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RAPID RECOMMENDATIONS

A living WHO guideline on drugs for covid-19

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ABSTRACT

UPDATES

This is the tenth version (ninth update) of the living guideline, replacing earlier versions, available as data supplements. New recommendations will be published as updates 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 evolving with numerous recently completed randomised controlled trials (RCTs). In this update the Guideline Development Group (GDG) developed new recommendations for patients with non-severe covid-19, concerning the use of nirmatrelvir/ritonavir (2 RCTs, 3100 participants) and remdesivir (5 RCTs, 2710 participants). We have also revised the structure of the guideline to accommodate for an increasing number of effective treatment options to choose between.

NEW RECOMMENDATIONS FOR PATIENTS WITH NON-SEVERE COVID-19

- Nirmatrelvir/ritonavir: a strong recommendation for its use in patients at highest risk of hospitalisation; and a conditional recommendation against its use in patients at low risk of hospitalisation. In the absence of trial data, no recommendation on nirmatrelvir/ritonavir was made in patients with severe or critical illness.
- Remdesivir: a conditional recommendation for its use in patients at highest risk of hospitalisation.

UNDERSTANDING THE NEW RECOMMENDATIONS

In patients with non-severe illness at highest risk of hospitalisation, the recommendations for treatment with nirmatrelvir/ritonavir and remdesivir reflect what the GDG considered to be important reductions in admission to hospital (moderate certainty) with little or no impact on mortality, mechanical ventilation, time to symptom resolution (low to very low certainty), and adverse effects leading to drug discontinuation (high certainty for nirmatrelvir/ritonavir, moderate certainty for remdesivir), though diarrhoea and altered taste were noted more often with nirmatrelvir/ritonavir.

Several treatment alternatives are now available for patients with non-severe covid-19 at highest risk of hospitalisation. In the absence of direct comparisons in trials, indirect comparisons from the living network meta-analysis have been used to inform the use of one drug over another with a related mechanism of action. Choices will depend on availability of the drugs, routes of administration (only intravenous for remdesivir), duration of treatment, and time from onset of symptoms to starting treatment in the trials. The strong recommendation for nirmatrelvir/ritonavir reflects what the GDG considered to represent a superior choice over other treatment options for those with non-severe illness at highest risk; it may prevent more hospitalisations than the alternatives, has fewer harms than molnupiravir, and is easier to administer than intravenous options such as remdesivir and the monoclonal antibodies. For monoclonal antibodies, efficacy may depend on the given SARS-CoV-2 variant, with a less certain benefit seen with the omicron BA1-2 variant which is dominating in many regions. There are no clinical data on combination treatment,

and currently the GDG advises against combining antivirals in the absence of supporting evidence.

UPDATES TO PRIOR RECOMMENDATIONS

The conditional (weak) recommendation for remdesivir in patients with non-severe illness at highest risk of hospitalisation replaces a previous conditional recommendation against treatment with remdesivir in all patients with covid-19 regardless of disease severity. The recommendation for patients with severe or critical illness is being updated using new evidence.

PRIOR RECOMMENDATIONS

- Recommended for patients with severe or critical covid-19—a strong recommendation for systemic corticosteroids; a strong recommendation for IL-6 receptor blockers (tocilizumab or sarilumab), in combination with corticosteroids; a strong recommendation for baricitinib as an alternative to IL-6 receptor blockers, in combination with corticosteroids; and a conditional recommendation for casirivimab-imdevimab, for those with seronegative status, (where rapid viral genotyping is available to confirm infection with a susceptible SARS-CoV-2 variant).
- Recommended for patients with non-severe covid-19—conditional recommendations for those at highest risk of hospitalisation for molnupiravir; sotrovimab; and for casirivimab-imdevimab (where rapid viral genotyping is available to confirm infection with a susceptible SARS-CoV-2 variant).
- Not recommended for patients with non-severe covid-19—a conditional recommendation against systemic corticosteroids; and a strong recommendation against convalescent plasma.
- Not recommended for patients with severe or critical covid-19—a recommendation against convalescent plasma, except in the context of a clinical trial; and a conditional recommendation against ruxolitinib and tofacitinib.
- Not recommended, regardless of covid-19 disease severity—a strong recommendation against hydroxychloroquine; a strong recommendation against lopinavir/ritonavir; and 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 two drugs for covid-19 and updates 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 making use of an innovative process to achieve efficiency in dynamic updating of recommendations. The methods are aligned with the WHO Handbook for Guideline Development and according to a pre-approved protocol (planning proposal) by the Guideline Review Committee (GRC). A box at the end of the article outlines key methodological aspects of the guideline process. MAGIC Evidence Ecosystem Foundation provides methodological support, including the coordination of living systematic reviews with network meta-analyses to inform the recommendations. The full version of the guideline is available online in MAGICapp and in PDF, with a summary version here in *The BMJ*.

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

More than 5000 trials investigating covid-19 interventions have been registered or are ongoing (see section on emerging evidence and appendix 10 for drug-by-drug breakdown[1]). Although most of these studies are small and of variable methodological quality, some large, international platform trials have provided 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.[2-5] An overview of ongoing trials is available from the Infectious Diseases Data Observatory, through their living systematic review of covid-19 clinical trial registrations[1] and the World Health Organization (WHO) website (https://www.covid-nma.com/dataviz/).

However, existing and emerging evidence demonstrates remaining uncertainties concerning treatment effects for all outcomes of importance to patients. There is also a need for better evidence on values and preferences of patients with covid-19. Moreover, the rapidly evolving evidence landscape requires trustworthy interpretation and expeditious clinical practice guidelines to inform clinicians and health care decision-makers.

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. To inform the living guidance, we also use additional relevant evidence on safety, prognosis, and patient values and preferences related to covid-19 treatments.

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

Versions of this guidance

- This article and infographic: Agarwal A, Rochwerg B, Siemieniuk RAC, et al. A living WHO guideline on drugs for covid-19 [Update 9]. *BMJ* 2020;370:m3379, doi:10.1136/bmj.m3379
  - The data from the living network meta-analyses on nirmatrelvir/ritonavir and remdesivir are available in appendix 11 on bmj.com
- WHO PDF: World Health Organization. *Therapeutics and COVID-19. Living guideline*. April 2022. https://www.who.int/teams/health-care-readiness-clinical-unit/covid-19/therapeutics
- MAGICapp (https://app.magicapp.org/#/guideline/nBkO1E)
  - Expanded version of the guideline, including methods, processes, and results with multi-layered recommendations, evidence summaries, and decision aids for use on all devices
  - MATCH-IT interactive decision support incorporating multiple treatment comparisons for recommended drugs in non-severe covid-19 at highest risk of hospitalisation: https://magicevidence.org/match-it/220404dist-covid-meds/

Linked research

- Siemieniuk RAC, Bartoszko JJ, Ge L, et al. Drug treatments for covid-19: living systematic review and network meta-analysis [Update 3]. *BMJ* 2021;370:m2980, doi:10.1136/bmj.m2980
  - Updated evidence available online: https://www.covid19ln-ma.com/
- Siemieniuk RAC, Bartoszko JJ, Díaz Martinez JP, et al. Antibody and cellular therapies for treatment of covid-19: a living systematic review and network meta-analysis. *BMJ* 2021;374:n2231, doi:10.1136/bmj.n2231
- Zeraatkar D, Cusano E, Diaz Martinez JP, et al. Tocilizumab and sarilumab alone or in combination with corticosteroids for COVID-19: a systematic review and network meta-analysis. *medRxiv* 2021; doi:10.1101/2021.07.05.21259867v1

- Izcovich A, Siemieniuk RAC, Bartoszko JJ, et al. Adverse effects of remdesivir, hydroxychloroquine, and lopinavir/ritonavir when used for COVID-19: systematic review and meta-analysis of randomized trials. *medRxiv* 2020; doi:10.1101/2020.11.16.20232876v1
- Lamontagne F, Agoritsas T, Siemieniuk R, et al. A living WHO guideline on drugs to prevent covid-19. *BMJ* 2021;372:n526. doi:10.1136/bmj.n526

What triggered this version of the guideline and what is coming next?

