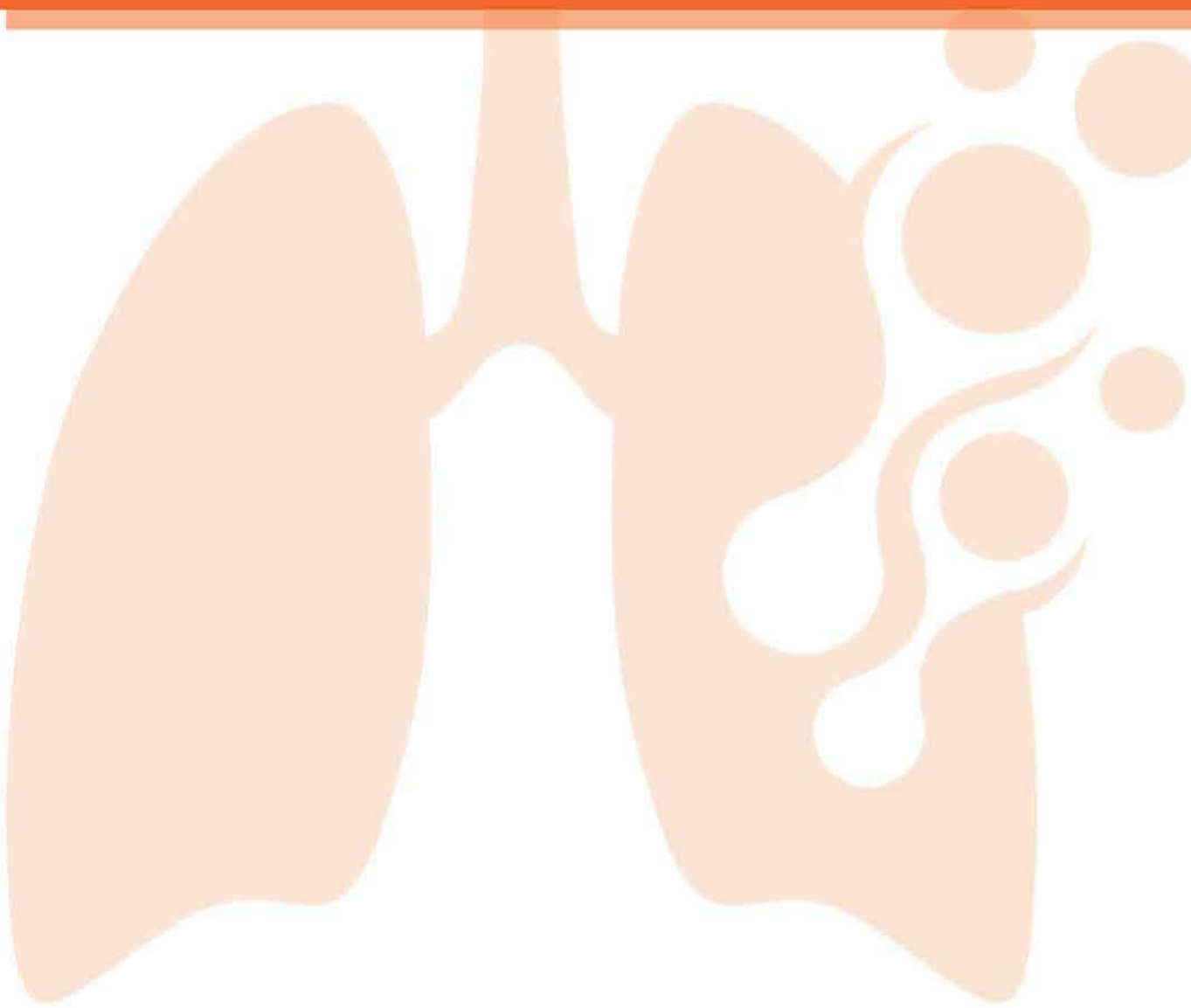
Therapeutics and COVID-19

LIVING GUIDELINE

16 SEPTEMBER 2022

World Health Organization



WHO/2019-nCoV/therapeutics/2022.5

Suggested citation. Therapeutics and COVID-19: living guideline, 16 September 2022. Geneva: World Health Organization; 2022 (WHO/2019-nCoV/therapeutics/2022.5). Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

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.

Contact

WHO Emerging Diseases Clinical Assessment and Response Network

EDCARN@who.int

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) recently completed and underway. The emerging SARS-CoV-2 variants (e.g. Omicron) and subvariants are also changing the role of therapeutics. This update provides updated recommendations for remdevisir, addresses the use of combination therapy with corticosteroids, interleukin-6 (IL-6) receptor blockers and Janus kinase (JAK) inhibitors in patients with severe or critical COVID-19, and modifies previous recommendations for the neutralizing monoclonal antibodies sotrovimab and casirivimab-imdevimab in patients with non-severe COVID-19.

