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The information in the PowerPoint will be changing as new information becomes available.

Please visit the Stewardship Webpage for the most updated information and to access the most updated version of this PowerPoint: https://www.med.umich.edu/asp
Approved Outpatient COVID Treatment Options

• Primary:
  – Ritonavir-boosted nirmatrelvir (Paxlovid)
  – Monoclonal Antibodies: Bebtelovimab
  – Remdesivir (3-day course)

• Secondary:
  – Molnupiravir
The Data on Approved Outpatient Therapies for COVID
Ritonavir-boosted nirmatrelvir (Paxlovid)

- Nirmatrelvir is a SARS-CoV-2 protease inhibitor
  - main protease (Mpro) inhibitor, otherwise called 3C-like protease (3CLpro)
  - Alone, would break down too quickly in oral form
- Ritonavir is an inhibitor of CYP3A, which BOOSTS nirmatrelvir by inhibiting its metabolism
- Prevents SARS-CoV2 viral replication
- Novel for SARS-CoV-2
- Oral only
- Nirmatrelvir 300 mg (2x 150 mg tabs) + ritonavir 100 mg (1x 100 mg tab) twice daily x5 days

https://www.science.org/content/article/pfizer-antiviral-slashes-covid-19-hospitalizations
Ritonavir-boosted nirmatrelvir (Paxlovid)

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<th>Methods</th>
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<th>Interpretation</th>
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<tr>
<td><strong>EPIC-HR:</strong> Phase 2/3, Double-Blind, RCT of Paxlovid in Nonhospitalized Patients With Mild to Moderate COVID-19</td>
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<tr>
<td>Key Inclusion Criteria:</td>
<td>Participant Characteristics:</td>
<td></td>
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<tr>
<td>• Aged ≥18 years</td>
<td>• Mean age 46; 51% male; 72% white; 5% Black; 45% Hispanic or Latino</td>
<td>• Compared to placebo in COVID-19-related hospitalizations or all-cause death</td>
</tr>
<tr>
<td>• + SARS-CoV-2 test</td>
<td>• 66% of subjects had onset of symptoms ≤3 days from treatment</td>
<td>• 88% risk reduction</td>
</tr>
<tr>
<td>• Symptom onset within 5</td>
<td></td>
<td></td>
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<tr>
<td>• ≥1 risk factor for severe COVID-19</td>
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<tr>
<td>• unvaccinated</td>
<td></td>
<td></td>
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<tr>
<td>Interventions:</td>
<td>Primary Outcomes:</td>
<td></td>
</tr>
<tr>
<td>• 5 day course:</td>
<td>• COVID-19-related hospitalizations or all-cause deaths through Day 28:</td>
<td></td>
</tr>
<tr>
<td>• PAX 300 mg/100 mg BID (n=1039) vs. placebo (n=1046)</td>
<td>• Within 3 days of onset:</td>
<td></td>
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<tr>
<td></td>
<td>• 0.8% PAX vs 7% placebo</td>
<td></td>
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<tr>
<td></td>
<td>• 3/389 vs. 27/385; (p=&lt;0.0001)</td>
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<tr>
<td></td>
<td>• Within 5 days of onset:</td>
<td></td>
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<tr>
<td></td>
<td>• 1% PAX vs. 6.7% placebo</td>
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<tr>
<td></td>
<td>• 6/607 vs. 41/612; (p=&lt;0.0001)</td>
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<tr>
<td></td>
<td>Secondary Outcome:</td>
<td></td>
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<tr>
<td></td>
<td>• All-cause mortality through Day 28</td>
<td></td>
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<tr>
<td></td>
<td>• 0 PAX vs 1.1% (N=12) placebo</td>
<td></td>
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<tr>
<td></td>
<td>• PAX was associated with 0.9 log\text{_{10}} copies/mL greater decline in viral RNA levels in NP samples through Day 5</td>
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</tbody>
</table>

Participant Characteristics: Mean age 46; 51% male; 72% white; 5% Black; 45% Hispanic or Latino; 66% of subjects had onset of symptoms ≤3 days from treatment.

Interventions: 5 day course:
- PAX 300 mg/100 mg BID (n=1039) vs. placebo (n=1046).

Primary Outcomes:
- COVID-19-related hospitalizations or all-cause deaths through Day 28:
  - Within 3 days of onset:
    - 0.8% PAX vs 7% placebo
    - 3/389 vs. 27/385; (p=<0.0001)
  - Within 5 days of onset:
    - 1% PAX vs. 6.7% placebo
    - 6/607 vs. 41/612; (p=<0.0001)
- All-cause mortality through Day 28:
  - 0 PAX vs 1.1% (N=12) placebo
  - PAX was associated with 0.9 log\text{_{10}} copies/mL greater decline in viral RNA levels in NP samples through Day 5

Interpretation:
- Compared to placebo in COVID-19-related hospitalizations or all-cause death.
- PAX 5 day course
- 88% risk reduction.

Participant Characteristics:
- Mean age 46; 51% male; 72% white; 5% Black; 45% Hispanic or Latino; 66% of subjects had onset of symptoms ≤3 days from treatment.

