8000 mg, the choice of dose depends on values and preferences, with due consideration to maximising effectiveness and minimising emergence of resistance with higher doses, compared with lower doses maximising accessibility in the face of low drug availability and high cost.

Diagnostic testing to identify patients with seronegative status at the time patients present with severe or critical covid-19 warrant rapid serological tests with adequate performance characteristics. Healthcare systems would need to implement such tests. Rapid serological tests with performance characteristics similar to the reference standard test used to characterise seronegative patients in the RECOVERY trial (that is, the Oxford fluorescent-based ELISA assay for serum IgG against the SARS-CoV-2 spike protein, with an arbitrary cut-off determined from a group of positive controls) are available and potentially affordable.

**Applicability**—None of the included randomised trials including RECOVERY enrolled children, and therefore the applicability of this recommendation to children is currently uncertain. Fortunately, very few children become critically ill with covid-19. For those who do and are seronegative, it is possible they may benefit from casirivimab-imdevimab. Lack of data precluded the GDG from making specific recommendations for other special populations, such as pregnant women.

**Practical information**—In terms of monitoring, although the available trials have not convincingly shown that casirivimab-imdevimab results in allergic reactions, the possibility remains. Administer through an intravenous line containing a sterile in-line or add-on 0.2 µm filter. Following infusion, patients should undergo monitoring for allergic reactions.

**Specific uncertainties, emerging evidence, and future research**

- Accurate clinical prediction guides to establish individual patient risk of hospitalisation in patients presenting with non-severe covid-19 in order to best identify patients that would most benefit from this intervention
- Dosing and administration routes in non-severe and severe or critical covid-19 patients
- Safety and efficacy in children and pregnant women.

**Interleukin-6 receptor blockers (Update 5 published 06 July 2021)**

In addition to the linked systematic review and network meta-analysis (see box 1) this recommendation was also informed by an independent prospective meta-analysis from the WHO Rapid Evidence Appraisal for covid-19 group. The network meta-analysis included 30 RCTs with 10 618 participants, and these data were used by the GDG for all outcomes other than mortality. All trials included patients with severe or critical covid-19: 37% were published in peer reviewed journals, 3% were available as preprints, and 60% were completed but unpublished. We used the prospective meta-analysis...
for mortality because it included additional, unpublished data. The prospective meta-analysis pooled data from 22 RCTs with 10 156 participants. 14

Overview

IL-6 receptor blockers tocilizumab and sarilumab are monoclonal antibodies approved for use in rheumatoid arthritis. Elevated IL-6 concentrations are associated with severe outcomes in covid-19, including respiratory failure and death. IL-6 receptor blockers antagonise membrane-bound and soluble forms of the IL-6 receptor, blocking the cytokine’s activation and regulation of the immune response to infection. See MAGICapp for detailed description of the drug mechanism of action, the evidence and subgroup analyses underpinning the recommendation (https://app.magicapp.org/#/guideline/nBk01E/section/LrV7OL).

Recommendation: We recommend treatment with interleukin-6 (IL-6) receptor blockers (tocilizumab or sarilumab) for patients with severe or critical covid-19 (strong recommendation)

Understanding the recommendation

Of note, corticosteroids have previously been strongly recommended in patients with severe and critical covid-19, and we recommend patients meeting these severity criteria should now receive both corticosteroids and IL-6 receptor blockers.

Balance of benefit and harm—There was high certainty evidence for a clinically important reduction in mortality and need for mechanical ventilation. The effects of IL-6 receptor blockers on duration of both hospitalisation and mechanical ventilation are uncertain (low certainty evidence; serious risk of bias due to lack of blinding and serious inconsistency).

There was uncertainty about the risk of serious adverse effects (low certainty evidence). The risk of bacterial infections with immunomodulatory IL-6 receptor blocker therapy may be similar to usual care. However, the GDG had some concerns that, given the short term follow-up of most trials and the challenges associated with accurately capturing adverse events such as bacterial or fungal infection, the evidence summary may under-represent the risks of treatment with IL-6 receptor blockers. Furthermore, the trials of IL-6 receptor blockers that inform this recommendation were mostly performed in high income countries where the risk of infectious complications may be less than in some other parts of the world, and so the generalisability of the data on these adverse events is unclear.

