Therapeutics and COVID-19

LIVING GUIDELINE
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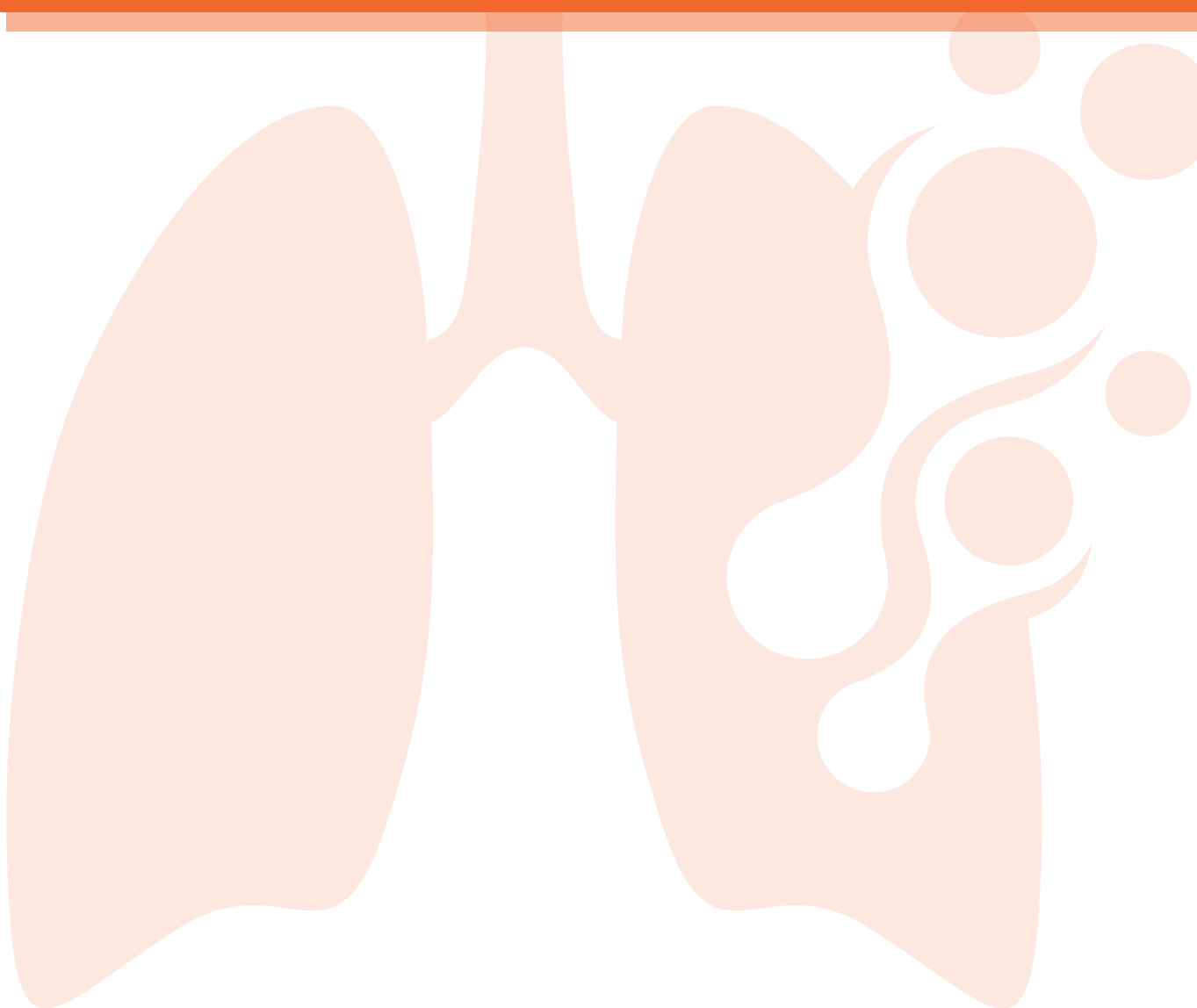
World Health Organization



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WHO continues to monitor the situation closely for any changes that may affect this interim guidance. Should any factors change, WHO will issue a further update. Otherwise, this interim guidance document will expire 2 years after the date of publication.

WHO reference number: WHO/2019-nCoV/therapeutics/2022.2

Sections

1. Summary of the 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 randomized controlled trials (RCTs) refcently completed and underway. This update adds a new recommendation on molnupiravir in patients with non-severe COVID-19, informed by data from 6 RCTs with 4796 patients.

