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RAPID RECOMMENDATIONS

A living WHO guideline on drugs for covid-19

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ABSTRACT

UPDATES

This is the fourteenth version (thirteenth 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 randomised controlled trials (RCTs) recently completed and underway. Emerging SARS-CoV-2 variants and subvariants are changing the role of therapeutics.

WHAT IS NEW?

The guideline development group (GDG) defined 1.5% as a new threshold for an important reduction in risk of hospitalisation in patients with non-severe covid-19. Combined with updated baseline risk estimates, this resulted in stratification into patients at low, moderate, and high risk for hospitalisation. New recommendations were added for moderate risk of hospitalisation for nirmatrelvir/ritonavir, and for moderate and low risk of hospitalisation for molnupiravir and remdesivir. New pharmacokinetic evidence was included for nirmatrelvir/ritonavir and molnupiravir, supporting existing recommendations for patients at high risk of hospitalisation. The recommendation for ivermectin in patients with non-severe illness was updated in light of additional trial evidence which reduced the high degree of uncertainty informing previous guidance. A new recommendation was made against the antiviral agent VV116 for patients with non-severe and with severe or critical illness outside of randomised clinical trials based on one RCT comparing the drug with nirmatrelvir/ritonavir. The structure of the guideline publication has also been changed; recommendations are now ordered by severity of covid-19.

ABOUT THIS GUIDELINE

This living guideline from the World Health Organization (WHO) incorporates new evidence to dynamically update recommendations for covid-19 therapeutics. The GDG typically evaluates a therapy when the 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 on the WHO website, with a summary version here in *The BMJ*. These formats should facilitate adaptation, which is strongly encouraged by WHO to contextualise recommendations in a healthcare system to maximise impact.

FUTURE RECOMMENDATIONS

Recommendations on anticoagulation are planned for the next update to this guideline. Updated data regarding systemic corticosteroids, azithromycin, favipiravir and umefenovir for non-severe illness, and convalescent plasma and statin therapy for severe or critical illness, are planned for review in upcoming guideline iterations.

Therapeutics for covid-19 remain highly relevant as a result of the persistence of severe disease and mortality, partly related to limitations in global access to vaccinations, uncertainties regarding the duration of protection and effectiveness offered, and changes in circulating SARS-CoV-2 variants and subvariants. Thousands of randomised controlled trials (RCTs) investigating covid-19 interventions have been registered or are ongoing. Although most of these studies are small and of variable methodological quality, some large international platform trials have provided robust evidence.[1-4] Rapidly evolving evidence, together with residual knowledge gaps regarding treatment effects on patient-important outcomes and the values and preferences underlying patient decision-making, warrant dynamic updating of evidence and trustworthy guidance.

This living guideline responds to emerging evidence from RCTs on existing and new drug treatments for covid-19. The guideline leverages several living network meta-analyses which iteratively incorporate newly available trial data and allow for analysis of comparative effectiveness of multiple covid-19 treatments.[5,6] Box 1 summarises these network meta-analyses (NMA) 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. For this fourteenth guideline update, the updated evidence from the living NMA is available online while a new publication on patients with non-severe covid-19 is undergoing peer review.

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

Versions of this guidance

- This article and infographic: Agarwal A, Hunt BJ, Stegemann M, et al. A living WHO guideline on drugs for covid-19 [Update 13, published November 2023]. *BMJ* 2020;370:m3379, doi:10.1136/bmj.m3379
- WHO PDF: World Health Organization. *Therapeutics and COVID-19. Living guideline*. November 2023. 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 among individuals at moderate or high risk of hospital admission: https://matchit.magicevidence.org/231006dist-covid-meds

Linked research

- Last published NMA version: Siemieniuk RAC, Bartoszko JJ, Zeraatkar D, et al. Drug treatments for covid-19: living systematic review and network meta-analysis [Update 4, published June 2022]. *BMJ* 2020;370:m2980, doi:10.1136/bmj.m2980
  - Most recent NMA version (Ibrahim S, Siemieniuk RAC, Oliveros MJ, et al) submitted for publication
  - 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
- Lamontagne F, Stegemann M, Agarwal A, et al. A living WHO guideline on drugs to prevent covid-19 [Update 1, published March 2023]. *BMJ* 2021;372:n526. Doi:10.1136/bmj.n526
- World Health Organization. *Clinical management of COVID-19 [Update 6]. Living guideline*. August 2023. https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2023.2
- Wynants L, Van Calster B, Collins GS, et al. Prediction models for diagnosis and prognosis of covid-19: systematic review and critical appraisal [Update 4, August 2022]. *BMJ* 2020;369:m1328

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

This fourteenth version of the WHO living guideline was triggered by

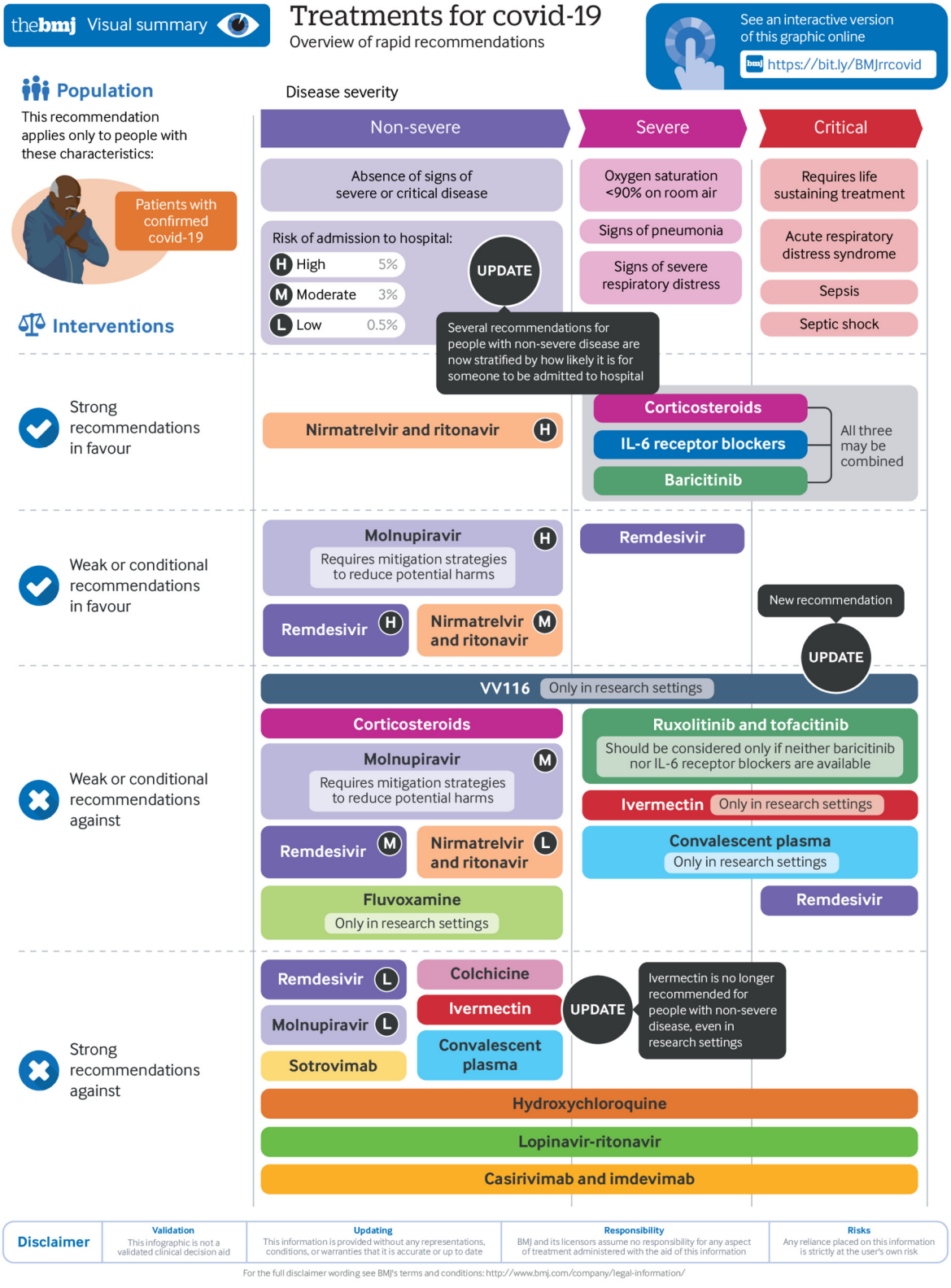
- Updated baseline risk estimates for hospital admission in patients with non-severe covid-19, warranting stratification of recommendations by low, moderate, and high risk groups
- Updated threshold for an important reduction in risk of hospitalisation in patients with non-severe covid-19
- Data demonstrating no basis for a change in pharmacokinetic and pharmacodynamic relationships of nirmatrelvir/ritonavir, remdesivir, and molnupiravir in this phase of the pandemic
- Additional trial data reducing uncertainty regarding anticipated benefits and harms associated with ivermectin
- Consideration of evidence from indirect comparisons between drugs of interest for patients with non-severe covid-19
- New evidence concerning VV116, an oral antiviral agent evaluated in one RCT with 822 patients with non-severe covid-19.