Values and preferences—The GDG inferred that almost all well informed patients with severe or critical covid-19 infection would want to receive IL-6 receptor blockers given the reduction in mortality and mechanical ventilation, despite the low certainty around serious adverse events. A minority of the GDG felt that a significant proportion of patients might decline the intervention due to the uncertainties around harms and taking account of the small reduction in mortality.

Resource implications, feasibility, equity, and human rights—IL-6 receptor blockers require intravenous administration but only require one, or at most two, doses.

Compared with other treatments for covid-19, IL-6 receptor blockers are expensive. The recommendation does not take account of cost effectiveness. Access to these drugs is challenging in many parts of the world, and this recommendation could exacerbate health inequity. However, this strong recommendation should provide a stimulus to improve global access to these treatments.

At a time of drug shortage, many jurisdictions have suggested triaging use of IL-6 receptor blockers. Strategies for this include prioritising patients with the highest baseline risk for mortality (those with critical disease over those with severe disease), in whom the absolute benefit of treatment is therefore greatest. The relative effects (odds ratio 0.87) for reduction in mortality with IL-6 receptor blockers result in 28 fewer deaths per 1000 (95% confidence interval 9 to 47 fewer deaths) in critically ill patients compared with 12 fewer deaths per 1000 (4 to 19 fewer deaths) in the severely ill.

Other suggestions, which lack direct evidence, include prioritising patients who are deteriorating despite corticosteroid treatment and avoiding use in those with established multi-organ failure (in whom the benefit is likely to be smaller). Finally, sarilumab is not indicated to be used in children, and therefore there could be a preference for tocilizumab in this subgroup.

Specific uncertainties, emerging evidence, and future research

- Long term mortality and functional outcomes in covid-19 survivors
- Safety data in terms of nosocomial infections
- Data in children, pregnant patients, and those who are already immunocompromised
- Patients with non-severe covid-19
- Immunity and the risk of a subsequent infection, which may affect the risk of death after 28 days
- Outcomes by different IL-6 receptor blocker dosing and optimal timing of drug initiation

Ivermectin (Update 4 published 31 March 2021)

The living systematic review and network meta-analysis pooled data from 16 RCTs with 2407 participants. Of the included trials, 75% examined patients with non-severe disease and 25% included both severe and non-severe patients. None of the included RCTs enrolled children under 15 years old or pregnant women. Given this, the applicability of this recommendation to children is uncertain, though there is no rationale to suggest they would respond differently.

Overview

Ivermectin is relatively inexpensive and accessible, and some countries have already witnessed its widespread use in the treatment of covid-19; in other countries, there is increasing pressure to do so. Ivermectin is an antiparasitic agent that interferes with nerve and muscle function of helminths through binding glutamate-gated chloride channels. We currently lack persuasive evidence of a mechanism of action for ivermectin in covid-19; any observed clinical benefit would be unexplained. See MAGICapp for detailed description of the drug mechanism of action, the evidence and subgroup analyses underpinning the recommendation (https://app.magicapp.org/#/guideline/nBk01E/section/LAqX7L).

No changes were made for the ivermectin recommendation in this version of the guideline. We are aware of a few new, relatively small trials published since our recommendation was made, and that one key trial has since been retracted given concerns about research fraud. 15 16 However, the updated evidence summary from the living network meta-analysis is consistent with our previous recommendation. This updated evidence summary will be fully considered by the GDG in an upcoming iteration of this guideline.
Recommendation: We recommend not to use ivermectin in patients with covid-19 except in the context of a clinical trial, regardless of disease severity or duration of symptoms (strong recommendation)

Understanding the recommendation

Balance of benefit and harm—For most important outcomes, the GDG considered the evidence to be of very low certainty. A combination of serious risk of bias and very serious imprecision contributed to very low certainty of evidence for mortality, despite a point estimate and confidence interval that seem to suggest benefit with ivermectin. The picture was similar for other important outcomes, including mechanical ventilation, hospital admission, duration of hospitalisation, and viral clearance. The very low certainty of evidence was a critical factor in the recommendation.

