

WHO Therapeutic Guidance: Review of current recommendations and application in children and young persons

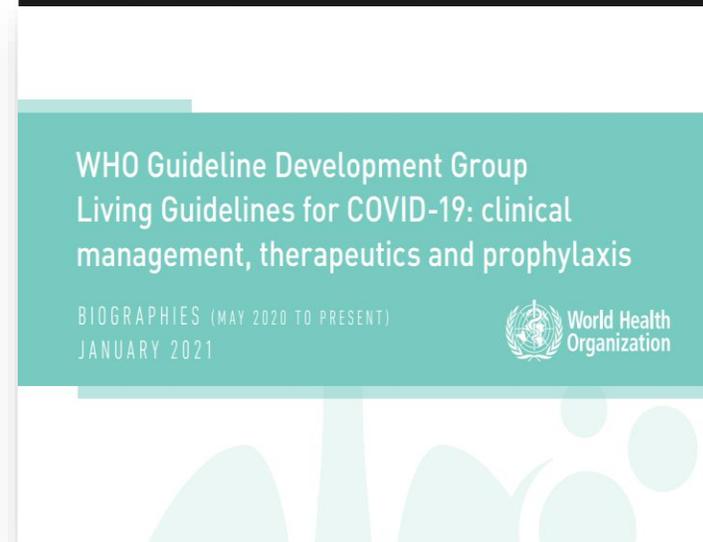
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22 March 2022

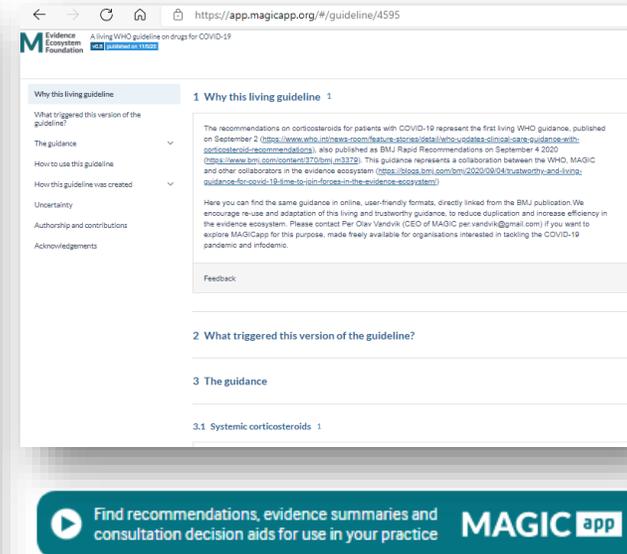
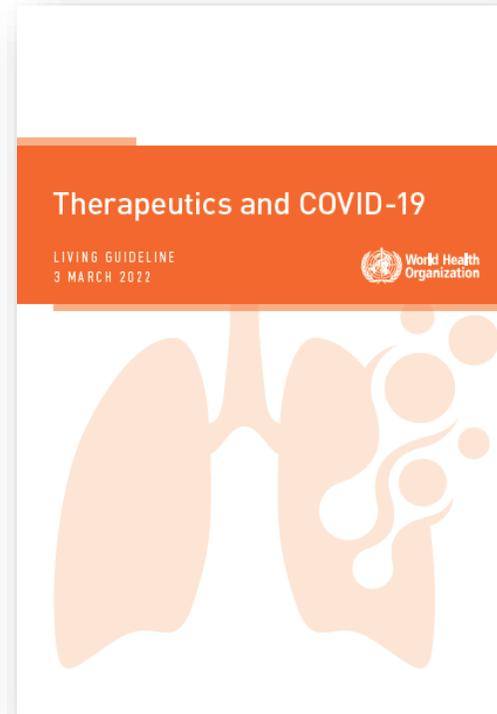
WHO Guideline Development Group Living Guidelines for COVID-19

- For the development of the ***WHO Living Guideline on Therapeutics for COVID-19***, ***WHO Living Guidance for Clinical Management of COVID-19*** and the new ***WHO Living Guideline for Prophylaxis for COVID-19***, a formal Guideline Development Group (GDG) comprising individuals with broad expertise spanning multiple specialties and all regions was convened in 2020.
- This group includes patient panel members.
- Confidentiality and declarations of interest are regularly collected and reviewed.