The WHO has a standing steering committee to evaluate possibilities for new drug recommendations and updates to existing drug recommendations. The WHO considers multiple factors, including the extent of available evidence, and whether and when additional evidence might be anticipated, to make decisions.

Other therapeutics in progress for this WHO living guideline include dosing of anticoagulation. Updated data regarding systemic corticosteroids, azithromycin, favipiravir and umefenovir for non-severe illness, and convalescent plasma and statin therapy for severe or critical illness, are planned for review in upcoming guideline iterations.

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. Recommendations are ordered by severity of covid-19. 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).[7] 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 Guideline Development Group (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

Identifying patients with non-severe covid-19 at high, moderate and low risk of hospitalisation

Several recommendations to use drugs apply only for those at high risk for hospitalisation, because the absolute benefit would be trivial if everyone with non-severe covid-19 were to receive treatment. The baseline risk estimates for hospital admission and mortality were updated in this fourteenth iteration of the guideline, where the Guideline Development Group (GDG) defined three risk categories for which the recommendations apply: low, moderate and high risk. In the absence of credible and relevant risk prediction tools, hese were developed based on observational data and updated to consider the evolving nature of the pandemic, incorporating considerations around patient factors, immunity status, virulence and resistance.[8]

- *Patients at high risk (6%) of hospitalisation*—Includes those with diagnosed immunodeficiency syndromes, those who have undergone sold organ transplant and are receiving immunosuppressants, and those with autoimmune illness receiving immunosuppressants.
- *Patients at moderate risk (3%) of hospitalisation*—Those over 65 years, those with obesity, diabetes and/or chronic cardiopulmonary disease, chronic kidney or liver disease, active cancer, those with disabilities, and those with comorbidities of chronic disease.
- *Patients at low risk (0.5%) of hospitalisation*—Includes those who are neither moderate nor high risk. Most patients are low risk.

Defining a threshold for an important reduction in risk of hospitalisation for patients with non-severe covid-19

No evidence was identified to inform the guideline development group (GDG) regarding what patients with non-severe covid-19 perceive as an important reduction in risk of hospitalisation. The GDG initially inferred an absolute reduction of 6% as being the threshold for a patient-important effect. In this fourteenth iteration, the GDG defined 1.5% as a new threshold for an important reduction in risk of hospitalisation in patients with non-severe covid-19. This new threshold reflects the evolution of COVID-19 with lower event rates for patient-important outcomes, increased availability of drugs and higher confidence in their safety profiles. The GDG acknowledged the residual uncertainties regarding anticipated baseline risks in the three defined risk groups—with the living prognosis review unable to provide evidence to inform these judgments—as well as the defined threshold for an important reduction in hospitalisation.

The GDG acknowledged that inherent uncertainties remain regarding baseline risks defined for individuals with non-severe covid-19 at low, moderate and high risk of hospitalisation; these baseline risks have natural implications on the absolute risk reduction that is considered patient-important. Reliable risk prognostication models for hospitalisation and other patient-important outcomes for patients with non-severe illness remain limited.[8] Similarly, regional data and event rates from the control arms of included trials may both help inform baseline risk estimates, but carry their own respective limitations (i.e. access to reliable data for the former, and issues with generalizability for the latter).

Selecting therapeutic agents

Several treatments are available for patients with non-severe covid-19, and for those with severe or critical covid-19. 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 choosing between therapeutic agents, and when re-using or adapting the recommendations in national or local contexts.

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 oral and 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, 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).

Choices will depend on availability of the drugs, routes of administration (such as parenteral route only for remdesivir), co-administered medication, duration of treatment, and time from onset of symptoms to treatment initiation. Some can be used in combination, while others are to be used as alternatives. Recommended combinations of treatments are based on direct comparisons from trials demonstrating additional benefit, such as adding the JAK inhibitor baricitinib to IL-6 receptor blockers and to systemic corticosteroids in patients with severe or critical covid-19.

An interactive decision support tool accompanying this guideline is available at: https://matchit.magicevidence.org/231006dist-covid-meds. It incorporates multiple treatment comparisons to inform the use of one drug over another for patients with non-severe covid-19 at moderate or high risk of hospitalisation. No drugs are recommended for use for patients with non-severe covid-19 at low risk of hospitalisation; this risk category is therefore not included in the interactive tool.

Uncertainties

Recommendations should be used in light of uncertainties around evidence. Uncertainties specific to therapeutics are accessible in the full guideline (see box1 for link to MAGICapp); uncertainties that are frequently common across therapeutics are summarized here:

- 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 who would most benefit from interventions[8]; 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 and longer term outcomes.
- 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.

Recommendations for patients with non-severe covid-19

Nirmatrelvir/ritonavir (updated 10 November 2023)

Overview

Nirmatrelvir is a SARS-CoV protease inhibitor which prevents viral replication. It is administered orally in combination with ritonavir, a HIV protease inhibitor, which improves its pharmacokinetics. In vitro animal studies and human models have demonstrated the antiviral effect of nirmatrelvir.[9-11] Nirmatrelvir retains activity against all SARS-CoV-2 variants studied in vitro to date,[12-15] but RCT evidence is not available for many newer variants.[13] There remains uncertainty regarding risk of emergence of resistance; in vitro and animal studies have suggested acquired mutations in the protease sequence may significantly reduce nirmatrelvir activity.[9] 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. Although these may be more easily managed with short durations of treatment, twice daily administration involves doubling ritonavir dose relative to most modern antiretroviral regimens.

Update—An initial strong recommendation for patients with non-severe covid-19 at highest risk of hospitalisation, and a conditional recommendation against use of nirmatrelvir/ritonavir for patients at low risk of hospitalisation, were published on 22 April 2022. In this 14th version of the guideline, these are maintained for high and low risk groups, now defined by baseline risks of 6% and 0.5% respectively. The GDG made a conditional recommendation in favour of treatment for the newly defined moderate risk group (3%), assuming they would find a 1.5% absolute risk reduction important. Breastfeeding and pregnant people with non-severe covid-19 may consider use of nirmatrelvir/ritonavir. Consistent with previous iterations, and based on data available through the WHO Vigibase, recommendations make clear that breastfeeding and pregnant people with non-severe covid-19 may consider use of nirmatrelvir/ritonavir.

See MAGICapp for detailed descriptions of the mechanism of action and evidence underpinning the recommendations, as well as key remarks for each recommendation.

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

Understanding the recommendation

There is high certainty evidence of an important reduction in the absolute risk of hospitalisation and moderate certainty in a survival benefit without an increase in adverse events.

Indirect comparisons in high risk patients demonstrated nirmatrelvir/ritonavir may reduce hospitalisation compared with molnupiravir (moderate certainty); little or no difference in effects was observed when compared with remdesivir (low certainty).

The GDG concluded that nirmatrelvir/ritonavir represents a superior choice to the other drugs when available and in patients in whom drug interaction is not an issue. This is based on evidence of benefit, concerns about possible harms of molnupiravir, and acceptability and feasibility concerns about remdesivir given its parenteral administration. There is no evidence for combining antiviral therapies; the GDG therefore advised against this.