New recommendations: The Guideline Development Group (GDG) suggests administering molnupiravir in patients with non-severe illness, who are at highest risk of hospitalization with implementation of mitigation strategies to reduce potential harms. No recommendation was made in patients with severe or critical illness as there are no data on molnupiravir for this population.

The Omicron variant has resulted in an update to the recommendations for casirivimab-imdevimab. Additional preclinical evidence has emerged demonstrating lack of efficacy of casirivimab-imdevimab against the Omicron BA1 variant (see Mechanism of Action) and reduced neutralizing activity of sotrovimab against the Omicron BA2 variant (see Mechanism of Action). See Section 4 for what drugs are currently under review.

Understanding the new recommendations: When moving from evidence to recommendations, the GDG considered a combination of evidence assessing relative benefits and harms, values and preferences, and feasibility issues. For patients with non-severe illness, the GDG recognized that molnupiravir reduces hospitalization risk and time to symptom resolution, and may have little to no effect on mortality. The effect on need for invasive mechanical ventilation was uncertain. The GDG also acknowledged that only patients at the highest risk of being hospitalized are likely to derive important benefits and would want to receive molnupiravir. This is especially true given the potential for harms associated with molnupiravir. Based on in vitro studies in human cells there is a theoretical risk of malignancy associated with the drug. No evidence for genetic toxicity was uncovered in animals but this has not been evaluated in long-term follow-up or human studies. There are also separate theoretical risks that molnupiravir may induce drug resistance in the virus and/or increase genetic diversity within viral genome sequences that promote the emergence of new variants.

The conditional recommendation for molnupiravir in non-severe illness acknowledges that it is challenging to accurately identify those at highest risk of hospitalization, the limited availability of the drug, and that efficacy against emerging variants remains uncertain. The absence of data on severe and critical COVID-19 prevented the GDG from making any recommendations for these particular risk categories.

Updates to prior recommendations:

- The conditional recommendations for casirivimab-imdevimab in patients with both non-severe (for those at highest risk of hospitalization) and severe or critical COVID-19 (for those with seronegative status) are now restricted to cases where rapid viral genotyping is available and confirms infection with a susceptible SARS-CoV-2 variant (such as Delta). This change follows pre-clinical evidence that casirivimab-imdevimab lacks efficacy against the Omicron BA1 variant.
- Regarding the previous conditional recommendation against remdesivir in patients with COVID-19, new trial data have resulted in an ongoing evidence review by the GDG with an anticipated update of the recommendation in the next iteration of this guideline.

Prior recommendations:

Recommended for patients with severe or critical COVID-19:

- a strong recommendation for systemic corticosteroids;
- a strong recommendation for interleukin-6 (IL-6) receptor blockers (tocilizumab or sarilumab), in combination with corticosteroids;
- a strong recommendation for baricitinib as an alternative to IL-6 receptor blockers, in combination with corticosteroids.

Recommended for patients with non-severe COVID-19:

- a conditional recommendation for sotrovimab, conditional for those at highest risk of hospitalization.

Not recommended for patients with non-severe COVID-19:

- a conditional recommendation against systemic corticosteroids;
- a strong recommendation against convalescent plasma.

Not recommended for patients with severe and critical COVID-19:

- a recommendation against convalescent plasma, except in the context of a clinical trial;
- a conditional recommendation against ruxolitinib and tofacitinib.

Not recommended, regardless of COVID-19 disease severity:

- a strong recommendation against hydroxychloroquine;
- a strong recommendation against lopinavir/ritonavir;
- a recommendation against ivermectin, except in the context of a clinical trial.

About this guideline: This living guideline from the World Health Organization (WHO) incorporates a new recommendation on molnupiravir for patients with non-severe COVID-19, and updates existing recommendations. The GDG typically evaluates a drug when WHO judges sufficient evidence is available to make a recommendation. While the GDG takes an individual patient perspective in making recommendations, it also considers resource implications, acceptability, feasibility, equity and human rights. This guideline was developed according to standards and methods for trustworthy guidelines. It is supported by living systematic reviews and network meta-analyses (LNMAs) *(1)(2)(3)*.