Ivermectin may have little or no effect on time to clinical improvement (low certainty evidence) and may increase the risk of adverse effects leading to drug discontinuation (low certainty evidence). A recommendation to only use a drug in the setting of a clinical trials is appropriate when there is very low certainty evidence and future research has a large potential for reducing uncertainty about the effects of the intervention and for doing so at reasonable cost.

Subgroup analyses indicated no effect modification based on dose. We were unable to examine subgroups based on patient age or severity of illness due to insufficient trial data. Therefore, we assumed similar effects in all subgroups.

Values and preferences—The GDG inferred that almost all well informed patients would not want to receive ivermectin, given the evidence left a very high degree of uncertainty in effect on critical outcomes and there was a possibility of harms, such as adverse events associated with treatment. The GDG did not expect there would be much variation among patients in values and preferences when it came to this intervention.

Resource implications, feasibility, equity, and human rights—Although the cost of ivermectin may be low per patient, the GDG raised concerns about diverting attention and resources away from care likely to provide a benefit such as corticosteroids in patients with severe covid-19 and other supportive care interventions. Also, use of ivermectin for covid-19 would divert supply away from pathologies for which it is clearly indicated, potentially contributing to drug shortages, especially for helminth control and elimination programmes. If corticosteroids are used in the treatment of covid-19, empiric treatment with ivermectin may still be considered in strongyloidiasis-endemic areas, albeit not for treatment of covid-19 itself.

Specific uncertainties, emerging evidence, and future research

Given the very low certainty in estimates for most critical outcomes of interest, the GDG felt that further high-quality clinical trials examining this drug would be essential before any recommendation for use as part of clinical care. This includes further RCTs examining both inpatients and outpatients, patients with varying disease severities, and using different ivermectin dosing regimens. The focus of these studies should be on outcomes important to patients such as mortality, quality of life, need for hospitalisation, need for invasive mechanical ventilation, and time to clinical or symptom improvement. Also, a better characterisation of potential harms with ivermectin in patients with covid-19 is important.

Hydroxychloroquine (Update 3 published 17 December 2020)

The recommendation addressing hydroxychloroquine was informed by results from the same systematic review and network meta-analysis that pooled data from 30 RCTs with 10 921 participants. Of note, none of the included RCTs enrolled children or adolescents under the age of 19 years. Given this, the applicability of this recommendation to children is currently uncertain. See MAGICapp for detailed description of the evidence and subgroup analyses underpinning the recommendation (https://app.magicapp.org/#/guideline/n8k01e/section/j1972).

Recommendation: We recommend against using hydroxychloroquine or chloroquine in addition to usual care for the treatment of patients with covid-19, regardless of disease severity or duration of symptoms (strong recommendation)

Understanding the recommendation

Balance of benefit and harm—Hydroxychloroquine and chloroquine probably do not reduce mortality or mechanical ventilation and may not reduce duration of hospitalisation. The evidence does not exclude the potential for a small increased risk of death and mechanical ventilation with hydroxychloroquine. The effect on other less important outcomes—including time to symptom resolution, admission to hospital, and duration of mechanical ventilation—remains uncertain.

Hydroxychloroquine may increase the risk of diarrhoea and nausea or vomiting, a finding consistent with evidence from its use in other conditions. Diarrhoea and vomiting may increase the risk of hypovolaemia, hypotension, and acute kidney injury, especially in settings where healthcare resources are limited. Whether and to what degree hydroxychloroquine increases the risk of cardiac toxicity, including life-threatening arrhythmias, when used in patients with covid-19 is uncertain.

Subgroup analyses indicated no effect modification based on severity of illness (comparing either critical versus severe/non-severe or non-severe versus critical/severe) or age (comparing those aged <70 years versus those ≥70 years). Further, the cumulative dose and predicted day 3 serum trough concentrations (lowest predicted blood concentration on day 3) did not modify the effect for any outcome. Therefore, we assumed similar effects in all subgroups.