Balance of benefits and harms—Beyond the benefits on reduced hospitalisations and mortality, nirmatrelvir/ritonavir may not impact time to symptom resolution (low certainty of evidence). The drug had no effect on adverse effects leading to drug discontinuation (high certainty of evidence), though diarrhoea and dysgeusia (loss of taste) have occurred more frequently with nirmatrelvir/ritonavir than with placebo.

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

Applicability—Nirmatrelvir/ritonavir represents an option for pregnant people with covid-19 to reduce the risk of disease progression. As detailed in the full guideline (see box 1 for links and WHO Vigibase https://who-umc.org/vigibase), the GDG acknowledged the uncertainty in terms of potential serious adverse reactions in pregnant or breastfeeding people - despite no reports of such reactions in the parent or child so far in the WHO Vigibase. With there being no reason to think the drug is less effective in pregnant people than others, the GDG believes that shared, fully informed decision making between parent and healthcare provider should determine the use of nirmatrelvir/ritonavir in pregnant or breastfeeding people with non-severe covid-19.

Practical issues—Nirmatrelvir/ritonavir is recommended to be administered as 300 mg/100 mg orally every 12 hours for five days, as early as possible in the course of the disease. Trials administered nirmatrelvir/ritonavir within five days of symptom onset and excluded patients with severe kidney impairment and severe liver impairment. Clinicians should use nirmatrelvir/ritonavir with caution in such patients; where estimated glomerular function rate is 30-59 mL/min, a dose reduction to 150 mg/100 mg orally every 12 hours for five days may be warranted. Through its impact on metabolism and clearance, ritonavir is a perpetrator of many drug-drug interactions, warranting serious consideration. The

Liverpool covid-19 drug interaction tool is an open repository of this information.[16] 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. Since this recommendation is for treatment with nirmatrelvir/ritonavir within five days of symptom onset, access to and appropriate use of diagnostic tests are essential for implementation.

Recommendation 2: For patients with non-severe covid-19 at moderate risk of hospitalisation, we suggest to use treatment with nirmatrelvir/ritonavir (weak or conditional recommendation).

Understanding the recommendation

There is high certainty of an important reduction in the risk of hospitalisation, though smaller than those observed for individuals at high risk of hospitalisation. A conditional recommendation was made due to the uncertainty regarding baseline risk estimates, uncertainty around GDG inferences regarding values and preferences, and likely considerable variability in values and preferences.

The GDG concluded that nirmatrelvir/ritonavir in general represents a superior choice to molnupiravir (due to greater reduction in hospitalisation, and safety concerns with molnupiravir) and also a superior choice to remdesivir (due to practical issues with intravenous administration), provided that the intended recipient is not using other drugs that interact with nirmatrelvir/ritonavir.

Balance of benefits and harms—The effect on admission to hospital is summarized above. Nirmatrelvir-ritonavir does not result in an important reduction in mortality (high certainty). Effects for outcomes other than mortality and admission to hospital are consistent across risk groups and are summarised under Recommendation 1 (high risk patients).

Values and preferences—The GDG inferred that many patients at moderate risk would place a high value on the reduction in hospitalisation afforded by nirmatrelvir/ritonavir, but a minority would not.

Applicability, practical issues, resource implications, feasibility, equity—In addition to the issues summarised in Recommendation 1, where availability of nirmatelvir-ritonavir is limited, it should be prioritised for those at high risk of hospital admission.

Recommendation 3: For patients with non-severe covid-19 at low risk of hospitalisation, we suggest not to use nirmatrelvir/ritonavir (conditional or weak recommendation).

Understanding the recommendation

Best estimates suggest that any benefit of nirmatrelvir/ritonavir in low risk patients with non-severe covid-19 are trivial (high certainty for mortality and hospitalisation). Nevertheless, the GDG noted the uncertainty in risk estimates, and uncertainty and variability of patient values and preferences, therefore deciding for a conditional rather than a strong recommendation against nirmatrelvir/ritonavir.

Balance of benefits and harms—Effects on mortality and admission to hospital are summarized above; effects for other outcomes are consistent across risk groups and are summarised under Recommendation 1 (high risk patients).

Values and preferences—Despite the trivial effects observed, the GDG made a conditional recommendation because of residual uncertainty in baseline risk, and because of the possibility that an appreciable minority of patients may place a high value on a very small reduction in hospitalisation.

Applicability, practical issues, resource implications, feasibility, equity—Summarised above (Recommendations 1 and 2).

Remdesivir (updated 10 November 2023)

Overview

Remdesivir was developed for treatment of hepatitis C virus infection, and was also studied in Ebola and Marburg virus infections before being repurposed for SARS-CoV-2. Remdesivir is a nucleoside analogue which interacts with the SARS-CoV-2 polymerase to elicit delayed chain termination during RNA genome synthesis.

Remdesivir activity across variants has been stable, given changes in sequences across new variants have occurred in the viral spike protein and not the RNA polymerase that is targeted by the drug.[14 15]

Update—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. An updated recommendation was made on 22 April 2022 for patients with non-severe illness, suggesting treatment with remdesivir for patients at highest risk of hospitalisation. In this 14th version of the guideline, the GDG made new recommendations for patients with non-severe covid-19 at low and moderate risk of hospitalisation; the recommendation for patients at high risk is unchanged.

See MAGICapp for detailed description of the mechanism of action and evidence underpinning the recommendations, as well as key remarks for each recommendation.

Recommendation 1: For patients with non-severe covid-19 at high risk of hospitalisation, we suggest treatment with remdesivir (conditional or weak recommendation).

Understanding the recommendation

This update was informed by additional trials confirming the benefits of remdesivir in reducing hospitalisations for patients in the high risk group, and the apparent little or no serious adverse effects, while noting uncertainty around these. A conditional, rather than strong recommendation, was informed by the complexity of administration, and the potential of the recommendation to exercerbate costs and access inequities.

Indirect comparisons in high risk patients demonstrated remdesivir may reduce hospitalisation when compared with molnupiravir, and found little or no difference when compared with nirmaltrelvir/ritonavir (both low certainty). Without direct data and with low certainty in indirect comparisons, the GDG chose not to make comparative recommendations between drugs, but rather remark that nirmatrelvir/ritonavir (the only drug with a strong recommendation for its use in high risk patients) may be superior based on its efficacy compared with standard care, and the practical difficulty that arises from the three days of intravenous administration of remdesivir. Remdesivir is likely to be the desirable option for specific subpopulations in patients for whom nirmatrelvir/ritonavir or molnupiravir are not options; this may apply, for instance, to patients who are using drugs with problematic interactions with nirmatrelvir/ritonavir, or those in whom molnupiravir would be contraindicated due to concerns regarding mutagenesis (e.g. pregnant people and children).

There is no evidence for combining antiviral therapies; the GDG therefore advised against this.

Balance of benefits and harms—Remdesivir probably results in an important reduction in risk of hospital admission (moderate certainty) with probably little or no impact on mortality (moderate certainty), mechanical ventilation (moderate certainty) and time to symptom resolution (low certainty). The impact on adverse events leading to discontinuation is uncertain (very low certainty). Planned subgroup analyses for remdesivir versus supportive care including for age, time of symptom onset and disease severity could not be performed in the absence of subgroup data reported publicly or provided by investigators. Relative to both nirmatrelvir/ritonavir and molnupiravir, there is little or no difference in mortality (high certainty). Remdesivir may reduce admission to hospital more than molnupiravir; there may be little or no difference when compared to nirmatrelvir-ritonavir (both low certainty).

Values and preferences—The GDG inferred that most well informed patients at high risk for hospitalisation would choose to receive remdesivir rather than no antiviral agent, but an appreciable minority would decline depending on their perception of the burden of administration.

The GDG concluded that patients for whom nirmatrelvir/ritonavir was available and not contraindicated would likely choose the drug over remdesivir because of the relative complexities of administration.

The GDG concluded that because of the possible toxicity of molnupiravir and the possible superiority of remdesivir in reducing hospitalisation, the majority of patients would choose remdesivir over molnupiravir.