Updates and access: This is the ninth update of the living guideline. It replaces earlier versions (2 September 2020, 20 November 2020, 17 December 2020, 31 March 2021, 6 July 2021, 24 September 2021, 7 December 2021 and 14 January 2022). The current guideline and its earlier versions are available through the WHO website *(4)*, the BMJ *(5)*, and MAGICapp (online and also as PDF outputs for readers with limited internet access). The living guideline is written, disseminated, and updated in an online platform (MAGICapp), with a user-friendly format and easy-to-navigate structure that accommodates dynamically updated evidence and recommendations, focusing on what is new while keeping existing recommendations updated within the guideline.

This living WHO guideline for COVID-19 treatments is related to the larger, more comprehensive guideline for COVID-19 clinical management *(6)*. Guidelines for the use of drugs to prevent (rather than treat) COVID-19 are published separately on the WHO website *(7)* and by the BMJ *(8)*, supported by a LNMA *(9)*.

2. Abbreviations

ALT	alanine aminotransferase
ARDS	acute respiratory distress syndrome
CAP	community-acquired pneumonia
CI	confidence interval
COVID-19	coronavirus disease 2019
DOI	declaration of interests
eGFR	estimated glomerular filtration rate
FDA	United States Food and Drug Administration
GDG	guideline development group
GI	gastrointestinal
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRC	guideline review committee
IL-6	interleukin-6
IMV	invasive mechanical ventilation
JAK	Janus kinase
LNMA	living network meta-analysis
MAGIC	Magic Evidence Ecosystem Foundation
MD	mean difference
OIS	optimal information size
OR	odds ratio
PICO	population, intervention, comparator, outcome
PMA	prospective meta-analysis
RCT	randomized controlled trial
RR	relative risk/risk ratio
SAE	serious adverse event
TACO	transfusion-associated circulatory overload
TRALI	transfusion-related acute lung injury
WHO	World Health Organization

3. Introduction

Info Box

As of 20 February 2022, there have been over 418 million confirmed cases of COVID-19 *(10)*. The pandemic has thus far claimed approximately 5.8 million lives *(10)*. Vaccination is having a substantial impact on case numbers and hospitalizations in a number of high-income countries, but limitations in global access to vaccines mean that many populations remain vulnerable *(10)(11)*. Even in vaccinated individuals, uncertainties remain about the duration of protection and efficacy of current vaccines – and the efficacy of existing treatments for COVID-19 – against emerging SARS-CoV-2 variants.

Taken together, there remains a need for more effective treatments for COVID-19. The COVID-19 pandemic – and the explosion of both research and misinformation – has highlighted the need for trustworthy, accessible, and regularly updated living guidance to place emerging findings into context and provide clear recommendations for clinical practice *(12)*.

This living guideline responds to emerging evidence from RCTs on existing and new drug treatments for COVID-19. More than 5000 trials investigating interventions for COVID-19 have been registered or are ongoing (see Section 9 for emerging evidence) *(13)*. Among these are large national and international platform trials (such as RECOVERY, WHO SOLIDARITY, REMAP-CAP, and ACTIV), which recruit large numbers of patients in many countries, with a pragmatic and adaptive design *(14)(15)(16)(17)*. An overview of ongoing trials is available from the Infectious Diseases Data Observatory, through their living systematic review of COVID-19 clinical trial registrations *(13)* and the WHO website.

Several living network meta-analyses associated with this guideline incorporate emerging trial data and allow for analysis of comparative effectiveness of multiple COVID-19 treatments. To inform the living guidance, we also use additional relevant evidence on safety, prognosis, and patient values and preferences related to COVID-19 treatments. A recently updated living systematic review of 232 risk prediction models for COVID-19 did not identify credible and applicable risk prediction tools that could inform recommendations in this ninth version of the guideline *(18)*.

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

4. What triggered this update and what is coming next?

This ninth version of the WHO living guideline addresses the use of molnupiravir in non-severe COVID-19. It follows the availability of six RCTs, which were incorporated in an update to the LNMA on drug treatments for COVID-19 *(2)*. It also includes updated recommendations for casirivimab-imdevimab, driven by the emergence of the Omicron BA1 variant, and an ongoing evidence review by the GDG for remdesivir with an anticipated update of the recommendation in the next iteration of the guideline.

Fig. 1 shows other therapeutics in progress for this WHO living guideline, also communicated through the WHO portal *(4)*. Each dot represents a week of time. In deciding which therapeutics to cover, the WHO considers multiple factors, including the extent of available evidence to inform recommendations, and makes a judgment on whether and when additional evidence might be anticipated. The WHO has a standing steering committee (see Section 10) to evaluate possibilities for new drug recommendations and updates to existing drug recommendations.

Fig 1. COVID-19 therapeutics under assessment