We also reviewed evidence comparing the use of hydroxychloroquine plus azithromycin versus hydroxychloroquine alone. There was no evidence that the addition of azithromycin modified the effect of hydroxychloroquine for any outcome (very low certainty).

Values and preferences—Applying the agreed values and preferences, the GDG inferred that almost all well informed patients would not want to receive hydroxychloroquine given the evidence suggesting there was probably no effect on mortality or need for mechanical ventilation and that there was a risk of adverse events including diarrhoea and nausea/vomiting. The GDG did not expect there would be much variation in values and preferences among patients when it came to this intervention.

Resource implications, feasibility, equity, and human rights—Hydroxychloroquine and chloroquine are relatively inexpensive compared with other drugs used for covid-19 and are already widely available, including in low income settings. Despite this, the GDG felt that almost all patients would choose not to use hydroxychloroquine or chloroquine because the harms outweigh the benefits. Although the cost may be low per patient, the GDG raised concerns about diverting attention and resources away from
care likely to provide a benefit such as corticosteroids in patients with severe covid-19 and other supportive care interventions.

Specific uncertainties, emerging evidence, and future research

Although some uncertainty remains, the GDG felt that further research was unlikely to uncover a subgroup of patients who would benefit from hydroxychloroquine on the most important outcomes (mortality, mechanical ventilation) given the consistent results in trials across disease severity and location.

Lopinavir-ritonavir (Update 2 published 17 December 2020)

The recommendation was informed by data from seven RCTs with 7429 participants. None of the included RCTs enrolled children or adolescents under the age of 19 years, so the applicability of this recommendation to children is uncertain. See MAGICapp for detailed description of the evidence and subgroup analyses underpinning the recommendation (https://app.magicapp.org/#/guideline/nBkO1E/section/EgylxL).

Recommendation: We recommend against using lopinavir-ritonavir in addition to usual care for the treatment of patients with covid-19, regardless of disease severity and duration of symptoms (strong recommendation)

Understanding the recommendation

Balance of benefit and harm—The GDG found a lack of evidence that lopinavir-ritonavir improved patient-important outcomes such as reduced mortality, need for mechanical ventilation, time to clinical improvement, and others. For mortality and need for mechanical ventilation, this was based on moderate certainty evidence; for the other outcomes, this was based on low or very low certainty evidence.

There was low certainty evidence that lopinavir-ritonavir may increase the risk of diarrhoea and nausea or vomiting, a finding consistent with the indirect evidence evaluating its use in patients with HIV infection. Diarrhoea and vomiting may increase the risk of hypovolaemia, hypotension, and acute kidney injury, especially in settings where healthcare resources are limited. There was an uncertain effect on viral clearance and acute kidney injury.

Subgroup analysis indicated no effect modification based on severity of illness (comparing either critical versus severe/non-severe or non-severe versus critical/severe) or age (comparing those aged <70 years versus those ≥70 years). As there was no evidence of a statistical subgroup effect, we did not formally evaluate credibility. Although the trials did not report subgroup effects by time from symptom onset, many of the trials enrolled patients early in the disease course. The GDG therefore felt that the evidence applies to all patients with covid-19.

Values and preferences—Applying the agreed values and preferences, the GDG inferred that almost all well informed patients would not want to receive lopinavir-ritonavir given that the evidence suggested there was probably no effect on mortality or need for mechanical ventilation and there was a risk of adverse events including diarrhoea and nausea or vomiting. The GDG did not expect there would be much variation in values and preferences between patients for this intervention.

Resource implications, feasibility, equity, and human rights—Although the cost of lopinavir-ritonavir is not as high as some other investigational drugs for covid-19 and the drug is generally available in most healthcare settings, the GDG raised concerns about opportunity costs and the importance of not drawing attention and resources away from best supportive care or the use of corticosteroids in severe covid-19.