Applicability—Only one included trial enrolled children (aged ≥12 years) with small numbers was 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 people. The decision regarding use should be made between the pregnant person and their healthcare provider while discussing whether the potential benefit justifies the potential risk to the parent and fetus.

The GDG also had concerns regarding whether the drug would retain efficacy against emerging variants of concern. Surveillance is needed for SARS-CoV-2 strains with reduced susceptibility to remdesivir, and further research is needed to examine the role of combination therapy in severely immunocompromised patients. In the absence of further data, the GDG did not have reason to believe that activity against known variants would be diminished.

Practical issues—Remdesivir should be administered via intravenous infusion as a three-day regimen; 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 for a brief period following infusions. In the included studies, remdesivir was administered within seven days of disease onset. Caution should be used when administering remdesivir to patients with significant liver or kidney disease. 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 outpatient settings, and availability of such treatment facilities may be limited. This reinforces that remdesivir should be reserved for those at high risk, and is an important consideration in choices between remdesivir and both nirmatrelvir/ritonavir and molnupiravir.

Since this recommendation emphasises the need to administer early treatment, increasing access and ensuring appropriate use of diagnostic tests is essential.

Recommendation 2: For patients with non-severe covid-19 at moderate risk of hospitalisation, we suggest not to use remdesivir (conditional or weak recommendation).

Understanding the recommendation

The GDG considered: the benefits of decreasing hospitalisation; uncertainty in adverse effects; the challenge of identifying patients at moderate risk in the absence of credible risk prediction tools; issues related to resource use and feasibility of administration (such as the complex administration); and the potential for widespread use to exacerbate health inequities.

The GDG concluded that nirmatrelvir/ritonavir represents a superior choice because it is easier to administer than a three-day course of intravenous remdesivir. The conditional recommendation against represents the panel's view that remdesivir will represent a good choice only in those in whom nirmatrelvir/ritonavir is unavailable or involves problematic interactions, and even then only in a minority of such individuals.

Balance of benefits and harms—Remdesivir probably results in an important reduction in admission to hospital (moderate certainty) with probably little or no impact on mortality (moderate certainty). Effects for other outcomes are consistent across risk groups and are summarised under Recommendation 1 (high risk patients).

Values and preferences—The GDG inferred that most well informed patients at moderate risk of hospitalisation would choose not to receive remdesivir, and a minority would choose to receive it rather than no antiviral agent.

Applicability, practical issues, resource implications, feasibility, equity—As summarised above (Recommendation 1).

Recommendation 3: For patients with non-severe covid-19 at low risk of hospitalisation, we recommend not to use remdesivir (strong recommendation).

Understanding the recommendation

The GDG considered the negligible benefits of decreased need for hospitalisation because of the very low risk of hospitalisation among untreated patients in this group, the uncertainty in adverse effects, and the feasibility issues related to administration. The GDG recognised that widespread use of remdesivir could exacerbate health inequities by using significant resources for a negligible benefit.

Balance of benefits and harms—Remdesivir does not result in important reductions in admission and has little or no impact on mortality (both high certainty). Effects for other outcomes are consistent across risk groups and are summarized under Recommendation 1 (high risk patients).

Values and preferences—The GDG inferred that almost all well informed patients with a low risk of hospitalisation would decline remdesivir.

Applicability, practical issues, resource implications, feasibility, equity—Summarised above (Recommendations 1 and 2).

Molnupiravir (updated 10 November 2023)

Overview

Molnupiravir is an orally administered antiviral which inhibits replication of SARS-CoV-2 with an in vitro potency broadly similar to remdesivir.[17 18] 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).[19-21] Due to the mutagenic mechanism of action, there remain potential safety concerns related to toxicity (see applicability section below).

New variants have shown major differences in sequences for the viral spike protein but not the RNA polymerase targeted by molnupiravir; the drug's activity across variants has therefore been stable, and no known change molecular, pharmacokinetic or pharmacodynamic basis exists for a change in activity since initial trials were conducted.

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 via MAGICapp (see box 1). *Update*—An initial conditional (weak) recommendation was made on 3 March 2022, suggesting treatment with molnupiravir for patients with non-severe covid-19 at highest risk of hospitalisation. In this 14th version of the guideline, the GDG maintained a conditional recommendation in favour of use for patients with non-severe illness at high risk of hospitalisation, given an updated baseline risk of admission. Conditional recommendations were made against its use in patients with non-severe covid-19 at moderate and low risks of hospitalisation.

See MAGICapp for detailed description of the mechanism of action and evidence underpinning the recommendations, as well as key remarks for each recommendation.

Recommendation 1: For patients with non-severe covid-19 at high risk of hospitalisation, we suggest treatment with molnupiravir (conditional or weak recommendation).

Understanding the recommendation

The GDG emphasised moderate certainty evidence of an important reduction in the absolute risk of hospitalisation, and a marginal but important reduction in the risk of death without an increased risk of adverse effects (high certainty). The GDG did not anticipate important variability in patient values and preferences. A combination of safety concerns based on preclinical data, values and preferences, and feasibility contributed to the conditional recommendation.

The GDG considered that nirmatrelvir/ritonavir and remdesivir represent superior choices to molnupiravir due to greater reductions in hospitalisation and due to safety concerns with molnupiravir.

Balance of benefits and harms—Molnupiravir probably reduces admission to hospital, mortality and time to symptom resolution (all moderate certainty). The drug may have no important effect on mechanical ventilation (low certainty) and has no important effect on adverse effects leading to drug discontinuation (high certainty). However, potential long term harms remain uncertain, and, in the absence of clinical data, a matter of concern. These include a risk of malignancy based on preclinical data (very low certainty) and emergence of resistance based on its mechanism of action.

Nirmatrelvir/ritonavir probably reduces hospitalisation to a greater extent than molnupiravir (moderate certainty) and is not associated with the same uncertainties over long term safety. Remdesivir similarly may result in a larger reduction in admission to hospital (low certainty). Neither drug has an important difference relative to molnupiravir in risk of mortality (high certainty).

Values and preferences—The GDG inferred that most well informed patients at high risk of hospitalisation would choose molnupiravir over no antiviral 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 people. If pregnancy status is unclear, one should perform a pregnancy test before starting molnupiravir treatment. People who might become 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.
- *Men planning to conceive*—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 planning to conceive should be oriented on the potential for temporary genotoxic effect on sperm cell production. Men who might father a child should use reliable contraception during treatment and for at least three months after the last dose of molnupiravir.
- *Younger adults*—The unknown long term risk of genotoxicity is likely to be higher in younger patients compared with older patients; thus its use in younger adults not at high risk should be avoided.
- *Strategies to mitigate potential harm 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—In the trials, molnupiravir was dosed as 800 mg orally every 12 hours for five days, and administered within five days of symptom onset; it should be used as early as possible from symptom onset. See MAGICapp for a detailed overview of mitigation strategies for potential harms.

Resource implications, feasibility, equity, and human rights—Molnupiravir is unlikely to be available in all settings and for all individuals who, given the option, would choose to receive it. This reinforces that, where supply is limited, molnupiravir should be reserved for those at high risk. Since the recommendation is for early treatment within five days of symptom onset, access to and appropriate use of diagnostic tests are essential for implementation.

Recommendation 2: For patients with non-severe covid-19 at moderate risk of hospitalisation, we suggest against treatment with molnupiravir (conditional or weak recommendation).

Understanding the recommendation

The GDG considered that benefits of molnupiravir in reducing hospitalisation are small, though possibly important to a majority of patients, and that the drug reduces duration of symptoms. The GDG judged that concerns regarding toxicity will, for the majority of patients, outweigh the benefits. However, an appreciable proportion of the moderate risk population may perceive the risk-benefit balance to justify treatment.

Nirmatrelvir/ritonavir was deemed a superior choice to molnupiravir, given it probably has a greater reduction in hospitalisation and because of concerns regarding possible harms of molnupiravir. In moderate-risk patients for whom nirmatrelvir/ritonavir is not an option, when a choice exists between molnupiravir and remdesivir, key considerations identified were the potential toxicity of molnupiravir, its possible reduction in duration of symptoms, and the burden of remdesivir administration.