Living Guidelines for Therapeutics and COVID-19

- Downloadable and online publishing platform
- First version, published 2 September 2020
- 9th version, published 3 March 2021



[Therapeutics and COVID-19: living guideline \(who.int\)](https://www.who.int/publications/m/item/therapeutics-and-covid-19-living-guideline)
[A living WHO guideline on drugs for COVID-19 \(magicapp.org\)](https://www.magicapp.org/#/guideline/4595)
[A living WHO guideline on drugs for covid-19 | The BMJ](https://www.bmj.com/2020/09/04/trustworthy-and-living-guidance-for-covid-19-treatment)



Step 1

WHO Therapeutic Steering Committee
Scanning and prioritization

Step 2

Meta Analysis

Step 3

Guideline Development Group Meetings

Step 4

Recommendation Writing
GRC, PRC, external review

Step 5

Publication
Dissemination and development of tools

Session objectives

At the end of this session, you will be able to relate the WHO recommendation for various therapeutics in the treatment of patients with COVID-19 and their application in children and young persons..

- **Systemic corticosteroids**
- **IL-6 receptor blockers**
Tocilizumab or sarilumab
- **Neutralizing monoclonal antibodies**
Casirivimab/imdevimab or sotrovimab
- **Janus kinase inhibitors**
Baricitinib
- **Antivirals**
Molnupiravir, nirmatrelvir/ritonavir, remdesivir
- **Heparin**

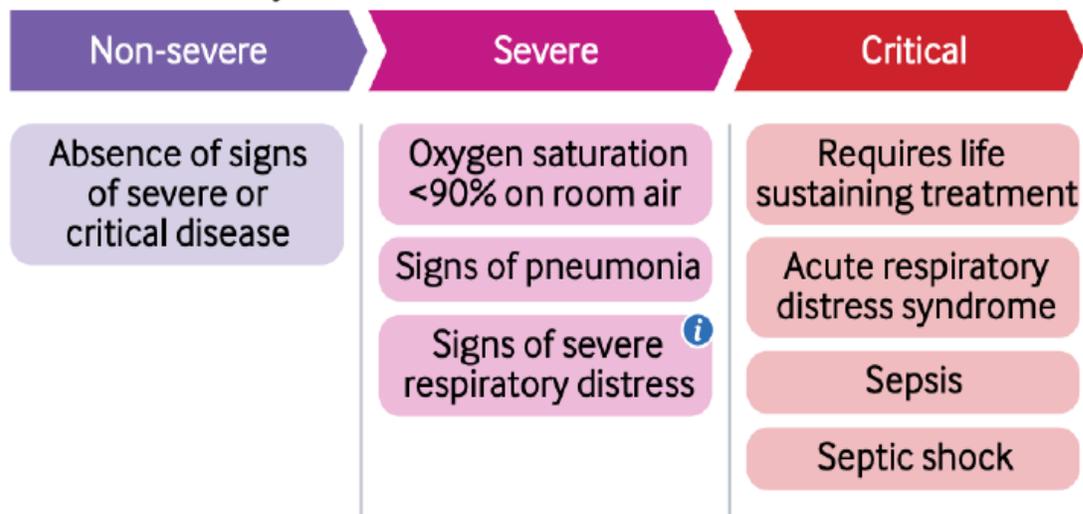
Characterizing COVID-19 by severity (I)

Population

This recommendation applies only to people with these characteristics:



Disease severity



Infographic co-produced by the BMJ and MAGIC; designer Will Stahl-Timmins (see [BMJ Rapid Recommendations](#)).

Characterizing COVID-19 by severity (II)

- 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
 - Respiratory rate > 30 breaths/min in children > 5 years old and adults
 - ≥ 40 in children 1–5 years old
 - ≥ 50 in children 2–11 months old
 - ≥ 60 in children < 2 months old
 - Signs of severe respiratory distress (accessory muscle use, inability to complete full sentences, and, in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs).

Corticosteroids in COVID-19: summary of recommendations

- In September 2020, the following recommendations regarding systemic corticosteroids for patients with COVID-19 were released by WHO:

Strong recommendation

We recommend systemic corticosteroids rather than no corticosteroids for the treatment of patients with **severe and critical COVID-19**.

Conditional recommendation:

We suggest **not to use** corticosteroids in the treatment of patients with **non-severe COVID-19**.