This tenth version of the WHO living guideline addresses the use of nirmatrelvir/ritonavir and remdesivir in non-severe covid-19. It follows the availability of new data from two and five trials addressing the drugs, respectively, which were analysed in a mini-network meta-analysis (appendix 11) and are included in an upcoming update to the living network meta-analysis on drug treatments for covid-19.[6]

Other therapeutics in progress for this WHO living guideline include fluvoxamine, colchicine, and therapeutic anticoagulation. The recommendation for sotrovimab is undergoing review due to new evidence regarding its efficacy against the omicron BA1-2 variant as well.

How to use this guideline and associated resources

This is a living guideline. The recommendations and evidence included here will be updated, and new recommendations will be added for other treatments for covid-19. The infographic provides a summary of the recommendations. Readers can find more detailed information in the full version of the WHO guideline (see box 1 for links to MAGICapp and the PDF version).

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, according to WHO severity definitions (box 2).[8] These definitions avoid reliance on access to healthcare to define patient subgroups.

Box 2: WHO definitions of illness severity for covid-19

- *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*
  - Signs of pneumonia
  - Signs of severe respiratory distress (in adults, accessory muscle use, inability to complete full sentences, respiratory rate › 30 breaths per minute; and, in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs including inability to breastfeed or drink, lethargy, convulsions, or reduced level of consciousness).
- *Non-severe covid-19*—Defined as the absence of any criteria for severe or critical covid-19.

*The GDG noted that the oxygen saturation threshold of 90% to define severe covid-19 was arbitrary and should be interpreted cautiously when defining illness severity. 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, clinicians may interpret a saturation of 90-94% on room air as abnormal in a patient with normal lungs, or as an early sign of severe disease in a patient with a downward clinical trajectory. Generally, in cases where there is any doubt, the GDG suggested erring on the side of considering disease as severe.

How to use the recommendations

Selecting therapeutic agents

Two years into the pandemic, there are several effective treatments to choose between. When moving from evidence to recommendations for these drugs, the GDG considered a combination of the evidence regarding relative benefits and harms, values and preferences, practical issues, resource considerations, and feasibility and equity considerations (box 3). The GDG notes that these issues have to be considered when re-using or adapting the recommendations in national or local contexts. Some therapies can be used in combination (such as corticosteroids and IL-6 receptor blockers for severe or critical covid-19) while others are to be used as alternative monotherapies (such as for patients with non-severe covid-19 at highest risk of hospitalisation).

Box 3: Resources, access and equity issues when choosing therapeutics

Several drugs may be unavailable or impractical for use in some contexts. Additional obstacles to access in low and middle income countries (LMICs) may include cost and availability, and limited access to services such as diagnostic testing and treatments within the first five days of symptoms, which may further limit access to interventions. Health inequities may be exacerbated if patients at higher risk receive the intervention. See the full version of the guideline (box 1) for more information.

WHO aims to provide a stimulus to engage all possible mechanisms to improve global access to diagnostic tests and effective interventions and how countries can address such challenges; such as the integration of a covid-19 clinical care pathway and establishing services to offer intravenous treatments.

At a time of drug shortage, it may be necessary to prioritise use through clinical triage such as selecting patients with the highest baseline risk for mortality (for instance, those with critical illness over those with severe illness), in whom the absolute benefit of treatment is greatest. Other suggestions for prioritisation, which lack direct evidence, include focusing on patients with an actively deteriorating clinical course and avoiding treatment in patients with established multi-organ failure (in whom the benefit is likely to be small).

An interactive decision support tool incorporates the multiple treatment comparisons for these patients: https://magicevidence.org/match-it/220404dist-covid-meds/. Choices will also depend on availability of the drugs, feasibility of administration, durations of treatment, covid-19 variant, and time from onset of symptoms (as different therapeutics vary in efficacy depending on when in the illness course they are started).

Identifying patients at highest risk of hospitalisation

Recommendations for therapeutics in patients with non-severe covid-19 apply to those at highest risk of hospitalisation, defined as beyond 10% risk of being hospitalised for covid-19. These patients should achieve what the GDG agreed would represent what most patients would value as an important benefit: a 6% absolute reduction in hospital admission (see box on how this guideline was created). Reliably identifying those at highest risk is challenging because of the changing global context, with evolution of the virus and patterns of vaccination. A living systematic review of 232 risk prediction models for covid-19 did not identify sufficiently credible and applicable risk prediction tools.[9] In the absence of credible tools, typical characteristics of people at highest risk include those

with older age, immunosuppression and/or chronic diseases, with lack of vaccination as an additional risk factor to consider.

Uncertainties

Uncertainties exist regarding covid therapeutics and emerging evidence which may both inform clinical conversations as well as future research. The recommendations therefore need to be used in light of these uncertainties. Specific uncertainties are listed with the relevant drug, but many uncertainties are common across therapeutics:

- For drugs recommended in non-severe illness: the lack of accurate clinical prediction guides to establish the individual patient risk of hospitalisation in order to best identify patients that would most benefit from interventions; data regarding emergence of resistance and efficacy against new variants; safety and efficacy in children and in immunocompromised, vaccinated, or pregnant patients and other specific subgroups of patients; optimal duration of therapies; head-to-head comparisons of recommended treatments; and relative effectiveness of combination therapy.
- For drugs recommended in severe or critical illness: safety and efficacy in children and in immunocompromised, vaccinated, or pregnant patients and other specific subgroups of patients; long term mortality and functional outcomes in covid-19 survivors; and immunity and the risk of a subsequent infection, which may affect the risk of death after 28 days.

The recommendations

Nirmatrelvir/ritonavir (Update 9, published 22 April 2022)

Nirmatrelvir is a SARS-CoV protease inhibitor which prevents viral replication. Nirmatrelvir/ritonavir is administered orally in combination with ritonavir, a HIV protease inhibitor, which boosts its pharmacokinetics. Through its impact on metabolism and clearance, ritonavir is a perpetrator of many drug-drug interactions during active treatment and possibly for several days after treatment completion. While these may be more easily managed with short durations of treatment, twice daily administration involves doubling ritonavir dose relative to most modern antiretroviral regimens.