Balance of benefits and harms—Although molnupiravir has a similar relative effect on the main outcomes of interest, the absolute effects are smaller in those at moderate risk. Molnupiravir does not have an important impact on mortality and results in little or no reduction in hospital admission (both high certainty). Effects for other outcomes are consistent across risk groups and are summarized under Recommendation 1 (high risk patients). Compared with nirmatrelvir/ritonavir in moderate risk patients, molnupiravir makes little or no difference to mortality (high certainty), probably has less benefit in reducing hospitalisation (moderate certainty), and may reduce duration of symptoms (low certainty). Compared with remdesivir, molnupiravir makes little or no difference to mortality (high certainty), may have little or no difference in reducing hospitalisation (low certainty), and may reduce duration of symptoms (low certainty).

Values and preferences—The GDG inferred that most well informed patients at moderate risk of hospitalisation would be reluctant to use a medication for which the evidence left high uncertainty regarding absolute effects on outcomes they consider important.

Applicability, practical issues, resource implications, feasibility, equity—As summarised above (Recommendation 1).

Recommendation 3: For patients with non-severe covid-19 at low risk of hospitalisation, we recommend against treatment with molnupiravir (strong recommendation).

Understanding the recommendation

The GDG considered benefits in low risk patients for reducing hospitalisation to be trivial. Although the drug probably reduces the duration of symptoms, the GDG considered that, for all or almost all patients, toxicity will be sufficient to more than counterbalance this benefit.

Balance of benefits and harms—Although molnupiravir has a similar relative effect on the main outcomes of interest, the absolute effects are smaller in those at low risk. Any possible benefits of molnupiravir in terms of admission to hospital and survival benefit were trivial (both high certainty). Effects for other outcomes are consistent across risk groups and are summarized under Recommendation 1 (high risk patients).

Values and preferences—The GDG believes that all or almost all patients at low risk of hospitalisation would decline to use a medication with high certainty of trivial benefit and serious concerns about possible long term harms.

Applicability, practical issues, resource implications, feasibility, equity—As summarised above (Recommendations 1 and 2).

Systemic corticosteroids (published 2 September 2020)

Status—A conditional (weak) recommendation against the use of corticosteroids in non-severe illness was initially published on 2 September 2020. No changes were made to the corticosteroids recommendations in this 14th version of the guideline.

Recommendation: 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.
- Pregnancy: antenatal corticosteroid therapy may be administered for pregnant people 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 individual presents with mild or moderate covid-19, the clinical benefits of antenatal corticosteroid might outweigh the risks of potential harm to the parent. In this situation, the balance of benefits and harms for the pregnant person and the preterm newborn should be discussed with the parent to ensure an informed decision, as this assessment may vary depending on the pregnant person's clinical condition, their wishes and those of their 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.

Fluvoxamine (published 14 July 2022)

Overview

Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) approved as an antidepressant. It increases concentrations of serotonin in the synaptic cleft. Indirect evidence from non-covid-19 disease models have suggested possible anti-inflammatory

properties, and mechanistic studies have suggested host-directed antiviral properties.

Status—The recommendation for fluvoxamine in non-severe illness was initially published on 14 July 2022. No changes were made to the recommendation in this 14th version of the guideline.

Recommendation: For patients with non-severe covid-19, we recommend not to use fluvoxamine, except in the context of a clinical trial (recommended only in a research setting).

Understanding the recommendation

Insufficient evidence of benefit, coupled with a lack of a clear mechanism of action and known drug interactions, drove the recommendation against use in clinical care.

Balance of benefits and harms—There was low to moderate certainty evidence suggesting little or no effect on hospitalisation, mortality, or mechanical ventilation, and an absence of reliable data on serious adverse effects attributable to the drug. Fluvoxamine is known for substantial pharmacological interactions. In the largest trial, markedly more patients discontinued treatment in the fluvoxamine group than in the placebo group. Acknowledging that its evaluation of the certainty of the evidence may differ from other published meta-analyses, GDG members pointed out that early stopping due to apparent benefit may have biased the results of the largest trial. They argued that, although the stopping rules were pre-specified, the decision to stop the trial was based on the effect estimate on a composite outcome of questionable importance; meanwhile the number of important events was lower and vulnerable to bias. The GDG also raised concerns regarding the uncertain applicability of this trial conducted in a single country.

Values and preferences—The GDG inferred that almost all well informed patients would choose not to receive fluvoxamine therapy for covid-19 based on available evidence. The GDG did not believe that other considerations, such as feasibility, acceptability, equity, and cost, would affect this specific recommendation. Specifically, the GDG did not consider the potential role of fluvoxamine as an antidepressant for this guideline of medications for covid-19.

Applicability—None of the included studies enrolled children, and the applicability of this recommendation to children is therefore uncertain. However, the GDG did not see a reason to assume that children with covid-19 would respond any differently to treatment with fluvoxamine.

Practical issues—The GDG made a recommendation against using fluvoxamine for treatment of patients with covid-19 outside the setting of a clinical trial, and therefore practical considerations are less relevant for this drug.

Resource implications, acceptability, feasibility, equity, and human rights—Fluvoxamine is relatively inexpensive compared with other drugs used for covid-19, and widely available, including in low income settings. Its use would risk diverting attention and resources away from interventions that are more likely to provide a benefit.

Sotrovimab (neutralising monoclonal antibodies) (updated 13 January 2023)

Overview

Sotrovimab is a single human monoclonal antibody that binds to a conserved epitope in the SARS-CoV-2 spike protein, preventing the virus from entering cells.

Status—The recommendation for sotrovimab was initially published on 14 January 2022, and was updated on 13 January 2023 incorporating updated evidence regarding in vitro neutralisation activity in circulating SARS-CoV-2 variants and subvariants. No changes were made to the recommendation in this 14th version of the guideline.

Recommendation: We recommend against treatment with sotrovimab for patients with non-severe covid-19 (strong recommendation).

Understanding the recommendation

Although previous clinical trial evidence available via the living network meta-analysis (LNMA) remains accurate,[6] the panel concluded that it is no longer applicable to covid-19 caused by the SARS-CoV-2 variants and subvariants that are currently circulating globally. The panel surmised that the likelihood of covid-19 caused by former variants was extremely low, and that, accordingly, evidence of sotrovimab's clinical effectiveness for covid-19 was inexistent.

The GDG reviewed additional in vitro neutralisation data pertaining to new variants and subvariants that was made available after the twelfth iteration of the guideline. This incremental evidence supports the change in recommendation, and strengthens the GDG's confidence that the strong recommendation not to use sotrovimab (and casirivimab-imdevimab) is applicable to the current SARS-CoV-2 ecology. More information on the interpretation of the results of in vitro neutralisation data can be found in MAGICapp and in correspondence published in the *Lancet*.[22] Of note, the GDG applied the same rationale to the recommendation for the monoclonal antibody combination casirivimab-imdevimab.

The GDG agreed that large, high quality clinical trials generally provide the best evidence of clinical effectiveness for therapeutic interventions. The GDG also continues to base its recommendations strictly on critically important outcomes. From the perspective of clinical guidelines, mechanistic studies and surrogate outcomes are useful to identify candidate therapies for clinical trials but are of no use in confirming clinical effectiveness. The panel concluded that the emerging evidence demonstrating the reduced neutralisation of current variants by sotrovimab in vitro would likely have justified not launching clinical trials and now renders the results of previous trials inapplicable. In vitro assays were deemed sufficient to rule out a clinical effect. Notwithstanding, proof of potent in vitro neutralisation would not be sufficient to confirm clinical effectiveness. Therefore, the GDG will only consider making recommendations for new monoclonal antibodies once they have been rigorously evaluated in clinical trials.

Balance of benefits and harms—There was consensus among the panel that it is highly unlikely that the clinical effectiveness of sotrovimab would persist in the absence of adequate in vitro neutralisation of the circulating variants and subvariants. Accordingly, the panel concluded that the evidence upon which hinged the previous recommendation was no longer applicable.