Corticosteroids in COVID-19: in children and adolescents

- The applicability of the recommendation is less clear for sub populations that were under-represented in the considered trials, such as **children**
- Notwithstanding, clinicians will also consider the risk of depriving these patients of potentially life-saving therapy.
- Dosing regimen: dexamethasone 0.15 mg/kg/dose (maximum dose 6 mg) once daily for up to 10 days.

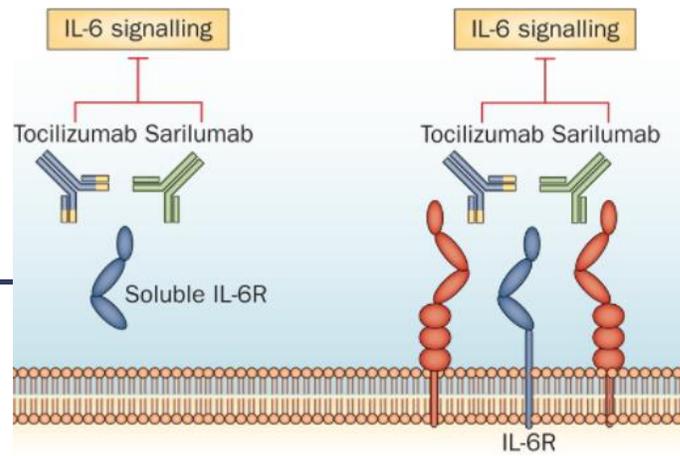
IL-6 receptor blockers in COVID-19: summary of recommendations

- In July 2021, the following WHO recommendations regarding IL-6 receptor blockers for patients with COVID-19 were released:

Strong recommendation:

We recommend treatment with IL-6 receptor blockers (tocilizumab or sarilumab) for patients with severe and critical COVID-19.

- Corticosteroids had previously been strongly recommended in patients with severe and critical COVID-19, and we recommend **patients meeting these severity criteria should now receive both corticosteroids and IL-6 receptor blockers.**



IL-6 receptor blockers in COVID-19: Use in children and adolescents

- None of the included RCTs enrolled children, and therefore the applicability of this recommendation to children is currently uncertain.
- However, the GDG had no reason to think that children with COVID-19 would respond any differently to treatment with IL-6 receptor blockers, given **tocilizumab is used in children safely for other indications** including polyarticular juvenile rheumatoid arthritis, systemic onset of juvenile chronic arthritis, and chimeric antigen receptor t-cell induced cytokine release syndrome. (≥ 2 years)
- **Sarilumab is not approved in children**, so if an IL-6 receptor blocker is used in this population, tocilizumab is preferred.
- The GDG also recognized that in many settings children are commonly admitted to hospital with acute respiratory illnesses caused by other pathogens; as a result, it may be challenging to determine who is ill with severe COVID-19, even with a positive test, and therefore likely to benefit from IL-6 receptor blockade.

Casirivimab-imdevimab in COVID-19: summary of recommendations

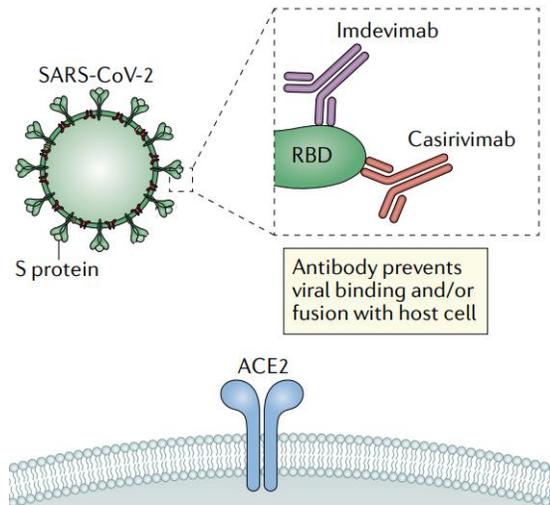
Recombinant human mAbs that bind to nonoverlapping epitopes of the spike protein RBD of SARS-CoV-2

- In September 2021, the following WHO recommendations regarding casirivimab-imdevimab for patients with COVID-19 were released, and subsequently revised in March 2022:

Conditional recommendation:

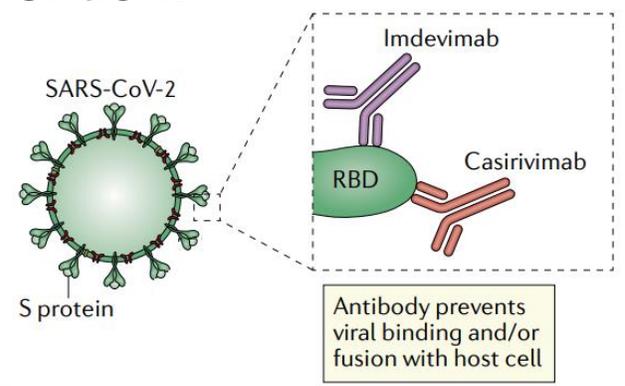
The conditional recommendations for casirivimab-imdevimab in patients with both non-severe (for those at highest risk of hospitalization) and severe or critical COVID-19 (for those with seronegative status) are now **restricted to cases where rapid viral genotyping is available and confirms infection 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.



Casirivimab and imdevimab in COVID-19: Use in children and adolescents

- The applicability of this recommendation to children is currently uncertain, as the included RCTs enrolled adults.
- The GDG had no reason to think that children with COVID-19 would respond any differently to treatment with casirivimab-imdevimab.
- However, the risk of hospitalization in children is generally extremely low and the GDG inferred that in the absence of immunosuppression or another significant risk factor children should not receive the intervention.



Sotrovimab in COVID-19: summary of recommendations

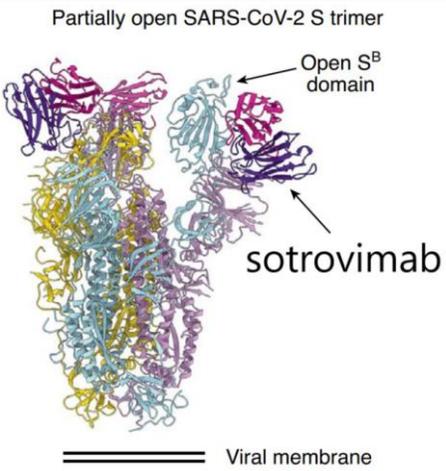
Binds to epitope in the RBD of the spike protein that is conserved between SARS-CoV and SARS-CoV-2

- In January 2022, the following recommendations regarding Sotrovimab for patients with COVID-19 were released by WHO:

Conditional recommendation:

We recommend treatment with sotrovimab for patients with non-severe COVID-19 at highest risk for hospitalization with COVID-19.

- Based on current evidence the benefit of sotrovimab in seronegative patients with severe or critical COVID-19 remains unclear.
- Careful clinical judgement needs to be applied if casirivimab and imdevimab is unavailable and sotrovimab is considered.