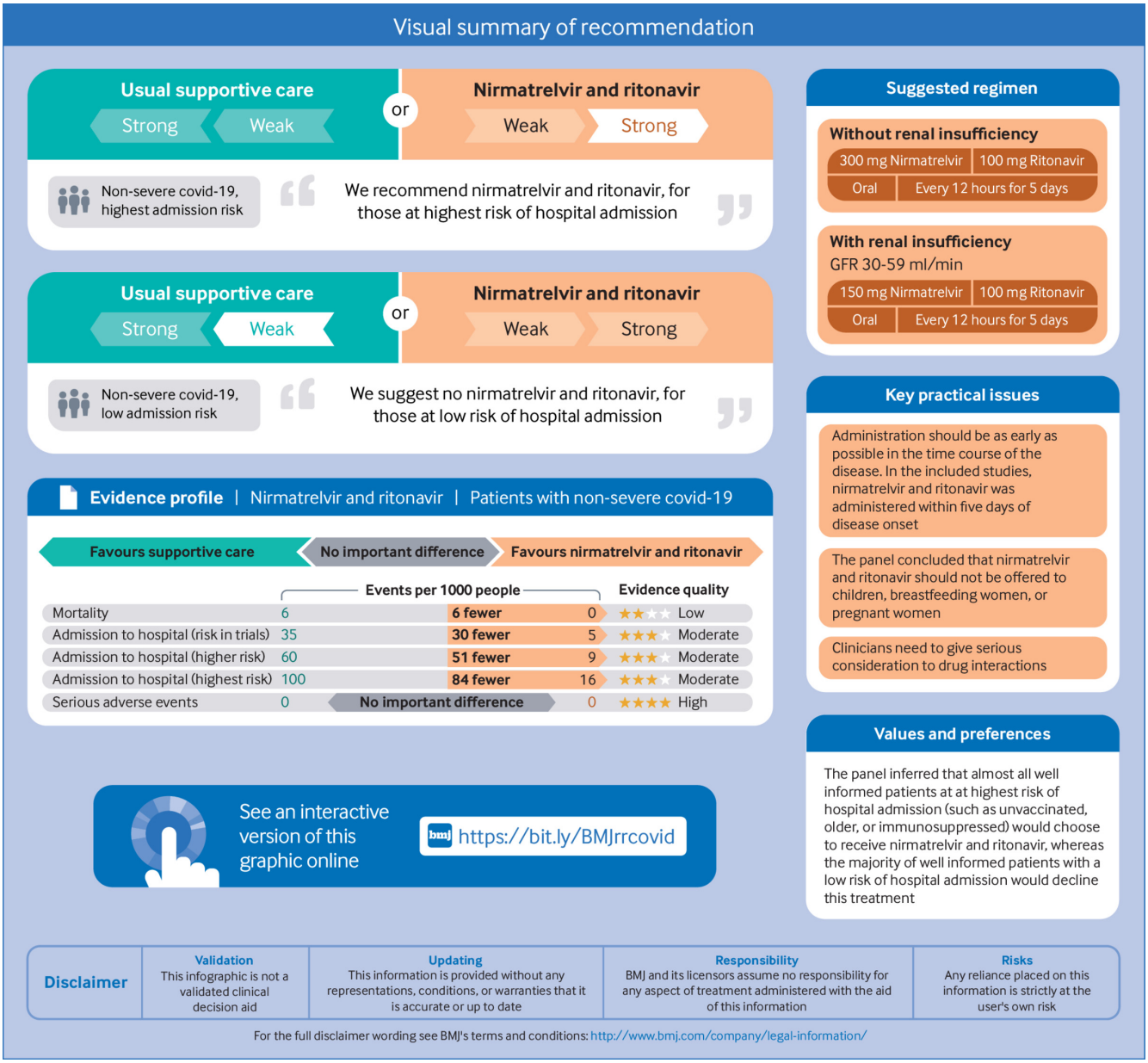
The antiviral effect of nirmatrelvir has been demonstrated through in vitro animal studies and human models.[10-12] Nirmatrelvir retains activity against the omicron BA1 variant in vitro, but clinical data are currently unavailable.[13] There remains uncertainty regarding risk of emergence of resistance; in vitro studies have suggested acquired mutations in the protease sequence may significantly reduce nirmatrelvir activity, though variably so depending on type and number of mutations.[10] The clinical evidence underpinning the recommendations (focused on the benefits and short- term harms from trial data) is outlined in box 4.

Box 4: Nirmatrelvir/ritonavir data for non-severe covid-19 (https://app.magicapp.org/#/guideline/nBkO1E/rec/LwrMyv and https://app.magicapp.org/#/guideline/nBkO1E/rec/Lrvo3R)

The living network meta-analysis for nirmatrelvir/ritonavir was informed by two trials (EPIC-SR and EPIC-HR) that enrolled 3100 patients with non-severe covid-19 in outpatient settings. Both trials were registered; one was published in a peer reviewed journal at the time of data synthesis. Studies did not enrol children, pregnant women, nor patients with severe or critical illness; all patients were unvaccinated and were randomised within five days from symptom onset. See more trial details in appendix 11 on bmj.com.

The trial data on nirmatrelvir/ritonavir provided moderate certainty evidence for a reduction in admission to hospital (odds ratio (OR) 0.15 (95% confidence interval 0.06 to 0.38); absolute difference 84 fewer admissions per 1000 patients (95% CI 93 fewer to 59 fewer)). Low certainty evidence suggested no important difference in mortality (OR 0.04 (0.00 to 0.67); absolute difference 6 fewer deaths per 1000 patients (6 fewer to 2 fewer)). No data to inform outcomes of need for invasive ventilation or time to symptom resolution were available. High certainty evidence showed little or no risk of adverse effects leading to drug discontinuation (OR 0.48 (0.29 to 0.80); absolute difference 0 fewer per 1000 patients).

See MAGICapp for details about the evidence and certainty ratings, and pre-specified subgroup analyses.



| Visual summary of recommendation for nirmatrelvir/ritonavir

Recommendation 1: For patients with non-severe covid-19 at highest risk of hospitalisation, we recommend treatment with nirmatrelvir/ritonavir (strong recommendation).

Understanding the recommendation

Only a minority of patients who are at highest risk are likely to achieve sufficient benefit in reduced admission to hospital. Nirmatrelvir/ritonavir likely represents a superior choice for these patients because it may have greater efficacy in preventing hospitalisation than available alternatives, has fewer concerns with respects to harms than molnupiravir, and is easier to administer than intravenous remdesivir and antibodies.

Balance of benefits and harms—Beyond the important benefits in reducing hospital admission in patients at highest risk of hospital admission, treatment may have little or no impact on mortality; data regarding effects on time to symptom resolution or mechanical ventilation are limited. Treatment does not increase the likelihood of serious adverse effects leading to drug discontinuation, though diarrhoea and altered taste were noted to occur more often with treatment relative to placebo (box 4). The GDG also acknowledged the paucity of information related to emergence of resistance.

Values and preferences—The GDG inferred that almost all well informed patients at highest risk of hospitalisation would choose to receive nirmatrelvir/ritonavir.

Applicability—Given included RCTs enrolled only non-pregnant adults, the GDG concluded that nirmatrelvir/ritonavir should not be offered to children or to breastfeeding or pregnant women with covid-19.

Practical issues—As per the large trials informing the recommendation, nirmatrelvir/ritonavir is administered as 300 mg/100 mg orally every 12 hours for five days. Administration should

be as early as possible in the course of the disease. In the included studies, nirmatrelvir/ritonavir was administered within five days of disease onset. Through its impact on metabolism and clearance, ritonavir is a perpetrator of many drug-drug interactions, warranting serious consideration by clinicians. The Liverpool covid-19 drug interaction checker may constitute a valuable tool for management of drug interactions with nirmatrelvir/ritonavir.[14] Additional considerations regarding practical issues are summarised in MAGICapp.

Resource implications, acceptability, feasibility, equity, and human rights—Nirmatrelvir/ritonavir is unlikely to be available for all individuals who, given the option, would choose to receive the treatment.

Recommendation 2: For patients with non-severe covid-19 at low risk of hospitalisation, we suggest no nirmatrelvir/ritonavir (conditional or weak recommendation).

Understanding the recommendation

Most patients with non-severe covid-19 at low risk of hospitalisation will experience trivial benefits with use of nirmatrelvir/ritonavir. The GDG inferred that most such patients would be uninterested in taking the drug for these trivial benefits. However, there are likely to be an appreciable number of individuals who place a high value on very small reductions in the risk of hospitalisation and would thus choose to use nirmatrelvir/ritonavir; therefore, a conditional (rather than a strong) recommendation was made. The benefits and harms and other factors the GDG considered are comprehensively described in the full version of the guideline (see box 1).

Specific uncertainties, emerging evidence, and future research (across disease severities)

No drug-specific uncertainties: see broadly applicable uncertainties section in "How to use this guideline" (above)

Remdesivir (Update 9, published 22 April 2022, replaces earlier recommendation)

Remdesivir is a nucleoside analogue which interacts with the SARS-CoV-2 polymerase to elicit delayed chain termination during RNA genome synthesis. The drug was repurposed for SARS-CoV-2.

An initial conditional (weak) recommendation was made on 20 November 2020, suggesting not to use remdesivir for patients with covid-19 regardless of illness severity. This was based on data from four RCTs which were available at the time, with 7333 participants hospitalised for covid-19. In this 10th iteration of the guideline, a new recommendation is made for the use of remdesivir for patients with non-severe illness. The clinical evidence underpinning this new recommendation (focused on the benefits and short term harms from trial data) is outlined in box 5.