Values and preferences—The GDG inferred that, in the absence of compelling evidence of clinical effectiveness for the currently circulating SARS-CoV-2 variants and subvariants, almost all well informed patients would not choose to receive sotrovimab.

Applicability—Given the updated recommendation against treatment, issues pertaining to applicability were felt to be less relevant.

Practical issues—Given the updated recommendation against treatment, related practical issues were felt to be less relevant.

Resource implications, equity, human rights, acceptability, and feasibility—The strong recommendation against the use of sotrovimab is further supported by their challenges with availability and feasibility, such as limited production, intravenous administration, and requirement for expertise to offer such treatment while oral antiviral therapies are available.

Colchicine (published 14 July 2022)

Overview

Colchicine is an anti-inflammatory drug used to treat gout, recurrent pericarditis, familial Mediterranean fever, and other inflammatory conditions. Proposed mechanisms for its anti-inflammatory effect include a reduction in neutrophil chemotaxis, inflammasome signalling inhibition, and decreased production of cytokines such as interleukin 1b.

Status—The recommendation for colchicine was initially published on 14 July 2022. No changes were made to the recommendation in this 14th version of the guideline.

Recommendation: For patients with non-severe covid-19, we recommend against treatment with colchicine (strong recommendation).

Understanding the recommendation

The lack of benefits on hospitalisations, mortality, and mechanical ventilation, combined with possible harms and toxicity, drove the strong recommendation against the use of colchicine in patients with non-severe covid-19.

Balance of benefits and harms—In patients with non-severe covid-19, colchicine has little or no impact on mortality or mechanical ventilation (moderate certainty). It is unclear whether it affects hospitalisations or adverse effects leading to drug discontinuation. The GDG discussed the risk of drug interactions and colchicine's narrow therapeutic window, particularly in patients with or at risk of hepatic and renal failure. Colchicine toxicity can be severe and sometimes fatal. The planned subgroup analyses for colchicine versus standard care did not show different relative effects for disease severity or age (children, adults, older adults), with no data reported from illness onset.

Values and preferences—The GDG inferred that almost all well informed patients would choose not to receive colchicine.

Applicability—The applicability of this recommendation to children is currently uncertain because none of the included studies enrolled children. However, the GDG did not consider that children with covid-19 would respond any differently to treatment with colchicine.

Practical issues—The GDG made a strong recommendation against using colchicine for treatment of patients with non-severe covid-19, and therefore practical considerations are less relevant.

Resource implications, acceptability, feasibility, equity, and human rights—These considerations did not affect this specific recommendation. Although colchicine is relatively inexpensive compared with other drugs used for covid-19, and widely available, including in low income settings, the evidence does not justify the use of colchicine for non-severe covid-19 anywhere. Although the cost of colchicine may be low, the GDG raised concerns regarding the risk of diverting attention and resources away from interventions that are more likely to provide a benefit.

Recommendations for patients with severe or critical covid-19

Systemic corticosteroids (published 4 September 2020)

Status—The recommendation for systemic corticosteroids for patients with severe or critical illness was initially published on 4 September 2020, with evidence summaries updated as of 6 July 2021 to reflect a new baseline risk for all-cause mortality. No changes were made to the recommendation in this 14th version of the guideline.

Recommendation: 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.

Interleukin-6 (IL-6) receptor blockers (updated 15 September 2022)

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.

Status—The recommendation for IL-6 receptor blockers was initially published on 6 July 2021, and updated on 15 September 2022 to reflect that IL-6 receptor blockers and baricitinib may be given together. No changes were made to the recommendation in this 14th version of the guideline.

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, possibly with baricitinib as combination therapy.

The GDG emphasised the high certainty evidence of improved survival and reduction in need for mechanical ventilation. Additional trial data from REMAP-CAP provided more conclusive evidence regarding the equivalence of tocilizumab and sarilumab.

The GDG acknowledged the uncertain data regarding serious adverse events and bacterial infections, but felt that the evidence of benefit for the two most important patient outcomes warranted a strong recommendation. Costs and access were important considerations, and it was recognised that this recommendation could exacerbate health inequities. Hopefully this strong recommendation will provide impetus to address these concerns and ensure access across regions and countries. The GDG did not anticipate important variability in patient values and preferences, and judged that other contextual factors would not alter the recommendation.

There were insufficient data to assess subgroup effect by elevation of inflammatory markers or age. Although the GDG considered a subgroup analysis of patients receiving corticosteroids at baseline (compared with those who were not), the panel did not see a need to consider subgroup recommendations for IL-6 receptor blockers in those not receiving corticosteroids as all patients with severe or critical covid-19 should be receiving corticosteroids. Taken together, the GDG felt that the recommendation applies to both tocilizumab and sarilumab and all adult patients with severe or critical covid-19.

The GDG had previously made a strong recommendation for use of baricitinib or IL-6 receptor blockers (tocilizumab and sarilumab) or baricitinib as alternative agents administered in addition to corticosteroids for patients with severe or critical covid-19. The GDG had elected to refrain from recommending combining these three immunosuppressive drugs until clear evidence of incremental benefit emerged. The RECOVERY trial has since provided this evidence that combining corticosteroids, IL-6 receptor blockers, and baricitinib provides incremental survival benefit.[23] Specifically, in RECOVERY 2659 patients received baricitinib along with corticosteroids and IL-6 receptor blockers. The effect of baricitinib in this subgroup was consistent with the beneficial effect of baricitinib in patients who were not treated with IL-6 receptor blockers.[23] Although these three immunosuppressIve drugs are recommended and may be administered jointly, the panel anticipated that there would be situations where clinicians may opt for less aggressive immunosuppressive therapy and/or to combine medications in a stepwise fashion in patients who are deteriorating. However, since the drugs have not undergone direct comparisons, if this situation arises, the GDG felt that clinicians should choose between baricitinib and IL-6 receptor blockers on the basis of experience and comfort using the drugs; local institutional policies; route of administration (baricitinib is oral; IL-6 receptor blockers are intravenous); and cost.

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 majority of the GDG inferred that almost all well informed patients with severe or critical covid-19 infection would want to receive IL-6 receptor blockers. The benefit of IL-6 receptor blockers on mortality was deemed of critical importance to patients, despite low certainty around serious adverse events. The GDG anticipated little variation in values and preferences between patients for this intervention.

Applicability—None of the included RCTs enrolled children or pregnant people. Although this resulted in uncertain applicability, the GDG did not have reason to believe that children or pregnant people with covid-19 would respond any differently to treatment with IL-6 receptor blockers. Sarilumab is not indicated for use in children; therefore, there could be a preference for tocilizumab in this subgroup.

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

Resource implications, acceptability, feasibility, equity, and human rights—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.

Janus kinase (JAK) inhibitors (updated 16 September 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.

Status—The recommendations for JAK inhibitors were initially published on 14 January 2022, and were updated on 15 September 2022 to reflect that baricitinib, IL-6 receptor blockers and corticosteroids may be given together. No changes were made to the recommendation in this 14th version of the guideline.

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

Understanding the recommendation

The update maintaining a strong recommendation was based on additional data from 8156 patients enrolled in the RECOVERY trial, which confirmed a survival benefit (now high certainty evidence) and other benefits, with little or no serious adverse events, of a drug that may be administered easily.[23] The GDG acknowledged that some serious adverse events, such as fungal infections, may not have been accurately captured during the relatively short follow-up period in the included trials. Because of different mechanisms of action, the GDG considered baricitinib separately from other JAK inhibitors.

Costs and access remain important considerations, and the GDG recognises that this recommendation could exacerbate health inequities. This strong recommendation further strengthens the impetus to address these concerns and maximise access across regions and countries. The GDG did not anticipate important variability in patient values and preferences, and judged that other contextual factors would not alter the recommendation.