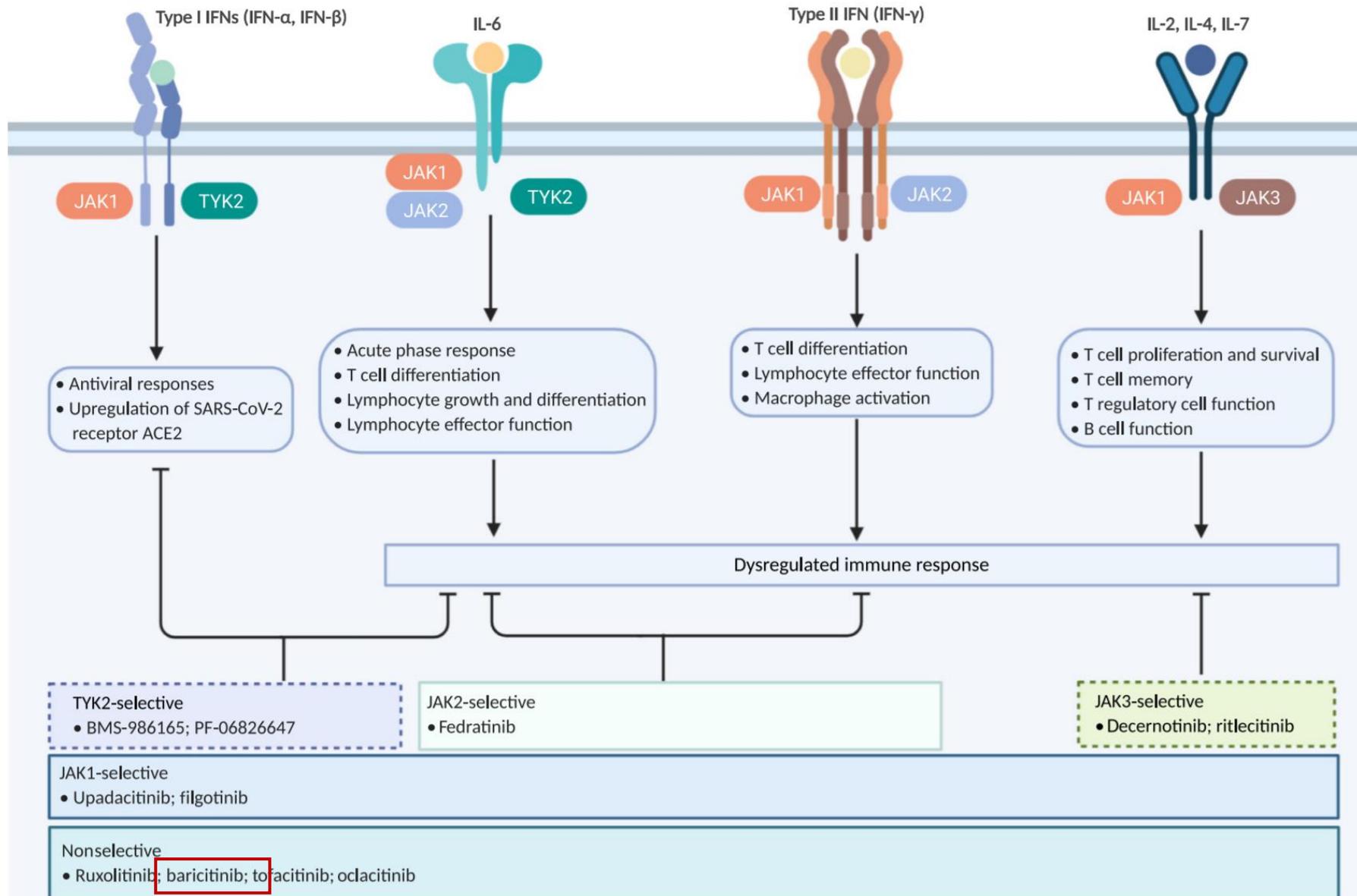




Sotrovimab in COVID-19: Use in children and adolescents

- The included RCT enrolled only non-pregnant adults; therefore, the applicability to children remains uncertain.
- The GDG had no reason to believe that children with COVID-19 would respond differently to treatment with sotrovimab.
- However, for children, as the risk of hospitalization is generally extremely low, the GDG inferred that, in the absence of immunosuppression or another significant risk factor, children should not receive the intervention.

JAK-STAT signaling in COVID-19



Janus Kinase Inhibitors in COVID-19: summary of recommendations

- In January 2022, the following WHO recommendations regarding the Janus Kinase Inhibitor (JAK-Inhibitor) baricitinib for patients with COVID-19.

Strong recommendation:

We recommend treatment with the jak-inhibitor (baricitinib) for patients with severe and critical COVID-19.

- Along with baricitinib, corticosteroids should also be administered in patients with severe and critical COVID-19.
- IL-6 receptor blockers had previously been strongly recommended in patients with severe and critical COVID-19.

Janus Kinase Inhibitors in COVID-19: Use in children and adolescents

- None of the included RCTs enrolled children, and therefore the applicability of this recommendation to children remains uncertain.

Remdesivir in COVID-19

- Intravenous nucleotide prodrug of an adenosine analog
- Binds to the viral RNA-dependent RNA polymerase and inhibits viral replication through premature termination of RNA transcription

In November, 2020 the following WHO recommendations regarding remdesivir for patients with COVID-19 were released:

Conditional recommendation against

We suggest not to use remdesivir (conditional recommendation against).

This initial recommendation followed the pre-print publication of the WHO SOLIDARITY trial on 15 October 2020, reporting results on treatment with remdesivir, hydroxychloroquine and lopinavir/ritonavir in hospitalized patients with COVID-19.

This recommendation is under review given new trials, and an update is planned in the next iteration of the guideline in April 2022. The current recommendation provided is based on the initial assessment made by the GDG and does not represent best current evidence.