Specific uncertainties, emerging evidence, and future research

Although some uncertainty remains, the GDG felt that further research was unlikely to uncover a subgroup of patients who would benefit from lopinavir-ritonavir on the most important outcomes (mortality, mechanical ventilation) given the consistent results in trials across disease severity and location.

Remdesivir (Update 1 published 20 November 2020)

The recommendation addressing remdesivir includes data from four RCTs with 7333 participants hospitalised for covid-19. None of the included RCTs enrolled children or adolescents under the age of 19 years, and, although older people were included in the trials, their outcomes were not reported separately. Also, there is no pharmacokinetic or safety data on remdesivir for children. Given this, the applicability of this recommendation to children is currently uncertain. See MAGICapp for detailed description of the evidence and subgroup analyses underpinning the recommendation (https://app.magicapp.org/#/guideline/nBkO1E/section/Egzoxn).

Recommendation: We suggest against administering remdesivir in addition to usual care for the treatment of patients hospitalised with covid-19, regardless of disease severity (conditional/weak recommendation)

Understanding the recommendation on remdesivir

When moving from evidence to the conditional recommendation against the use of remdesivir for patients with covid-19, the GDG emphasised the evidence of possibly no effect on mortality, need for mechanical ventilation, time to clinical improvement, and other patient-important outcomes, albeit of low certainty; it also noted the anticipated variability in patient values and preferences and other contextual factors, such as resource considerations, accessibility, feasibility and impact on health equity (see below).

Balance of benefit and harm—The GDG found a lack of evidence that remdesivir improved outcomes that matter to patients such as reduced mortality, need for mechanical ventilation, time to clinical improvement, and others. However, the low certainty evidence for these outcomes, especially mortality, does not prove that remdesivir is ineffective; rather, there is insufficient evidence to confirm that it does improve patient-important outcomes.

There was no evidence of increased risk of serious adverse events in patients receiving remdesivir, at least from the included trials. Further pharmacovigilance is required, because serious adverse events are commonly underreported and rare events could be missed, even in large RCTs.

Data from the network meta-analysis indicated that a subgroup of people with non-critical disease might benefit from remdesivir. However, the GDG judged the credibility in this subgroup analysis to be insufficient to make subgroup recommendations. Important factors influencing this decision included a lack of a priori hypothesised direction of subgroup effect by trial investigators, little or no previously existing supportive evidence for the subgroup finding, and relatively arbitrary cut points used to examine the subgroups of interest. The overall low certainty evidence for the benefits and harms of remdesivir, driven by risk of bias and imprecision limitations, also contributed to the judgment (see WHO guidance and MAGICapp linked from box 1 for full details). The GDG highlighted that, despite the conditional recommendation against remdesivir, they support further enrolment into RCTs evaluating remdesivir, especially to provide higher certainty of evidence for
specific subgroups of patients. The GDG had a priori requested analyses of other important subgroups of patients, including children and older people, but there were no data to address these groups specifically.

Values and preferences—Applying the agreed values and preferences, the GDG inferred that most patients would be reluctant to use remdesivir, given the evidence left high uncertainty regarding effects on mortality and the other prioritised outcomes. This was particularly so as any beneficial effects of remdesivir, if they do exist, are likely to be small, and the possibility of important harm remains. The GDG acknowledged, however, that values and preferences are likely to vary, and there will be patients and clinicians who choose to use remdesivir given that the evidence has not excluded the possibility of benefit.

Resource implications, feasibility, equity, and human rights—A novel therapy typically requires higher certainty evidence of important benefits than is currently available for remdesivir, preferably supported wherever possible by cost effectiveness analysis. In the absence of this information, the GDG raised concerns about opportunity costs and the importance of not drawing attention and resources away from best supportive care or the use of corticosteroids in severe covid-19. It was noted that, currently, remdesivir is administered only by the intravenous route and global availability is limited.

Practical issues—Its use is contraindicated in those with liver dysfunction (ALT >5 times normal at baseline) or renal dysfunction (eGFR <30 mL/minute). To date, it can only be administered intravenously, and it has relatively limited availability.