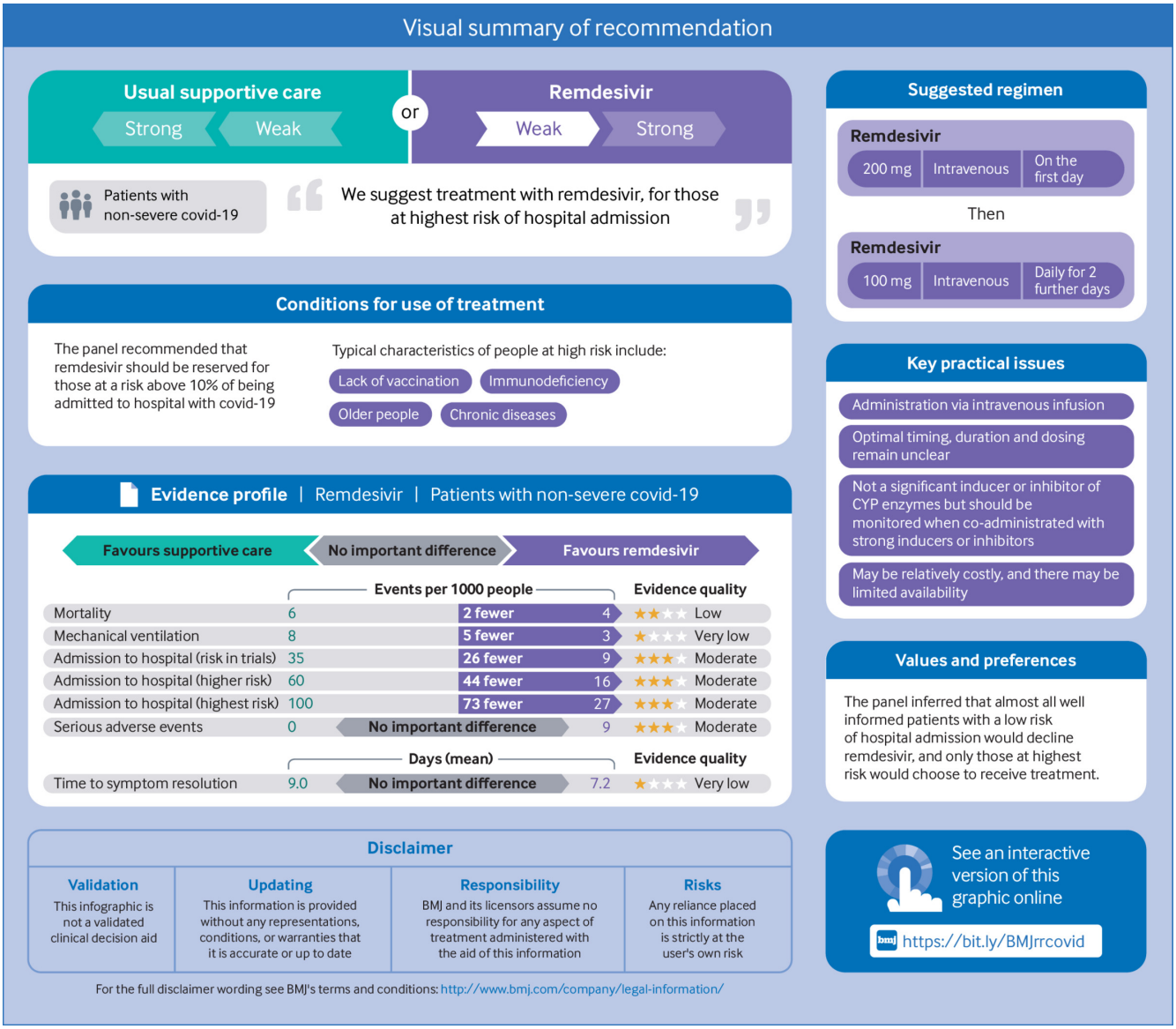
Box 5: Remdesivir data for non-severe covid-19 (https://app.magicapp.org/#/guideline/nBkO1E/rec/nBMO8R)

The living network meta-analysis for remdesivir was informed by five trials that enrolled 2731 patients with non-severe covid-19 in outpatient settings; the LNMA team had access to data for 2710 patients. All trials were registered; four were published in peer reviewed journals at the time of data synthesis. Only one study enrolled children; no studies enrolled pregnant women. See more trial details in appendix 11 on bmj.com.

The trial data on remdesivir provided moderate certainty evidence for a reduction in admission to hospital (odds ratio (OR) 0.25 (95% confidence interval 0.06 to 0.88); absolute difference 73 fewer admissions per 1000 patients (95% CI 93 fewer to 11 fewer)). Low certainty evidence suggested little or no important difference in mortality (OR 0.68 (0.39 to 1.21); absolute difference 2 fewer deaths per 1000 patients (4 fewer to 1 more)). Impact of treatment on mechanical ventilation (OR 0.42 (0.08 to 1.96); absolute difference 5 fewer per 1000 patients (7 fewer to 8 more) and time to symptom resolution (mean difference (MD) 1.8 fewer (5.7 fewer to 3.5 more) days) is uncertain (both very low certainty). Moderate certainty evidence showed little or no risk of adverse effects leading to drug discontinuation (absolute difference 9 more per 1000 patients, 95% CI 3 fewer to 21 more).

The PINETREE trial was the only study to report subgroups within the non-severe subgroup.[15] The planned subgroup analyses were limited by available data; no credible subgroup effects were detected for serological status and age. As all patients were unvaccinated, randomised within seven days of symptom onset, and did not receive therapeutic co-interventions, these subgroup analyses could not be performed. Of note, 1.4% (n=8) of patients in the PINETREE trial were between 12 and 18 years old, and none of them died or were hospitalised; no subgroup effect was noted for >60 *v* ≤60 year old patients (P=0.78).[15]

See MAGICapp for details about the evidence and certainty ratings.



| Visual summary of recommendation for remdesivir

Recommendation 1: We suggest treatment with remdesivir for patients with non-severe covid-19, conditional to those at highest risk of hospitalisation (conditional or weak recommendation).

Understanding the recommendation

The GDG emphasised the benefits on decreased need for hospitalisation, along with little or no serious adverse effects attributable to the drug. Feasibility, costs, access, and complexity of administration were also carefully considered and led to the conditional recommendation for use only in patients at highest risk of hospitalisation.

Balance of benefits and harms—In highest risk patients with non-severe illness, moderate certainty evidence showed that remdesivir probably provides an important reduction in hospital admissions, and may have little or no effect on mortality. The impact of remdesivir on mechanical ventilation and time to symptom resolution is very uncertain. Treatment probably does not increase the likelihood of serious adverse effects leading to drug discontinuation (box 5).

Values and preferences—The GDG inferred that almost all well informed patients with a low risk of hospitalisation would decline remdesivir, and only those at highest risk would choose to receive treatment.

Applicability—Only one included trial enrolled children (aged 12 years and older) with small numbers included; the applicability of this recommendation to children therefore remains uncertain. In the absence of trial data for children aged ≤12 years with weight <40 kg, the use of remdesivir in these children is not recommended. Uncertainty also remains with regard to administration of remdesivir to pregnant or lactating women. The decision regarding use should be made between the pregnant individual and their healthcare provider while discussing whether the potential benefit justifies the potential risk to the mother and fetus.

The GDG also had concerns regarding whether the drug would retain efficacy against emerging variants of concern, such as omicron BA-1 or BA-2. Surveillance is needed for SARS-CoV-2 strains with reduced susceptibility to remdesivir, and further research examining the

role of combination therapy in severely immunocompromised patients. In the absence of further data, the GDG did not have reason to believe the activity against known variants would be diminished.

Practical issues—Remdesivir is administered via intravenous infusion as a three-day regimen, in keeping with the large trials informing the recommendation; 200 mg is administered intravenously on day 1, followed by 100 mg given intravenously on days 2 and 3. Administration should be as early as possible in the course of the disease, with monitoring for allergic, infusion related, or other adverse outcomes. In the included studies, remdesivir was administered within seven days of disease onset.

Additional considerations regarding practical issues are summarised in MAGICapp.

Resource implications, acceptability, feasibility, equity, and human rights—The infusion schedule represents a feasibility challenge in the outpatient settings. Furthermore, remdesivir is unlikely to be available for all individuals who, given the option, would choose to receive the treatment. See box 3 for concerns about costs, availability, and health inequities.