Molupiravir in COVID-19: summary of recommendations

- In March 2022 the following WHO recommendation regarding the Molnupiravir for patients with COVID-19 was released:

Conditional recommendation

We suggest treatment with molnupiravir, conditional to those at highest risk of hospitalization excluding pregnant and breastfeeding women, and children

- In the absence of credible tools to predict risk for hospitalization in people infected with SARS-CoV-2, typical characteristics of people at highest risk include those that lack COVID-19 vaccination, with older age, immunosuppression and/or chronic diseases (e.g. diabetes).
- The longer-term harms of molnupiravir remain unknown in the absence of clinical evidence, both for individual patients and at the population level. These include genotoxicity, emergence of resistance, and emergence of new variants.
- The conditional recommendation reflects the concern for widespread treatment with molnupiravir before more safety data become available. Use of molnupiravir should be accompanied by mitigation strategies such as **avoiding the drug in younger adults**, active pharmacovigilance programmes, and monitoring viral polymerase and spike sequences

Molnupiravir in COVID-19: Use in children and adolescents

- **In vitro genetic toxicity**
 - Molnupiravir is mutagenic in vitro but there was no evidence of mutagenicity in animal models.
 - Molnupiravir may or may not be carcinogenic in humans (these studies have not been done).
- **Growth plate thickness**
 - An increase in thickness of growth plate associated with decreased bone formation was observed growing in rats but not mice, rats or dogs.
 - **Molnupiravir should not be administered to paediatric patients.**
- **Developmental and reproductive toxicity**
 - Reduced fetal body weights in rats and rabbits, as well as embryo-fetal lethality and teratogenicity was observed.
 - **Molnupiravir should not be administered during pregnancy.**
 - If a woman of child-bearing age is given molnupiravir she should be counselled and provided contraception for 4/7 post treatment, men with partners that of child-bearing age should be counseled and provided contraceptives for 3/12 post treatment.

Nirmatrelvir/Ritonavir in COVID-19

- WHO Guideline Development Committee publication of recommendation of use is anticipated in April 2022.
- Nirmatrelvir given in combination with low dose of ritonavir and blocks the SARS-CoV-2-3CL protease, so the active molecule can remain in body longer at higher concentrations
- Numerous drug interactions
 - Alfuzosin
 - Pethidine, piroxicam, propoxyphene
 - Ranolazine
 - Amiodarone, dronedarone, flecainide, propafenone, quinidine
 - Colchicine
 - Lurasidone, pimozide, clozapine
 - Dihydroergotamine, ergotamine, methylergonovine
 - Lovastatin, simvastatin
 - Sildenafil
 - Triazolam, oral midazolam
 - Apalutamide
 - Carbamazepine, phenobarbital, phenytoin
 - Rifampin
 - St. John's Wort

Oral antiviral agents against SARS-CoV-2

Generic Name	Nirmatrelvir/ritonavir	Molnupiravir
Branded Names	Paxlovid	Lagevrio
Manufacturer	Pfizer	Merck
FDA EUA Date	12/22/2021	12/23/2021
Drug Type	Antiviral	Antiviral
Drug Class	SARS-CoV-2 main protease inhibitor (nirmatrelvir) HIV-1 protease inhibitor & CYP3A inhibitor (ritonavir)	Nucleoside analogue
Mechanism of Action versus SARS-CoV-2	Inhibits main protease (mPRO), preventing viral replication	Viral lethal mutagenesis
Cross-Resistance with Anti-SARS-CoV-2 Monoclonal Antibodies	Not expected	Not Expected
Cross-Resistance with Remdesivir	Not Expected	Not Expected
Delta Variant Activity	Yes	Yes
Omicron Variant Activity	Expected	Expected

Generic Name	Nirmatrelvir/ritonavir (Paxlovid)	Molnupiravir (Lagevrio)
Indication	At risk patients with mild-moderate COVID-19	At risk patients with mild-moderate COVID-19
Age Limit	Must be 12 years or older	Must be 18 years or older
Weight Limit	Must be 40 kg or more	None stated
Need Positive Direct SARS-CoV-2 Test?	Yes	Yes
Can Initiate if Hospitalized for COVID-19?	No	No
Can Continue if Hospitalized During Therapy?	Yes	Yes
Authorized for Pre or Post Exposure Prophylaxis?	No	No
When to Start	Within 5 days symptom onset	Within 5 days symptom onset
Route	Oral	Oral
Dose	300 mg nirmatrelvir with 100 mg ritonavir every 12 hrs	800 mg every 12 hrs
Pills per Dose and duration	3 for 5 days	4 for 5 days