Specific uncertainties, emerging evidence, and future research

- Critical outcomes of interest, particularly those that impact resource allocation, such as the need for mechanical ventilation, duration of mechanical ventilation, and duration of hospitalisation
- Specific subgroups, such as different severities of illness, different time (days) since onset of illness, children and older adults, pregnant women, duration of therapy
- Long term outcomes (such as 1-year endpoint) examining mortality or long term quality of life
- Long term safety and rare but important side effects
- Patient-reported outcomes such as symptom burden
- Outcomes when used in combination with other agents such as, but not limited to, corticosteroids
- Impact on viral shedding, viral clearance, patient infectivity.

Corticosteroids (Original publication published 4 September 2020)

On 17 July 2020 the GDG reviewed evidence from eight RCTs (7184 patients) evaluating systemic corticosteroids versus usual care in treatment of covid-19, seven of which 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 were not available by subgroup. The GDG did not consider transdermal or inhaled administration of corticosteroids, high dose or long term regimens, or prophylaxis. The GDG did not reach consensus on recommendation 1, which required a vote. The second recommendation was made by consensus. Whereas the recommendations remain unchanged, the evidence summary available via MAGICapp for corticosteroids was updated before the fifth iteration of the living guideline (https://app.magicapp.org/#/guideline/nBkO1E/section/nByvRL) (the baseline risk estimates for mortality are now based on the WHO SOLIDARITY trial (as for other drugs in this guideline)) rather than the initial ISARIC cohort study that likely overestimates current mortality risks at the global level. This update was also needed to inform the baseline risk for mortality in the evidence summary informing the strong recommendation for IL-6 inhibitors in addition to standard care for patients with severe or critical covid-19, where corticosteroids provide a relative reduction in mortality by 21%.

Recommendation 1: We recommend systemic corticosteroids rather than no systemic corticosteroids for the treatment of patients with severe and critical covid-19 (strong recommendation)

Understanding the recommendation

Who does it apply to? This recommendation applies to patients with severe and critical covid-19. The GDG 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 GDG 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 GDG made its recommendation on the basis of the moderate certainty evidence of a 28-day mortality reduction of 3.4% in severe and critical covid-19 combined. Systemic corticosteroids compared with no corticosteroid therapy probably reduce the risk of 28-day mortality in these patients (moderate certainty evidence; relative risk 0.79 (95% confidence interval 0.70 to 0.90); absolute effect estimate 34 fewer deaths per 1000 patients (95% CI 48 fewer to 16 fewer)). Therapy also probably reduces the need for mechanical ventilation (moderate certainty evidence, relative risk 0.74 (0.59 to 0.93); absolute effect estimate 30 fewer cases per 1000 patients (48 fewer to 8 fewer)). The effects of systemic corticosteroids on other outcomes are described in the summary of findings.

Overall, the GDG has high certainty that the adverse effects when considered together are sufficiently limited in importance and frequency and suggested that corticosteroids administered in these doses for 7-10 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 hypernatraemia (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 GDG was reassured by their overall safety profile.
Values and preferences—The GDG 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 were 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. 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 GDG 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/weak recommendation)

Understanding the recommendation

Who does it apply to? This recommendation applies to patients with non-severe disease regardless of their hospitalisation status. The GDG 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 are 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 those 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; relative risk 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 conditional recommendation was driven by likely variation in patient values and preferences. The GDG 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.

Specific uncertainties, emerging evidence, and future research

Remaining uncertainties include effects on:

- Long term mortality and functional outcomes in covid-19 survivors
- Patients with non-severe covid-19 (that is, pneumonia without hypoxaemia)
- When used in combination with additional therapies for covid-19, such as 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
- Immunity and the risk of a subsequent infection, which may affect the risk of death after 28 days
- By different steroid preparation, dosing, and optimal timing of drug initiation.

How patients were involved in the creation of this article

The guideline GDG included four patients who previously had covid-19. Their perspectives were crucial in considering the values and preferences associated with convalescent plasma, IL-6 receptor blockers, ivermectin, hydroxychloroquine, lopinavir-ritonavir, remdesivir, and corticosteroids.

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Main infographic: Summary of recommendations and evidence