COVID-19

Test-to-Treat: Oral antiviral outpatient therapy algorithm

v2022.5

Modified from the **WHO COVID-19 CLINICAL CARE PATHWAY**

This algorithm is intended to help clinicians at the point of care initiate oral antiviral treatment for COVID-19. Based on efficacy data, **nirmatrelvir/ritonavir (NMV/r)** is the preferred agent, followed by **molnupiravir.**

Confirm Assess **Respond** Evaluate

START HERE

* **Symptomatic COVID-19 infection confirmed** by PCR, NAAT, Antigen test or home test

YES

E.g. worsening dyspnea, SpO2 <94% on room air, new O2 requirement, confusion, respiratory distress, need for labs/imaging

Signs of **SEVERE MEDICAL ILLNESS?**

YES → **STOP**. Evaluate patient for a higher level of care.

NO

<5 days from **SYMPTOM ONSET?**

YES

A **HIGH RISK PATIENT?**

YES

Assess for NMV/r treatment

*pregnant patients, see note in table on accompanying page

AGE: Is the patient ≥18, or ≥12yrs AND ≥40kg? (88lbs)?

NO → **Not eligible for oral antivirals.** Consider IV therapeutics, see accompanying table.

YES

B **DRUG INTERACTIONS:** Is the patient on any drugs that interact with NMV/r and cannot be substituted?

There are several potential drug-drug interactions with NMV/r. See sidebar for more information.

NO

C Known/expected severe **RENAL** (GFR <30) or **HEPATIC** impairment?

YES

NO

Consider NMV/r

If NMV/r is not available, assess for molnupiravir eligibility.

YES

Not eligible for NMV/r. Assess for molnupiravir.

Is the patient pregnant, trying to get pregnant, or breastfeeding?

YES → **Not eligible for oral antivirals.** Consider IV therapeutics, see accompanying table.

NO

≥18 years old?

NO → **Not eligible for oral antivirals.** Consider IV therapeutics, see accompanying table.

YES

Consider molnupiravir

If molnupiravir is not available, consider IV antivirals.

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* **Has your patient tested positive for COVID-19?**
If you are not sure if your patient has COVID-19, consider testing.

Common symptoms:
- Fever
- Cough
- Rhinorrhea
- Chills
- Dyspnea

Common indications to test:
- New severe symptoms
- Symptoms with a COVID-19 exposure
- Symptoms in an area with high COVID-19 prevalence

This algorithm is intended to get eligible symptomatic COVID-19 patients treated as soon as possible. If the patient has symptoms but tests negative, consider re-testing at a later point.

A **High-risk factors include:**
- Age ≥ 50
- BMI ≥ 30 kg/m2
- Pregnancy
- Diabetes
- Sickle cell disease
- Neurodevelopmental disorders
- Chronic kidney disease, stage 3b or worse
- Cardiovascular disease, hypertension, or lung disease
- Immunocompromising condition (e.g. HIV)
- Tuberculosis
- Clinician-determined medical condition, or demographic factor presumed to place the patient at high risk for disease progression

B **Manageable drug interactions with NMV/r include:**
Dose adjustments may be necessary for the following drugs
- **Statins** – hold 8 days, pitavastatin and pravastatin do not need to be held
- **DOACs**—dabigatran and edoxaban likely safe, apixaban seek expert advice, avoid rivaroxaban
- **Alpha-1 blockers** – hold tamsulosin and others for 8 days
- **Warfarin** —monitor, INR may fall out of therapeutic range
- **Inhaled beta agonists** — hold salmeterol for 8 days, formoterol/albuterol fine
- **Calcineurin inhibitors** — Avoid if possible, careful monitoring and dose adjustment
- **Calcium channel blockers** — monitor and consider dose decrease
- **Antipsychotics** — avoid if possible, dose reduction needed
- **Opiates** —consider dose decrease by 50-75% for 8 days, except methadone
- **Oral contraceptives**— Barrier method recommended until next cycle
- **SSRIs** — monitor, toxicity unlikely in short course
- **Triptans** — hold eletriptan and zolmitriptan, sumatriptan fine
- **Benzodiazepines**— monitor, consider dose reduction, don't use triazolam
- **Chemotherapy and small molecule inhibitors**— review with oncology
- **Oral corticosteroids** — monitor, consider 50-75% dose reduction
- **Sildenafil/tadalafil/vardenafil** — hold for 8 days
- **Rifampin** — concomitant use contraindicated
- **Established ritonavir therapy** — do not change established ritonavir dose

For a comprehensive list visit:
https://covid19-druginteractions.org/checker.