New recommendations:

- a conditional recommendation for remdesivir in patients with severe COVID-19, and a conditional recommendation against remdesivir in patients with critical COVID-19;
- concerning the concomitant use of IL-6 receptor blockers (tocilizumab or sarliumab), and the JAK inhibitor baricitinib, these drugs may now be combined, in addition to corticosteroids in patients with severe or critical COVID-19;
- strong recommendations against the use of sotrovimab and casirivimab-imdevimab in patients with COVID-19, replacing the previous conditional recommendations for their use.

Understanding the new recommendations: When moving from new evidence to updated recommendations, the GDG considered a combination of evidence assessing relative benefits and harms, values and preferences, and feasibility issues.

For remdesivir, new trial data were added to a previous subgroup analysis and provided sufficiently trustworthy evidence to demonstrate benefits in patients with severe COVID-19, but not critical COVID-19. Added to existing drugs strongly recommended for these patients, the GDG considered benefits of remdesivir to be modest and of moderate certainty for key outcomes such as mortality and mechanical ventilation, resulting in a conditional recommendation.

For baricitinib, the GDG considered clinical trial evidence (RECOVERY) demonstrating reduced risk of death also in patients already receiving corticosteroids and IL-6 receptor blockers. The GDG acknowledged that the clinical trials were not representative of the world population and that the risk-benefit may be less advantageous, particularly in areas where certain pathogens like HIV, tuberculosis, and fungal infections are endemic. 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. The decision to combine the medications will depend on their availability, and the clinician's perception of the risk-benefit associated with combination immunosuppressive therapy, particularly in patient populations at risk of opportunistic infections who may have been underrepresented in clinical trials.

When making a strong recommendation against the use of monoclonal antibodies for patients with COVID-19 the GDG considered in vitro neutralization data demonstrating whether sotrovimab and casirivimab-imdevimab evaluated in clinical trials have meaningfully reduced neutralization activity of the currently circulating variants of SARS-CoV-2 and their subvariants. There was consensus among the panel that the absence of in vitro neutralization activity strongly suggests absence of clinical effectiveness of these monoclonal antibodies. However, there was also consensus regarding the need for clinical trial evidence in order to confirm clinical efficacy of new monoclonal antibodies that reliably neutralize the circulating strains in vitro. Whether emerging new variants and subvariants might be susceptible to sotrovimab or casirivimab-imdevimab, or other anti-SARS-CoV-2 monoclonal antibodies cannot be predicted.

Prior recommendations, unchanged from previous:

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);
- a strong recommendation for the JAK inhibitor baricitinib.

Recommended for patients with non-severe COVID-19 at highest risk of hospitalization:

- a strong recommendation for nirmatrelvir-ritonavir;
- a conditional recommendation for molnupiravir;
- a conditional recommendation for remdesivir.

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

- a conditional recommendation against systemic corticosteroids;
- a strong recommendation against convalescent plasma;
- a recommendation against fluvoxamine, except in the context of a clinical trial;
- a strong recommendation against colchicine.

Not recommended for patients with non-severe COVID-19 at low risk of hospitalization:

- a conditional recommendation against nirmatrelvir-ritonavir.

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 the JAK inhibitors 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 new evidence to dynamically update recommendations for COVID-19 therapeutics. The GDG typically evaluates a drug 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. It is supported by living network meta-analyses (LNMAs) *(1)(3)(4)*.

Updates and access: This is the 12th version (11th update) of the living guideline. It replaces earlier versions, latest published 14 July 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 format should also facilitate adaptation, which is strongly encouraged by WHO to contextualise recommendations in a health care system perspective to maximize country impact.

This living WHO guideline for therapeutics for COVID-19 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
EUA	emergency use authorization
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
LMIC	low- and middle-income countries
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
SSRI	selective serotonin reuptake inhibitor
TACO	transfusion-associated circulatory overload
TRALI	transfusion-related acute lung injury
WHO	World Health Organization

3. Introduction

Info Box

As of August 2022, there have been over 572 million confirmed cases of COVID-19 *(9)*. The pandemic has thus far claimed approximately 6.39 million lives *(9)*. Vaccination is having a substantial impact on hospitalizations and death in a number of high-income countries, but limitations in global access to COVID-19 vaccines mean that many populations remain vulnerable *(9)(10)*. Even in vaccinated individuals, uncertainties remain about the duration of protection and effectiveness of current vaccines – and the efficacy of existing treatments for COVID-19 – against emerging SARS-CoV-2 variants and subvariants.

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 *(11)*.

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 and are ongoing or completed (see Section 9 for emerging evidence and linked appendix) *(12)*. Among these are large national and international platform trials (such as ACCT, RECOVERY, WHO SOLIDARITY, REMAP-CAP, and ACTIV), which recruit large numbers of patients in many countries, with a pragmatic and adaptive design *(13)(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 *(12)* and the WHO website.

Several LNMAs 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 in hospitalized patients with COVID-19 identified two promising risk prediction tools that could inform recommendations in this 11th version of the guideline; these include the Jehi diagnostic model and the 4C mortality model (see Section 6.1 for more details) *(14)*.