Specific uncertainties, emerging evidence, and future research—Resistance to remdesivir under selective pressure has been observed in vitro and in a previous case study, associated with a mutation (E802D) within the sequence coding for the polymerase. The clinical importance of this if remdesivir were widely used in patients with non-severe covid-19 is unclear,[16 17] as further described in the full version of the guideline (see box 1).

Molnupiravir (Update 8, published 01 March 2022)

Overview

Molnupiravir is an antiviral administered orally. It was re-purposed as an antiviral for covid-19 because it inhibits replication of SARS-CoV-2 with an in vitro potency broadly similar to remdesivir.[18 19] This inhibitory effect has been shown in animal studies, both at higher and lower doses, with possibly greater efficacy when combined with favipiravir (compared with either drug alone).[20 -22] The drug is active against alpha and beta variants in vivo based on studies in hamsters and human cell models, and delta and omicron variants in vitro (no data in vivo).[23 -25] In vitro and animal studies have suggested the possibility of carcinogenesis; no human data with long term follow-up are available regarding this. There is also residual uncertainty regarding other long term harms; the efficacy of the drug against variants, particularly those with higher replication or transmission rates; the possibility of a selective pressure for resistant mutations at an individual level, with the potential to spread at a population level; and the emergence of new variants related to random mutagenesis arising from molnupiravir's mechanism of action. These issues are comprehensively described in the full version of the guideline (see box 1).

Evidence—For patients with non-severe covid-19, data were derived from six trials that enrolled 4827 patients, of which the LNMA team had access to data for 4796 patients. See MAGICapp for detailed description of the mechanism of action, evidence, and subgroup analyses underpinning the recommendation (https://app.magicapp.org/#/guideline/nBkO1E/rec/E85WNb).

Recommendation 1: We suggest treatment with molnupiravir for patients with non-severe covid-19, conditional to those at highest risk of hospitalisation (conditional or weak recommendation).

Understanding the recommendation

Only a minority of patients who are at highest risk are likely to achieve sufficient benefit. Especially given the safety concerns related to molnupiravir, the WHO and the GDG recognise the need to mitigate risks, both for individual patients and at the population level.

Balance of benefits and harms—Molnupiravir probably provides benefits on admission to hospital and time to symptom resolution (both moderate certainty), and may have a small effect on mortality (low certainty), without an increase in short term adverse effects (high certainty). Absolute benefits depend on the prognosis of the individual patient. The GDG also considered potential long term harms of molnupiravir, including risk of malignancy based on preclinical data (very low certainty), in what they ultimately considered to be a close balance between benefits and harms.

Values and preferences—The GDG inferred that almost all well informed patients with a low risk of hospitalisation would decline molnupiravir, and only those at highest risk would choose to receive treatment.

Applicability—

- Children. Due to evidence of impact on growth plate thickness and decreased bone formation in some animal studies, molnupiravir should not be used in children.
- Pregnancy, breastfeeding, and conception. Since molnupiravir elicited embryo-fetal lethality and teratogenicity in offspring when given to pregnant animals, it should not be used in pregnant or breastfeeding women. If pregnancy status is unclear, one should perform a pregnancy test before starting molnupiravir treatment. Women and people who can get pregnant should be counselled regarding reducing the risk of conception (such as using birth control) during treatment and for at least four days after the last dose of molnupiravir.
- Uncertainty remains regarding consequences to children conceived by fathers receiving or having recently received molnupiravir, and whether spermatogenesis may be especially prone to mutagenic effects. Men who might father a child should use birth control during treatment and for at least three months after the last dose of molnupiravir.
- Mitigation strategies at the population level include active sequence monitoring of SARS-CoV-2 detected in clinical respiratory samples for patients receiving therapy and active pharmacovigilance programmes.

Practical issues—As per large trials informing the recommendation, molnupiravir is dosed as 800 mg orally every 12 hours for five days. Administration should be as early as possible in the course of the disease. In the included studies, molnupiravir was administered within five days of symptom onset.

Resource implications, feasibility, equity, and human rights—Molnupiravir is unlikely to be available for all individuals who, given the option, would choose to receive the treatment.

Specific uncertainties, emerging evidence, and future research

- Need for clinical data to investigate safety and applicability concerns (including in children, lactating or pregnant women, and men; and long term impact on mutagenesis and cancer risk).

Janus kinase (JAK) inhibitors (Update 7, published 14 January 2022)

Overview

JAK inhibitors inhibit intracellular signalling in response to numerous interleukins, interferons, colony stimulating factors, and hormones. As a consequence, they interfere with many cellular responses, including antiviral responses, angiotensin-converting enzyme 2 (ACE2) expression, T cell function and differentiation, and macrophage activation. Baricitinib, ruxolitinib, and tofacitinib are three of at least nine JAK inhibitors. Their inherent differences, as well as variation in dosing and administration and pharmacokinetics, limit class-wide recommendations, and the GDG decided to make separate recommendations for individual drugs.

Evidence—For patients with covid-19, data were derived from three trials that enrolled 2659 inpatients for baricitinib, two trials that enrolled 475 inpatients for ruxolitinib, and one trial that enrolled 289 inpatients for tofacitinib. See MAGICapp for detailed description of the mechanism of action, evidence, and subgroup analyses underpinning the recommendation (https://app.magicapp.org/#/guideline/nBkO1E/rec/E5AOaN).

Recommendation 1: We recommend treatment with baricitinib for patients with severe or critical covid-19 (strong recommendation).

Understanding the recommendation

Evidence of improved survival and decreased length of hospital stay, coupled with no evidence of serious adverse events, drove the strong recommendation for baricitinib. The GDG acknowledged that some serious adverse events such as invasive fungal infections may not have been accurately captured during the relatively short follow-up period in the included trials.

The GDG carefully considered whether to make a recommendation or to wait for new data (RECOVERY trial data was not available at the time). However, given that moderate to high certainty evidence already showed benefits with baricitinib, the panel made an immediate strong recommendation for use of the drug, with readiness to update the recommendation as necessary once RECOVERY trial data are publicly available.

The GDG has previously made a strong recommendation for the use of interleukin-6 (IL-6) receptor blockers (tocilizumab or sarilumab) in patients with severe or critical covid-19. Based on their mechanism of action as immune modulators, both baricitinib and IL-6 receptor blockers should have fairly similar benefits. Combining them may unacceptably increase harms, including secondary bacterial and fungal infections. In the absence of evidence of incremental benefit, the GDG advises that clinicians do not administer the drugs together.

Balance of benefits and harms—In patients with severe or critical illness, baricitinib probably reduces mortality and duration of mechanical ventilation (both moderate certainty), and reduces hospital length of stay (high certainty). Treatment probably results in little or no increase in harm, specifically drug discontinuation (moderate certainty). Some serious adverse events such as fungal infections may not have been accurately captured during the relatively short follow-up in the included trials. This risk may vary in different parts of the world according to the local prevalence of infections such as tuberculosis. This risk may also be less pertinent, given the short course of baricitinib used for the treatment of covid-19.

Values and preferences—The GDG inferred that almost all well informed patients with severe or critical covid-19 would choose to receive baricitinib due to the likely reduction in mortality, and moderate certainty evidence of little or no increase in serious adverse events.

Applicability— None of the included RCTs for baricitinib enrolled children, or pregnant or lactating women; therefore, the applicability of this recommendation remains uncertain. The GDG did not have reason to believe that patients in these groups with covid-19 would respond differently; decisions regarding the use of JAK inhibitors in these groups should be guided by discussion between the individual and their healthcare provider.

Practical issues—Baricitinib is administered orally once daily as tablets; it can be crushed, dispersed in water, or given via a nasogastric tube. Based on trials informing the recommendation, the recommended dose is 4 mg daily orally in adults with normal renal function for a duration of 14 days or until hospital discharge, whichever is first.

Dose adjustments may be needed for patients with leucopenia, renal impairment, or hepatic impairment, all of which should be monitored during treatment, and for patients taking strong organic anion transporter 3 (OAT3) inhibitors such as probenecid, where drug interactions warrant dose reductions.

Baricitinib, like IL-6 receptor blockers, should be initiated at the same time as systemic corticosteroids; there are currently no data to suggest that specific timing during hospitalisation or the course of illness is beneficial.