Other interactions may be manageable. If an interacting drug cannot be managed, another antiviral (e.g. molnupiravir) might be indicated.

C **Renal and liver function** do not need to be routinely assessed before starting treatment.
- Patients with mild renal impairment (GFR 30-60) should receive a reduced dose
- Severe hepatic impairment means decompensated liver failure, or Child-Pugh Class C liver disease. To calculate Child-Pugh, go to: www.hepatitisc.uw.edu/page/clinical-calculators/ctp

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C A **R** E
Confirm Assess **Respond** Evaluate

Additional medication specific information

	NMV/r	Molnupiravir
Indications	Age ≥18, and ≥12yrs and ≥40kg	Age ≥18
Modifications	Renal impairment: Moderate, reduce dose as below. Severe impairment, avoid use. Hepatic: Not recommended in severe impairment	No renal adjustment. No hepatic adjustment.
Dose	Nirmatrelvir 300mg + ritonavir 100mg every 12 hours x5 days. For moderate renal impairment use nirmatrelvir 150mg + ritonavir 100mg.	800mg orally every 12 hours for 5 days
Special requirements	Drug interactions with CYP3A metabolized medications require special management	Outpatient only
Pregnancy/ Lactation	Limited data (see * at right). May reduce hormonal contraception efficacy, alternative method should be used.	**Not recommended**, contraception should be used while taking and for 4 days (females) or 3 months (males) after
Route	Oral	Oral
Cost	Brand name: $$ Generic: $	Brand name: $$ Generic: $

* Consensus does not exist on the recommendation of NMV/r for pregnant patients. The FDA states that for a mother and unborn baby, the benefit of taking NMV/r may be greater than the risk from the treatment, given existing animal studies and the extensive use of ritonavir in pregnant women with HIV. By contrast, WHO states that their strong recommendation for its use does not apply to pregnant patients.

Note: The test-to-treat strategy relies on oral agents, as they can be easily initiated at the point of care. If these agents are not available, consider the use of IV therapeutics (e.g. remdesivir, sotrovimab).

Prioritization of therapeutics for COVID-19 when there are logistical constraints

It may not always be possible to treat every patient who meets criteria. If this is the case, patients with the highest risk for progression to severe disease should be treated first (Tier 1), followed by those in successive tiers.

		Vaccination status	
		Not fully vaccinated, or no booster	Fully vaccinated and boosted
Age	Age ≥ 75	Tier 1	Tier 3
	≥ 60 Age <75	High risk condition = Tier 1	High risk condition = Tier 3
		No high risk condition = Tier 2	No high risk condition = Tier 4
	Age <60	High risk condition = Tier 2	High risk condition = Tier 4

All severely or moderately immunocompromised patients are considered Tier 1, regardless of immunization status or other conditions

High risk conditions

- Cancer
- Cardiovascular disease: e.g. heart failure, coronary artery disease (not isolated hypertension)
- Chronic kidney disease
- Diabetes
- Pregnancy
- Chronic lung disease (e.g. moderate/severe asthma, COPD, ILD, pulmonary hypertension)
- Immunocompromising conditions or receipt of immunosuppressive medications
- Obesity (e.g. body mass index ≥30)

Immunocompromising conditions

- Patients who are within 1 year of receiving B cell–depleting therapies (e.g., rituximab, ocrelizumab, ofatumumab, alemtuzumab)
- Patients receiving Bruton's tyrosine kinase inhibitors
- Chimeric antigen receptor T cell recipients
- Transplant recipients:
  - Post-hematopoietic cell transplant recipients who have chronic graft-versus-host disease or who are taking immunosuppressive medications for another indication
  - Lung transplant recipients
  - Patients who are within 1 year of receiving a solid organ transplant (other than lung transplant)
  - Solid organ transplant recipients who had recent treatment with T cell– or B cell–depleting agents for acute rejection
- Cancer
  - Patients with hematologic malignancies who are on active therapy
- Patients with severe combined immunodeficiencies
- Patients with HIV

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