Test-to-Treat: Oral antiviral outpatient therapy algorithm

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.

START HERE

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

- YES
  - Signs of SEVERE MEDICAL ILLNESS?
    - YES
      - <5 days from SYMPTOM ONSET?
        - NO
          - STOP. Evaluate patient for a higher level of care.
        - YES
          - DRUG INTERACTIONS: Is the patient on any drugs that interact with NMV/r and cannot be substituted?
          - YES
            - Known/expected severe RENAL (GFR <30) or HEPATIC impairment?
              - NO
                - Age: Is the patient ≥18, or ≥12yrs and ≥40kg? (88lbs)?
                  - NO
                    - NO
                  - YES
                    - Not eligible for oral antivirals. Consider IV therapeutics, see accompanying table.
                - YES
                  - Is the patient pregnant, trying to get pregnant, or breastfeeding?
                    - NO
                      - NO
                    - YES
                      - ≥18 years old?
                        - NO
                          - YES
                            - Not eligible for oral antivirals. Consider IV antivirals.
                          - NO
                            - Consider molnupiravir.
                          - YES
                            - Consider molnupiravir.
                            - If molnupiravir is not available, consider IV antivirals.
                            - If NMV/r is not available, assess for molnupiravir eligibility.
                  - YES
                    - NO
                      - YES
                        - Consider NMV/r.
                      - NO
                        - Not eligible for NMV/r. Assess for molnupiravir.
        - YES
          - If NMV/r is not available, assess for molnupiravir eligibility.
          - If molnupiravir is not available, consider IV antivirals.

- NO
  - HIGH RISK PATIENT?
    - YES
      - Assess for NMV/r treatment
    - NO
      - NO

STOP. Evaluate patient for a higher level of care.

*pregnant patients, see note in table on accompanying page

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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.

- YES
  - Known/expected severe RENAL (GFR <30) or HEPATIC impairment?
    - NO
      - Age: Is the patient ≥18, or ≥12yrs and ≥40kg? (88lbs)?
        - NO
          - NO
        - YES
          - Not eligible for oral antivirals. Consider IV therapeutics, see accompanying table.
    - YES
      - Is the patient pregnant, trying to get pregnant, or breastfeeding?
        - NO
          - NO
        - YES
          - ≥18 years old?
            - NO
              - YES
                - Not eligible for oral antivirals. Consider IV antivirals.
              - NO
                - Consider molnupiravir.
                - If molnupiravir is not available, consider IV antivirals.
                - If NMV/r is not available, assess for molnupiravir eligibility.
          - YES
            - NO
              - YES
                - Not eligible for oral antivirals. Consider IV antivirals.
              - NO
                - Consider molnupiravir.
                - If NMV/r is not available, assess for molnupiravir eligibility.

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High-risk factors include:
- Age ≥ 50
- BMI ≥ 30 kg/m²
- Pregnancy
- Diabetes
- Sickle cell disease
- Neurodevelopmental disorders
- Cardiovascular disease, hypertension, or lung disease
- Chronic kidney disease, stage 3b or worse
- Severe hepatic impairment

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

Manageable drug interactions with NMV/r include:

- **Dose adjustments may be necessary for the following drugs:**
  - Statins: hold 5-6 days, pravastatin and pravastatin do not need to be held
  - DOACs: individual and education likely safest, apixaban seek expert advice, avoid rivaroxaban
  - **Alpha-1 blockers:** hold tomsulide and others for 8 days
  - **Warfarin:** monitor, INR may fall out of therapeutic range
  - **Insulin and beta agonists:** hold for 6 days, hormones/adrenaline free
  - **Calcium channel blockers:** avoid if possible, careful monitoring and dose adjustment

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

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**Disclaimer:** This algorithm is intended to be educational in nature and is not a substitute for clinical decision making based on the medical condition presented. It is the responsibility of the user to ensure all information contained herein is current and accurate and applicable to the local context by using published references.
# Additional medication specific information

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

*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.

<table>
<thead>
<tr>
<th>Vaccination status</th>
<th>Age ≤75</th>
<th>≥60 Age &lt;75</th>
<th>Age &lt;60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not fully vaccinated, or no booster</td>
<td>Tier 1</td>
<td>High risk condition = Tier 1</td>
<td>High risk condition = Tier 2</td>
</tr>
<tr>
<td>Fully vaccinated and boosted</td>
<td>Tier 3</td>
<td>High risk condition = Tier 3</td>
<td>High risk condition = Tier 4</td>
</tr>
<tr>
<td>All severely or moderately immunocompromised patients are considered Tier 1, regardless of immunization status or other conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 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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