Resource implications, feasibility, equity, and human rights—Compared with some other candidate treatments for covid-19, baricitinib is expensive. The recommendation does not take into account cost effectiveness.

Recommendation 2: We suggest not to use ruxolitinib or tofacitinib for patients with severe or critical covid-19 (conditional or weak recommendation).

Understanding the recommendation

Low to very low certainty evidence for mortality and duration of mechanical ventilation and a possible increase in serious adverse events, particularly for tofacitinib, drove the weak recommendation not to use ruxolitinib or tofacitinib in patients with severe or critical covid-19. Clinicians should consider using ruxolitinib or tofacitinib only if neither baricitinib nor IL-6 receptor blockers (tocilizumab or sarilumab) are available. The GDG emphasised the need for more trial evidence to better inform the recommendations; this is anticipated through ongoing trials for these JAK inhibitors.

Benefits and harms—Low to very low certainty evidence from small trials failed to demonstrate benefits for mortality or duration of mechanical ventilation, and suggested tofacitinib may increase adverse events leading to drug discontinuation. When more evidence is available, the GDG acknowledged that these drugs may prove to have similar benefits as baricitinib.

Values and preferences—Most well informed patients would decline ruxolitinib or tofacitinib. However, a minority might choose to receive one or the other drug if neither baricitinib nor IL-6 receptor blockers are available, given the possibility of benefit has not been excluded, and a class effect of JAK inhibitors might exist.

Applicability—None of the included RCTs enrolled children; therefore, the applicability of this recommendation to children remains uncertain. Uncertainty also remains with regards to the administration of ruxolitinib or tofacitinib to pregnant or lactating women.

Practical issues—Both drugs are administered orally twice daily as tablets and can be dispersed in water or administered via nasogastric tube.

The GDG referred to treatment regimens in the included trials, available via MAGICapp, in the absence of other available information. If ruxolitinib or tofacitinib is administered, like with IL-6 receptor blockers, it should be given with systemic corticosteroids; specific timing during hospitalisation or in the context of the course of illness is not specified.

Resource implications, equity, and human rights—Efforts to ensure access to drugs should focus on those that are currently recommended.

Specific uncertainties, emerging evidence, and future research (for all JAK inhibitors)

- Incremental benefit for patients receiving baricitinib and IL-6 blockers together, rather than either drug individually.
- Impact of tofacitinib and ruxolitinib relative to that of baricitinib.

Sotrovimab (Update 7, published 14 January 2022)

Overview

Sotrovimab is a single human monoclonal antibody that binds to a highly conserved epitope in the SARS-CoV-2 spike protein, preventing the virus from entering cells. Monoclonal antibodies such as sotrovimab and casirivimab-imdevimab are expected to have similar benefits against the SARS-CoV-2 virus. However, their action against the spike protein may render them less effective against emerging variants of the virus such as omicron, where the spike protein is altered.

Update—The GDG is currently assessing to what extent the increasingly predominant omicron BA2 variant is substantially reducing the clinical efficacy of sotrovimab, at this stage demonstrated through preclinical in vitro data.

Evidence—For patients with non-severe covid-19, data were derived from one trial that enrolled 1057 non-hospitalised patients with symptomatic covid-19 for five days or less since symptom onset, and at least one risk factor for illness progression; data was available for 1044 patients. See MAGICapp for detailed description of the mechanism of action, evidence, and subgroup analyses underpinning the recommendation (https://app.magicapp.org/#/guideline/nBkO1E/rec/LA69PM).

Recommendation: We suggest treatment with sotrovimab for patients with non-severe covid-19, conditional to those at highest risk of hospitalisation (conditional or weak recommendation).

Understanding the recommendation

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 sufficient benefit to compensate for the risks and other disadvantages of this therapy. Other limitations, in addition to a lack of reliable tools to identify high risk patients, including delivering a parenteral therapy to patients who are typically cared for in the community, and limited availability of the drug.

The GDG advised that clinicians do not administer multiple monoclonal antibodies (including casirivimab-imdevimab) together, given an absence of supporting evidence and low likelihood mechanistically of incremental benefit.

The GDG then considered how to choose between the two drugs. No trials provide head-to-head comparisons. With alpha and delta variants, there may be little or no difference in the agents' impact on critical outcomes, according to an indirect comparison from the network meta-analysis. Now and in the future, the choice of monoclonal antibodies will depend on emerging evidence regarding effectiveness with different variants and their availability, as well as clinical and contextual factors. Of note, the trials included in the living network meta-analysis were conducted before the emergence of the omicron variant.

Preclinical evidence has recently emerged suggesting that casirivimab-imdevimab lacks neutralisation activity against the omicron variant in vitro.[26] Sotrovimab has been reported to retain activity against omicron in pseudo-virus assays, but with higher concentrations being required for neutralisation.[27] More data are required to ascertain whether efficacy against the omicron variant will be maintained at the studied doses of monoclonal antibodies, and recommendations will be updated when additional data becomes available.

Balance of benefits and harms—In patients with non-severe illness, sotrovimab probably reduces hospitalisation, with little or no impact on mortality (both moderate certainty) and mechanical ventilation (low certainty). There is little or no increase in infusion reactions (high certainty). Indirect comparison data with casirivimab-imdevimab versus sotrovimab provides moderate certainty evidence of little or no difference on mortality, mechanical ventilation and hospitalisation, and high certainty of no difference in infusion reactions.

Values and preferences—The GDG inferred that almost all well informed patients with a low risk of hospitalisation would decline sotrovimab, and only those at highest risk would choose to receive treatment.

Applicability—The included trial enrolled only non-pregnant adults; the applicability to children and pregnant women remains uncertain. The GDG had no reason to believe that children or pregnant women with covid-19 would respond differently to treatment with sotrovimab. However, for children, the risk of hospitalisation is generally extremely low; the GDG therefore inferred that, in the absence of immunosuppression or another major risk factor, children should not receive the intervention.

The GDG did not provide a recommendation for sotrovimab in severe or critical illness. A recently published RCT randomised 546 adults hospitalised with covid-19 to two neutralising monoclonal antibody therapies (sotrovimab and BRII-196 plus BRII-198) or placebo.[28] The results did not demonstrate benefits from these antibodies therapies, including a subgroup analysis on patients with seropositive versus seronegative status. Although the role of sotrovimab in severe or critical covid-19 is not supported by the new trial, it was not assessed by the GDG, as they focused on patients with non-severe covid-19 where evidence was available at the time of recommendation development; this trial, and any other new evidence that is publicly available, will be fully considered by the GDG for future recommendations for sotrovimab.

Practical issues—The authorised regimen for sotrovimab is one single intravenous infusion of 500 mg over 30 minutes, administered as soon as possible after a positive viral test for SARS-CoV-2 and within 10 days of symptom onset. Sotrovimab is available as a concentrated solution and must be diluted before administration. Patients should be clinically monitored during the infusion and observed for at least one hour after the infusion is completed.

Additional considerations regarding practical issues are summarised in MAGICapp.

Resource implications, equity, human rights, acceptability, and feasibility—Sotrovimab is unlikely to be available for all individuals who, given the option, would choose to receive the treatment. Additional challenges include the requirement for intravenous administration to patients who would normally be treated at home.

Specific uncertainties, emerging evidence, and future research

- Efficacy and safety for severe or critical seronegative covid-19 patients

Convalescent plasma (Update 6, published 6 December 2021)

Overview

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 to measure antibody levels are available.

Evidence—Data were derived from 16 trials enrolling 16 236 patients across illness severities, of which four RCTs with 1602 patients informed estimates for outcomes in non-severe illness. See MAGICapp for detailed description of the mechanism of action, evidence, and subgroup analyses underpinning the recommendation (https://app.magicapp.org/#/guideline/nBkO1E/section/LG5NRE).

Recommendation 1: We recommend not to use convalescent plasma for patients with non-severe covid-19 (strong recommendation).

Understanding the recommendation

The GDG noted that, although not demonstrated in the evidence summary, there remains a potential for harms with blood product transfusion. Most importantly, given there was no benefit demonstrated for 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.