Generic Name	Nirmatrelvir/ritonavir (Paxlovid)	Molnupiravir (Lagevrio)
Storage	Room Temperature	Room Temperature
Take with Food?	With or without, but high fat meal increases absorption ~15%	With or without
Okay to Crush?	No	No
Renal Dose Adjustment	For eGFR 30 to below 60 Avoid if eGFR below 30	None
Hepatic Dose Adjustment	Avoid in severe hepatic impairment (Child-Pugh Class C)	None
Contraindications	Hypersensitivity to ingredients, certain drugs that have CYP3A4 interactions	None listed
Warnings	Drug interactions, Hepatotoxicity HIV-1 drug resistance in patients with HIV-1	Embryo-fetal toxicity Bone and cartilage toxicity
Most Common Adverse Reactions	Dysguesia, diarrhea, hypertension, myalgia	Diarrhea, nausea, dizziness
Special Populations	No human data on use in pregnancy or breastfeeding	Not recommended in pregnancy Not recommended if breastfeeding (Has pregnancy surveillance program)

The use of heparins in hospitalised COVID-19 patients should be part of therapeutics – awaiting review by WHO COVID-19 GDG, May 2022

- Review underway, publication, anticipated May 2022

Recommended

Offer a standard prophylactic dose of a low molecular weight heparin as soon as possible, and within 14 hours of admission, to young people and adults with COVID-19 who need low-flow or high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation, and who do not have an increased bleeding risk.

Treatment should be continued for a minimum of 7 days, including after discharge.

See the [NICE recommendation on low molecular weight heparin self-administration](#).

Research evidence (3) Evidence to decision Rationale Decision Aids References

Conditional recommendation

Consider a treatment dose of a low molecular weight heparin (LMWH) for young people and adults with COVID-19 who need low-flow oxygen and who do not have an increased bleeding risk.

Treatment should be continued for 14 days or until discharge, whichever is sooner. Dose reduction may be needed to respond to any changes in a person's clinical circumstances.

Population

This recommendation applies only to people with these characteristics:



Interventions

Strong recommendations in favour

Weak or conditional recommendations in favour

Disease severity



Non-severe	Severe	Critical
Absence of signs of severe or critical disease	Oxygen saturation <90% on room air Signs of pneumonia Signs of severe respiratory distress ⁱ	Requires life sustaining treatment Acute respiratory distress syndrome Sepsis Septic shock

Corticosteroids

IL-6 receptor blockers
or
Baricitinib ⁱ
Depending on availability as well as clinical and contextual factors

Molnupiravir ⁱ
For those with highest risk of hospital admission

Sotrovimab ⁱ
For those with highest risk of hospital admission

Casirivimab and imdevimab ⁱ
For those with highest risk of hospital admission

Casirivimab and imdevimab ⁱ
Evidence of limited efficacy against Omicron BA1 variant
For those with seronegative status for SARS-CoV-2 antibodies

Summary of a living WHO guideline on drug for COVID-19

References

- Rochwerg B, Agoritsas T, Lamotagne F, et al (2020). A living WHO guideline on drugs for covid-19. *BMJ* 2020;370:m3379. doi: <https://doi.org/10.1136/bmj.m3379>
- RECOVERY trial homepage: <https://www.recoverytrial.net/>
- SOLIDARITY trial homepage: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments>
- Ader, F., & Discovery French Trial Management Team (2020). Protocol for the DisCoVeRy trial: multicentre, adaptive, randomised trial of the safety and efficacy of treatments for COVID-19 in hospitalised adults. *BMJ open*, 10(9), e041437. <https://doi.org/10.1136/bmjopen-2020-041437>
- Siemieniuk RA, Bartoszko JJ, Ge L, Zeraatkar D, et al. Drug treatments for COVID-19: Living systematic review and network metanalysis. *BMJ (Clinical research ed.)* 2020;370:m2980. <https://doi.org/10.1136/bmj.m2980>
- WHO: World Health Organization: Therapeutics and COVID-19: Living Guideline. 3 March 2022 <https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.2> or <https://app.magicapp.org/#/guideline/nBkO1E>

Thank you