The GDG had previously made a strong recommendation for use of IL-6 receptor blockers (tocilizumab and sarilumab) or baricitinib as alternative agents administered in addition to corticosteroids for patients with severe or critical covid-19. The GDG had elected to refrain from recommending the combination of these three immunosuppressive drugs until clear evidence of incremental benefit emerged. The RECOVERY trial has now provided this evidence, demonstrating that combining corticosteroids, IL-6 receptor blockers, and baricitinib provides incremental survival benefit.[23] In RECOVERY, 2659 patients received baricitinib along with corticosteroids and IL-6 receptor blockers. The effect of baricitinib in this subgroup was consistent with the beneficial effect of baricitinib in patients who were not treated with IL-6 receptor blockers.[23]

Although these three immunosuppressive drugs are recommended and may be administered jointly, the panel anticipated that there would be situations where clinicians may opt for less aggressive immunosuppressive therapy or choose to combine medications in a stepwise fashion in patients who are deteriorating. However, since the drugs have not undergone direct comparisons, the GDG felt that clinicians should choose between baricitinib and IL-6 receptor blockers on the basis of experience and comfort using the drugs, local institutional policies, route of administration (baricitinib is oral; IL-6 receptor blockers are intravenous), and cost.

Balance of benefits and harms—In patients with severe or critical illness, baricitinib reduces mortality (high certainty), and probably reduces duration of mechanical ventilation and hospital length of stay (both moderate certainty). Treatment probably results in little or no increase in serious adverse events leading to drug discontinuation (moderate certainty). Some serious adverse events such as severe infections which may arise from immunosuppressive therapy like baricitinib 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.

Subgroup analyses were undertaken for JAK inhibitors as a class (rather than on individual drugs) and revealed no evidence of a subgroup effect on relative risk in younger (<70 years old) versus older patients, those with critical versus severe covid-19, those receiving or not receiving corticosteroids at baseline, and those receiving or not receiving remdesivir or IL-6 blockers at baseline.

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. The GDG anticipated little variation in values and preferences between patients for this intervention.

Applicability—None of the included RCTs for baricitinib enrolled children, or pregnant or lactating people; therefore, the applicability of this recommendation to these groups 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. The optimal duration of treatment is unknown.

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.

See MAGICapp for more information regarding practical issues.

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. See box 3 for related considerations. As baricitinib is administered orally once daily, hospitalised patients should find it easy to accept this treatment.

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 that 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 people.

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.

Remdesivir (updated 16 September 2022)

Overview—See above (non-severe illness) for a summary of mechanism of action for remdesivir.

Status—The recommendations for remdesivir were initially published on 20 November 2020. No changes were made to the recommendation in this 14th version of the guideline.

Recommendation1: For patients with severe covid-19, we suggest treatment with remdesivir (weak or conditional recommendation).

Understanding the recommendation

When moving from evidence to the conditional recommendation to use remdesivir in patients with severe covid-19, the GDG emphasised the benefits on survival and reduction in need for invasive mechanical ventilation, and the likelihood of little or no serious adverse events attributable to the drug. The GDG acknowledged that some serious adverse events may not have been accurately captured during the relatively short follow-up period in the included trials. Of note, although the GDG has recommended for other antiviral drugs in patients with non-severe illness, remdesivir is the only one with a recommendation for use in patients with severe covid-19.

The GDG did not anticipate important variability in patient values and preferences, although the low certainty of evidence and ongoing uncertainty in effect contributed to the conditional recommendation. There was insufficient trial level data to examine subgroups based on age or to consider patients requiring non-invasive ventilation (those on bilevel ventilation or high flow nasal cannula) as a separate subgroup of interest.

When making the recommendation for treatment with remdesivir, the GDG carefully considered the credibility of subgroup findings based on severity of disease, where remdesivir demonstrated a possible survival benefit in patients with severe covid-19, while possibly having no impact on mortality in patients with critical covid-19. The GDG used the ICEMAN tool to assess the credibility of subgroup effects, and ultimately decided the credibility of the observed subgroup finding based on severity of illness was moderate, therefore warranting separate recommendations for each, while recognising residual uncertainties (see MAGICapp for full details regarding ICEMAN assessments).

Balance of benefits and harms—There was low certainty evidence suggesting remdesivir possibly reduces mortality, and moderate certainty evidence suggesting probable reduction in need for mechanical ventilation with probably little or no impact on time to symptom improvement. The drug is well tolerated, and adverse events are rare.

Values and preferences—The GDG inferred that the majority of well informed patients with severe covid-19 would choose to receive remdesivir due to the possible reduction in mortality and need for mechanical ventilation and the safety of the drug. The GDG anticipated little variation in values and preferences between patients for this intervention.

Applicability—Insufficient evidence exists to inform a recommendation around use in children. Decisions regarding its use in pregnant or breastfeeding people should, in the absence of trials enrolling such participants, be made between the pregnant person and their healthcare provider while discussing whether the potential benefit justifies the potential risk to the mother and fetus. See MAGICapp for additional guidance.

Practical issues—Remdesivir is administered as one intravenous infusion daily over five consecutive days. The recommended dose is 200 mg intravenously on day 1, followed by 100 mg intravenously on days 2 to 5-10 days. Regimens of five days are described in the smaller trials, and local practices may vary. Administration should be as early as possible in the time course of the disease. Patients with severe liver or kidney disease warrant additional caution. See MAGICapp for additional guidance.

Resource implications, acceptability, feasibility, equity, and human rights—Given the daily intravenous administration of remdesivir, this is more easily done for hospitalised patients with severe disease, as opposed to the outpatient setting. Obstacles to access in low and middle income countries due to cost, feasibility, and availability are of concern (see box 3 for more details).

Recommendation 2: For patients with critical covid-19, we suggest not to use remdesivir (weak or conditional recommendation).

Understanding the recommendation

When moving from evidence to the conditional recommendation not to use remdesivir in patients with critical covid-19, the GDG emphasised the lack of benefit on survival or other patient-important outcomes as demonstrated in the subgroup analysis judged to be of moderate credibility. The GDG recognised there is ongoing uncertainty, and there may still be a subset of patients who would benefit (for example, immunocompromised, persistent viraemia), but there is insufficient evidence to make recommendations specific to these subsets of critical patients.

The GDG did not anticipate important variability in patient values and preferences, although the low certainty of evidence and ongoing uncertainty in effect contributed to the conditional recommendation. There was insufficient trial level data to examine subgroups based on age, or to consider patients requiring non-invasive ventilation (those on bilevel ventilation or high flow nasal cannula) as a separate subgroup of interest.

Balance of benefits and harms—Low certainty evidence suggests remdesivir possibly has little or no effect on mortality and need for mechanical ventilation, and an uncertain effect on time to symptom improvement. The drug is well tolerated, and adverse events are rare.

Values and preferences—The GDG inferred that the majority of well informed patients with critical covid-19 would choose not to receive remdesivir due to little or no impact on patient-important outcomes. The GDG anticipated little variation in values and preferences between patients for this intervention.

Applicability, practical issues, resource implications, acceptability, feasibility, equity, and human rights—Similar issues exist as for patients with severe illness. Such considerations are less relevant for patients with critical illness, given the weak or conditional recommendation against use.

Recommendations against therapeutics applicable across disease severities

VV116 (published 10 November 2023)

Overview

VV116 is a nucleoside prodrug which, similar to remdesivir, induces chain termination (though the drug is different from remdesivir in chemical activity, in vitro antiviral activity, pharmacokinetic profiles, and dosing regimens).

Status—A new recommendation was made in the current iteration against the use of VV116 except in the context of a clinical trial, given the high degree of uncertainty regarding its effects on patient-important outcomes of most critical importance.

Recommendation: We recommend not to use VV116 for patients with covid-19 except in the context of a clinical trial, regardless of illness severity (strong recommendation).

Understanding the recommendation

The GDG emphasised the high degree of uncertainty in the most critical outcomes such as mortality and need for hospital admission. The GDG noted that VV116 does not seem to be associated with increased adverse effects. The GDG did not anticipate important variability in patient values and preferences. Other contextual factors, such as resource considerations, accessibility, feasibility, and impact on health equity did not alter the recommendation.