Balance of benefits and harms—In patients with non-severe illness, convalescent plasma does not have an important impact on mortality (high certainty). Convalescent plasma probably does not affect mechanical ventilation (moderate certainty). There were no data evaluating the risk of hospitalisation with convalescent plasma; the impact is therefore very uncertain. Convalescent plasma probably does not result in important increases in risks of transfusion-related acute lung injury, transfusion-associated circulatory overload (both moderate certainty), or allergic reactions (low certainty).

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.

Acceptability and applicability—Although blood transfusion is acceptable to most, there is a subset of the population who will not accept allogenic blood transfusions. There are also regulatory challenges in most jurisdictions related to blood product transfusions. The included RCTs enrolled non-pregnant women and men. The GDG did not have reason to believe that children or pregnant women with covid-19 would respond any differently to treatment with convalescent plasma; the GDG therefore inferred that children and pregnant women should not receive the intervention either.

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.

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 illness, who are most often outpatients. Also, this process is costly and time consuming. Given the number of patients with non-severe illness 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.

Recommendation 2: We recommend not to use convalescent plasma for patients with severe or critical covid-19, except in the context of a clinical trial (recommended only in research settings).

Understanding the recommendation

Given relative benefits and harms, the GDG agreed further research addressing these patient-important outcomes would be valuable for patients with severe or critical illness. 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 benefits and harms—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 (all low or very low certainty). Convalescent plasma probably does not result in important increases in risks of transfusion-related acute lung injury, transfusion-associated circulatory overload (both moderate certainty), or allergic reactions (low certainty). However, there is always potential for harms with blood product transfusions.

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

Specific uncertainties, emerging evidence, and future research

- 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 5, published 23 September 2021, updated 01 March 2022)

Update to initial recommendation (part of eighth update of guideline)

Following the publication of the conditional recommendation for casirivimab-imdevimab, additional pre-clinical evidence has emerged. There is a substantial body of in vitro data, and a confirmatory in vivo evaluation, demonstrating lack of efficacy of casirivimab-imdevimab against the omicron BA1 variant. As a result,

casirivimab-imdevimab is no longer recommended for covid-19 treatment except in cases where rapid viral genotyping is available and confirms infection with a SARS-CoV-2 variant (such as delta) that is susceptible to the neutralising activity of this combination of monoclonal antibodies. The text below reflects the initial assessment made by the GDG, adding issues relevant to the omicron variant.

Overview

Casirivimab and imdevimab are two fully human antibodies (REGN10933 and REGN10987) that bind to the SARS-CoV-2 spike protein and have demonstrated antiviral 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.

There is a predicted lack of efficacy for casirivimab and imdevimab with the omicron variant; other monoclonal antibodies such as sotrovimab, however, may retain some efficacy.[29]

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

Recommendation 1: We suggest treatment with casirivimab-imdevimab for patients with non-severe covid-19, conditional to those at highest risk of hospitalisation and where viral genotyping can confirm a susceptible SARS-CoV-2 variant (that is, excluding omicron BA1) (conditional or weak recommendation).

Understanding the updated recommendation

Although there is moderate certainty evidence of a substantial relative risk reduction in hospitalisation, only a minority of patients at highest risk hospitalisation and with infection with a SARS-CoV-2 variant susceptible to this drug combination (that is, a variant other than omicron BA1) are likely to achieve important benefit. Limited availability and need for parenteral administration for a group of patients who are typically cared for in the community present important challenges.

Balance of benefits and harms—In non-severely ill patients without the omicron BA1 variant, casirivimab-imdevimab probably reduces the risk of hospitalisation and duration of symptoms (both moderate certainty); however, the absolute benefit will be trivial in absolute terms for all but those at highest risk, for whom the intervention should be reserved. 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. Casirivimab-imdevimab is unlikely to have serious adverse effects (high certainty), including allergic reactions (moderate certainty). We found no evidence of subgroup effects with 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 would choose to receive treatment.

Applicability—Available trials only enrolled adults; the applicability of this recommendation to children is therefore uncertain. The GDG did not have reason to believe that children with covid-19 would respond any differently to treatment. However, given the risk of hospitalisation in children is extremely low, 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 issues—Casirivimab-imdevimab should be administered 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; although available trials have not convincingly shown that casirivimab-imdevimab results in allergic reactions, the possibility remains.

Resource implications, acceptability, feasibility, equity, and human rights—Major feasibility challenges include the requirement for parenteral administration.

Casirivimab-imdevimab is unlikely to be available for all individuals who would choose to receive treatment.

The trials used different doses of the monoclonal antibody combination, and health systems will face the choice of which dose to use; this can be informed, in part, by system 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 to ensure effectiveness in every individual who receives treatment and minimise the risk of emergence of resistance, one might use a higher total 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-analysis, 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 of 1200 mg (600 mg of each antibody).

Recommendation 2: We suggest treatment with casirivimab-imdevimab for patients with severe or critical covid-19, conditional to those with seronegative status and where viral genotyping can confirm a susceptible SARS-CoV-2 variant (that is, excluding omicron BA1) (conditional or weak recommendation).

Understanding the recommendations

In patients with severe or critical illness, the conditional recommendation in favour reflects the likelihood that benefits are restricted to patients who have seronegative status and without the omicron BA1 variant. In order to translate trial findings into clinical practice, assessment of serological status will need to be integrated into a clinical decision pathway before treatment is administered.

Balance of benefits and harms—A credible subgroup effect based on RECOVERY trial data demonstrated that casirivimab-imdevimab probably reduces mortality and may reduce need for mechanical ventilation in patients with seronegative status (moderate and low

certainty, respectively). Impact on duration of hospitalisation is very uncertain (very low certainty).

In all patients with severe or critical covid-19, casirivimab-imdevimab may not have an impact on mortality (low certainty), and the impact on mechanical ventilation and duration of hospitalisation is very uncertain (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 or 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 with seropositive status or whose status is uncertain—are likely to decline the intervention.

Applicability—None of the included randomised trials, including RECOVERY, enrolled children; therefore, the applicability of this recommendation to children is uncertain. Fortunately, very few children become critically ill with covid-19. For those who do and have seronegative status, 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 issues—Same as prior recommendation (see above).

Resource implications, acceptability, feasibility, equity, and human rights—Challenges include cost, availability, and serologic testing to identify patients with seronegative status.

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 or 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 patients with severe or critical illness, when compared with non-severe illness, 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 or critical covid-19 patients with doses lower than 8000 mg, the choice of dose depends on system 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.

Specific uncertainties, emerging evidence, and future research

No specific uncertainties: see uncertainties section in "How to use this guideline" (above)

Interleukin-6 (IL-6) receptor blockers (Update 4, published 6 July 2021)

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.

WHO has made a strong recommendation for JAK inhibitors, specifically baricitinib, in patients with severe or critical covid-19. An IL-6 receptor blocker and baricitinib should not be given together and should be viewed as alternatives (see discussion for JAK inhibitors above).

Evidence—In addition to the linked network meta-analysis, this recommendation was also informed by an independent prospective meta-analysis from the WHO Rapid Evidence Appraisal for covid-19 group.[30] 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. We used the prospective meta-analysis for mortality because it included additional data that was unpublished at the time. The prospective meta-analysis pooled data from 22 RCTs with 10 156 participants.[30] See MAGICapp for detailed description of the mechanism of action, evidence, and subgroup analyses underpinning the recommendation (https://app.magicapp.org/#/guideline/nBkO1E/section/LG5NRE).

Recommendation: We recommend treatment with 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 or critical covid-19, and we recommend that patients meeting these severity criteria should now receive both corticosteroids and IL-6 receptor blockers, alternatively baricitinib (see above).

Balance of benefits and harms— IL-6 receptor blockers reduce mortality and need for mechanical ventilation (both high certainty), and may reduce durations of mechanical ventilation and hospitalisation (both low certainty).

There was uncertainty about the risk of serious adverse effects (very low certainty). There may be little or no increased risk of bacterial infections. 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 infections, that 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; the generalisability of the data on these adverse events is therefore 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 low certainty around evidence for 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 into account the small reduction in mortality.

Applicability—None of the included RCTs enrolled children or pregnant women. Although this resulted in uncertain applicability, the GDG did not have reason to believe that children or pregnant women with COVID-19 would respond any differently to treatment with IL-6 receptor blockers.

Practical issues—IL-6 receptor blockers require intravenous administration but only require one, or at most two, doses. See

MAGICapp for practical information, including considerations if IL-6 receptor blockers are considered in children and pregnant women.

Resource implications, acceptability, 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 and may be inaccessible. The recommendation does not consider cost-effectiveness. Given limited availability of the drug, one may consider the relative effects (odds ratio 0.87) for reduction in mortality with IL-6 receptor blockers result in 28 fewer deaths per 1000 patients (95% confidence interval 9 to 47 fewer deaths) in critically ill patients, compared with 12 fewer deaths per 1000 patients (4 to 19 fewer deaths) in severely ill patients.

Finally, sarilumab is not indicated for use in children; therefore, there could be a preference for tocilizumab in this subgroup.

Specific uncertainties, emerging evidence, and future research

- Safety data, including nosocomial infections.
- Immunity and the risk of 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 3, published 31 March 2021)

Overview

Ivermectin is an antiparasitic agent that interferes with nerve and muscle function of helminths through binding glutamate-gated chloride channels. The treatment is relatively inexpensive and accessible internationally. We currently lack persuasive evidence of a mechanism of action for ivermectin in covid-19; any observed clinical benefit would be unexplained.

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.[31 32] 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 the guideline.

Evidence—The living systematic review and network meta-analysis pooled data from 16 trials with 2407 participants. Of the included trials, 75% examined patients with non-severe illness, and 25% included patients with both severe and non-severe illness. See MAGICapp for detailed description of the mechanism of action, evidence, and subgroup analyses underpinning the recommendation (https://app.magicapp.org/#/guideline/nBkO1E/section/LG5NRE).

Recommendation: We recommend not to use ivermectin for patients with covid-19, regardless of illness severity, except in the context of a clinical trial (recommended only in research settings).

Understanding the recommendation

Very low certainty evidence was a critical factor in the recommendation.

Balance of benefits and harms—Certainty of evidence for mortality was deemed very low, despite a point estimate and confidence interval that seemed to suggest benefit with ivermectin; similar judgments were made for other outcomes, including mechanical ventilation, hospital admission, duration of hospitalisation, and viral clearance.

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

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

Values and preferences—The GDG inferred that almost all well informed patients would not want to receive ivermectin, given available evidence left a very high degree of uncertainty in effects on critical outcomes and the possibility of harms, such as adverse events associated with treatment.

Applicability—None of the included trials enrolled children or pregnant women; the applicability of the evidence to these subgroups is therefore uncertain, though there is no rationale to suggest they would respond differently.

Resource implications, acceptability, 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

No specific uncertainties: see uncertainties section in "How to use this guideline" (above).

Hydroxychloroquine (Update 2, published 17 December 2020)

Evidence—The recommendation addressing hydroxychloroquine was informed by results from the living network meta-analysis, pooling data from 30 RCTs with 10 921 participants. See MAGICapp for detailed description of the evidence and subgroup analyses underpinning the recommendation (https://app.magicapp.org/#/guideline/nBkO1E/section/j197zj).

Recommendation: We recommend not to use hydroxychloroquine or chloroquine for patients with covid-19, regardless of illness severity (strong recommendation).

Understanding the recommendation

Balance of benefits and harms—Hydroxychloroquine and chloroquine probably do not reduce mortality or mechanical ventilation (both moderate certainty) and may have no effect on duration of hospitalisation (low certainty). 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 viral clearance, remains uncertain.

Hydroxychloroquine may increase the risk of diarrhoea and nausea or vomiting (both low certainty), 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 (very low certainty).

Subgroup analyses indicated no effect modification based on severity of illness, age, cumulative dose, or predicted day 3 serum trough concentrations. 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.

Applicability—None of the included trials enrolled children or adolescents; the applicability to this subgroup is therefore uncertain.

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. 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 illness severity and location.

Lopinavir-ritonavir (Update 2, published 17 December 2020)

Evidence—The recommendation was informed by data from seven RCTs with 7429 participants. 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 not to use lopinavir-ritonavir for patients with covid-19, regardless of illness severity (strong recommendation).

Balance of benefits and harms— Lopinavir-ritonavir probably has little or no effect on mortality and mechanical ventilation (both moderate certainty); effects on time to clinical improvement and other patient-important outcomes were uncertain (low or very low certainty). Treatment probably increases the risk of diarrhoea and nausea or vomiting (both moderate certainty), 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 or age. 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 illness 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.

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 illness severity and location.

Systemic corticosteroids (Original publication, published 4 September 2020)

Evidence—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. See MAGICapp for detailed description of the evidence and subgroup analyses underpinning the recommendation and practical information on how to administer systemic corticosteroids (https://app.magicapp.org/#/guideline/nBkO1E/section/nByvRL).

Update—Whereas the recommendations remain unchanged, the evidence summary available via MAGICapp for corticosteroids was updated before the fifth iteration of the living guideline. The baseline risk estimates for mortality are now based on the WHO SOLIDARITY trial (as for other drugs in this guideline)[4] rather than the initial ISARIC cohort study that likely overestimates current mortality risks at the global level.[33] 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 treatment with systemic corticosteroids for patients with severe or critical covid-19 (strong recommendation).

Balance of benefits and harms—Ultimately, the GDG made its recommendation on the basis of a 28-day mortality reduction of 3.4% in severe or critical covid-19 combined (moderate certainty). Systemic corticosteroids probably reduce the need for mechanical ventilation (moderate certainty).

Overall, the GDG has reasonable 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 and hyponatremia (both moderate certainty). In contrast with new agents proposed for covid-19, clinicians have vast experience administering 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.

Applicability—Applicability 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.

Acceptability and practical issues—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. Practical issues are summarised in detail on MAGICapp.

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.

Recommendation 2: We suggest not to use systemic corticosteroids for patients with non-severe covid-19 (conditional or weak recommendation).

Balance of benefits and harms—Systemic corticosteroids may increase the risk of 28-day mortality (low certainty).

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.

Applicability—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* hyper-infection associated with corticosteroid therapy, diagnosis or empiric treatment may be considered in endemic areas if steroids are used.

Resource implications, feasibility, equity, and human rights—To help guarantee access to systemic corticosteroids for patients with severe or 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:

- Patients with non-severe covid-19 (that is, pneumonia without hypoxaemia).
- 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 this living guideline was created (see MAGICapp for full details https://app.magicapp.org/#/guideline/nBkO1E)

Standards, methods, and processes for living and trustworthy guidance

The Guideline Development Group (GDG) 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*,[34] the Institute of Medicine, and the Guideline International Network (G-I-N).[35]

Selection and support of the GDG

WHO convened a Guideline Development Group (GDG) with content experts (clinicians, methodologists, scientists) and 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 2). The GDG considered an individual patient perspective, but also took account of contextual factors (such as resources, feasibility, acceptability, and 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. 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.[6 7]

Derivation of 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 or 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.[4] Systemic corticosteroids now represent standard of care in patients with severe or critical covid-19 (see strong recommendation issued by WHO in September 2020). Therefore, the baseline risk estimates in the evidence summaries for JAK inhibitors, convalescent plasma and IL-6 receptor blockers were adjusted for treatment effects of corticosteroids for the outcome of mortality and mechanical ventilation.[4] 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. Recommended combinations of treatments are based on direct comparisons from trials demonstrating additional benefit, such as adding baricitinib or interleukin-6 receptor blockers to systemic corticosteroids in patients with severe or critical covid-19. In patients with non-severe covid-19 the absence of direct comparisons from RCTs necessitate indirect comparisons from the living network meta-analysis to inform judgments made about alternative treatment options.

How patients were involved in the creation of this article

The GDG included four patients who previously had covid-19. Their perspectives were crucial in considering the values and preferences associated with the various treatments.

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Main infographic: Summary of recommendations and evidence

Appendix 10: Summary of ongoing or completed trials by candidate drug

Appendix 11: Living network meta-analyses on nirmatrelvir/ritonavir and remdesivir