Compared with previous drugs evaluated in this guideline, there was a substantially higher degree of uncertainty with only a single RCT available comparing VV116 with nirmatrelvir/ritonavir. No comparison to placebo is available, and the single trial reported no deaths in the 771 patients enrolled. This results in very low certainty in effect estimates for the main outcomes of interest (mortality, mechanical ventilation, hospital admission, and symptom duration), primarily driven by extremely serious imprecision (and risk of bias for duration of symptoms). There are no data examining need for hospital admission, which has been a major driver of recommendations for other interventions in non-severe illness, given the perceived patient importance of this outcome. A lack of within-trial comparisons prevented subgroup analyses based on variables such as age, serological status, or covid-19 vaccination status; and any related subgroup recommendations.

Balance of benefits and harms—Summarised above.

Values and preferences—The GDG inferred that almost all well informed patients would want to receive VV116 only in the context of a randomised trial, given that the evidence left a very high degree of uncertainty in beneficial effects despite the fact that harms such as treatment-associated serious adverse events were unlikely. The panel anticipated little variation in values and preferences between patients.

Applicability—The included RCTs did not enrol children, and therefore the applicability of this recommendation to children is uncertain. However, the panel had no reason to think that children with covid-19 would respond any differently to treatment with VV116. There were similar considerations for pregnant people, with no data directly examining this population, but no rationale to suggest they would respond differently to other adults.

Practical issues—Given the recommendation against treatment, related practical issues were felt to be less relevant.

Resource implications, acceptability, feasibility, equity, and human rights—The cost of VV116 is uncertain. However the lack of availability of this novel intervention, especially in low income settings, may influence the ability to administer this drug, even if it proves useful in patients with non-severe disease. The drug is administered orally which is easier than intravenous options (such as remdesivir).

Ivermectin (updated 10 November 2023)

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.

Update—The recommendation for ivermectin across disease severities was initially published on 31 March 2021. In this 14th iteration of the guideline, the GDG considered new trial evidence that resulted in updated recommendations for patients with non-severe illness.

Recommendation 1: For patients with non-severe covid-19, we recommend not to use ivermectin (strong recommendation).

Understanding the recommendation

New trial evidence reduced the high degree of uncertainty informing the previous recommendation to continue with ivermectin within the context of RCTs. The GDG emphasised the very low likelihood of benefit given both the evidence from randomised trials and the lack of biological basis for any effect of ivermectin on the virus, and the probable (although modest) harm associated with treatment. A strong recommendation reflected the potential harm associated with using an ineffective medication which could divert resources from interventions known to have benefit. The GDG did not anticipate important variability in patient values and preferences.

Balance of benefits and harms—The absolute benefits of ivermectin on hospital admission vary from being of low certainty among patients at high risk of hospitalisation to trivial (high certainty) in patients at low risk. Ivermectin does not result in an important reduction in mortality (high certainty) and probably does not result in an important reduction in mechanical ventilation, time to symptom resolution, and duration of hospitalisation, while probably increasing the risk of serious adverse events leading to drug discontinuation (all moderate certainty).

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

Values and preferences—The GDG inferred that the all or almost all of well informed patients would not want to receive ivermectin given the very low likelihood of important benefit.

Practical issues—Given the strong recommendation against using ivermctin, practical considerations are not relevant for this drug.

Applicability, resource implications, acceptability, feasibility, equity, and human rights—Ivermectin is a relatively inexpensive drug and is widely available, including in low income settings, providing an incentive to use the medication. Given both the published evidence summarised in the evidence profile, and the lack of a plausible biological mechanism of action against the virus, the GDG concluded that the drug is very likely to be ineffective. Use of ivermectin risks diverting attention and resources away from care likely to provide a benefit such as nirmatrelvir/ritonavir, remdesivir, and molnupiravir as well as supportive care interventions. Also, use of ivermectin for covid-19 would divert drug supply away from pathologies for which it is clearly indicated, potentially contributing to drug shortages, especially for helminth control and elimination programmes.

Recommendation 2: For patients with severe or critical covid-19, we recommend not to use ivermectin 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; this was primarily due to serious risk of bias and very serious imprecision. Similar judgments were made for other outcomes, including mechanical ventilation, hospital admission, duration of hospitalisation, and time to viral clearance (all very low certainty). 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 people; 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. Resource use considerations apply as with Recommendation 1. For covid-19 patients treated with corticosteroids in strongyloidiasis-endemic areas, presumptive treatment with ivermectin for helminth infection may be appropriate.

Convalescent plasma (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.

Status—Recommendations for convalescent plasma across disease severities were initially published on 7 December 2021. No changes were made to the recommendations in this 14th version of the guideline.

Recommendation 1: We recommend against treatment with 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 people. The GDG did not have reason to believe that children or pregnant people with covid-19 would respond any differently to treatment with convalescent plasma; the GDG therefore inferred that children and pregnant people 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.

Casirivimab-imdevimab (neutralising monoclonal antibodies) (published 13 January 2023)

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.

Status—The recommendation for casirivimab-imdevimab was initially published on 24 September 2021, and was updated on 3 March 2022. No changes were made to the recommendation in this 14th version of the guideline.

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

Understanding the recommendation

Although previous clinical trial evidence available via the LNMA remains accurate,[6] the GDG concluded that it is no longer applicable to covid-19 caused by the SARS-CoV-2 variants and subvariants that are currently circulating globally. The panel surmised that the likelihood of covid-19 caused by former variants was extremely low and that, accordingly, evidence of casirivimab-imdevimab clinical effectiveness for covid-19 was inexistent.

The GDG reviewed additional in vitro neutralisation data pertaining to new variants and subvariants that was made available after the twelfth iteration of the guideline. This incremental evidence supports the change in recommendation, and strengthens the GDG's confidence that the strong recommendation not to use casirivimab-imdevimab (and sotrovimab) is applicable to the current SARS-CoV-2 ecology. More information on the interpretation of the results of in vitro neutralisation data can be found in MAGICapp and in a letter to the editor published in the *Lancet*.[22] Of note, the panel applied the same rationale to the recommendation for sotrovimab.

The GDG agreed that large, high quality clinical trials generally provide the best evidence of clinical effectiveness for therapeutic interventions. The GDG also continues to base its recommendations strictly on predefined patient-important outcomes. From the perspective of clinical practice guidelines, mechanistic studies and surrogate outcomes are useful to identify candidate therapies for clinical trials but are of no use in the evaluation of clinical effectiveness. The panel concluded that the emerging evidence demonstrating that casirivimab-imdevimab did not comparatively neutralise current variants in vitro would have justified not launching clinical trials and now renders the results of previous trials inapplicable. In vitro assays were deemed sufficient to rule out a clinical effect. Notwithstanding, proof of potent in vitro neutralisation would not be sufficient to confirm clinical effectiveness. Therefore, the GDG will only consider making recommendations for new monoclonal antibodies once they have been rigorously evaluated in clinical trials.

Balance of benefits and harms—There was consensus among the panel that it is highly unlikely that the clinical effectiveness of casirivimab-imdevimab would persist in the absence of adequate

in vitro neutralisation of the circulating variants and subvariants. Accordingly, the panel concluded that the evidence upon which hinged the previous recommendations was no longer applicable.

Values and preferences—The GDG inferred that, in the absence of compelling evidence of clinical effectiveness for the currently circulating SARS-CoV-2 variants and subvariants, almost all well informed patients would not choose to receive casirivimab-imdevimab.

Applicability—Given the updated recommendation against treatment, issues pertaining to applicability were felt to be less relevant.

Practical issues—Given the updated recommendation against treatment, related practical issues were felt to be less relevant.

Resource implications, acceptability, feasibility, equity, and human rights—The strong recommendation against the use of casirivimab-imdevimab is further supported by their challenges with availability and feasibility, such as limited production, intravenous administration and requirement for expertise to offer such treatment while oral options are available.

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*,[24] the Institute of Medicine, and the Guideline International Network (G-I-N).[25]

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. The WHO technical unit collected and managed declarations of interests (DOIs) and found no GDG member, chair, or systematic review team member to have a conflict of interest. The GDG aimed to create a recommendation based on consensus with a provision for voting that proved unnecessary for this recommendation. Co-chairs were not eligible to vote in this setting. For recommendations revised or added in the current iteration, there was no need for voting.

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.[5 6]

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.[3] 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.[3] 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 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