Interventions:
- 5 day course:
  - PAX 300 mg/100 mg BID (n=1039) vs. placebo (n=1046).

Primary Outcomes:
- COVID-19-related hospitalizations or all-cause deaths through Day 28:
  - Within 3 days of onset:
    - 0.8% PAX vs 7% placebo
    - 3/389 vs. 27/385; (p=<0.0001)
  - Within 5 days of onset:
    - 1% PAX vs. 6.7% placebo
    - 6/607 vs. 41/612; (p=<0.0001)
- All-cause mortality through Day 28:
  - 0 PAX vs 1.1% (N=12) placebo
  - PAX was associated with 0.9 log\text{_{10}} copies/mL greater decline in viral RNA levels in NP samples through Day 5
Monoclonal Antibody

• Bamlanivimab/Etesevimab AND Casirivimab/Imdevimab NOT EFFECTIVE against Omicron variant, sotrovimab is not effective against BA.2 subvariant
  – Bebtelovimab \(\rightarrow\) EFFECTIVE against Omicron BA.2 subvariant
• mAbs bind to a conserved epitope (from SARS-CoV) on the spike protein RBD of SARS-CoV-2 but does not compete with human ACE2 receptor binding
• Inhibits an undefined step that occurs after virus attachment and prior to fusion of the viral and cell membranes
• IV only
• 175 mg x1 (30 sec. infusion, 1 hr observation)
### Monoclonal Antibody Therapy (SOT)

**BLAZE-4, Treatment Arms 9–11:** Double-Blind RCT of Bamlanivimab Plus Etesevimab Plus Bebtelovimab Versus Bebtelovimab Alone Versus Placebo in Low-Risk, Nonhospitalized Patients With Mild to Moderate COVID-19

**Key Inclusion Criteria:** Aged 18–64 years
- No risk factors for progression to severe COVID-19

**Key Exclusion Criteria:**
- ≥1 of the following:
  - SpO2 ≤93% on room air
  - Respiratory rate ≥30 breaths/min
  - Heart rate ≥125 bpm

**Interventions:**
- Within 3 days of a positive SARS-CoV-2 test result, single infusion of:
  - BAM 700 mg plus ETE 1,400 mg plus BEB 175 mg (n = 127)
  - BEB 175 mg (n = 125)
  - Placebo (n = 128)

**Primary Endpoint:**
- Proportion of patients with PHVL (defined as SARS-CoV-2 VL >5.82 log10 by Day 7)

**Participant Characteristics:**
- Median age 35 years; 56% women
- 36% Hispanic/Latinx, 19% Black/African American
- Mean duration of symptoms prior to enrollment was 3.6 days

**Primary Outcomes:**
- Proportion with PHVL:
  - 13% in BAM plus ETE plus BEB arm vs. 21% in placebo arm (P = 0.098), with a relative reduction of 38% (95% CI, -9% to 65%)
  - 14% in BEB arm vs. 21% in placebo arm (P = 0.147), with a relative reduction of 34% (95% CI, -15% to 62%)

**Secondary Outcomes:**
- Mean decline in VL greater in mAb arms vs. placebo arm at Day 5 but not at Days 3, 7, or 11
- COVID-19-related hospitalizations or all-cause deaths by Day 29:
  - 3 (2.4%) in BAM plus ETE plus BEB arm, including 1 death
  - 2 (1.6%) in BEB arm
  - 2 (1.6%) in placebo arm
- Median time to sustained symptom resolution:
  - 7 days in BAM plus ETE plus BEB arm vs. 8 days in placebo arm (P = 0.289)
  - 6 days in BEB arm vs. 8 days in placebo arm (P = 0.003)

**Key Limitations:**
- Only low-risk patients included
- Not powered to assess hospitalizations and deaths
- Conducted before widespread circulation of the Omicron VOC

**Interpretations:**
- There were no differences in the proportion of patients with PHVL across the arms.
- Few COVID-19-related hospitalizations or deaths from any cause occurred by Day 29 across the arms, as is expected for a population of individuals who were at low risk of severe COVID-19.
- Compared to placebo, the median time to sustained symptom resolution was shorter in the BEB arm.
Monoclonal Antibody Therapy (SOT)


Key Inclusion Criteria:
- Aged ≥12 years
- Weight ≥40 kg
- ≥1 risk factor for progression to severe COVID-19

Key Exclusion Criteria:
- ≥1 of the following:
  - SpO₂ ≤93% on room air
  - Respiratory rate ≥30 breaths/min
  - Heart rate ≥125 bpm

Interventions:
- Within 3 days of a positive SARS-CoV-2 test result, single infusion of:
  - BAM 700 mg plus ETE 1,400 mg plus BEB 175 mg (n = 50)
  - BEB 175 mg (n = 100)

Participant Characteristics:
- Median age 50 years; 52% women
- 18% Hispanic/Latinx, 18% Black/African American
- Mean duration of symptoms prior to enrollment was 4.7 days
- 21% had at least 1 dose of COVID-19 vaccine

Efficacy Outcomes:
- COVID-19-related hospitalization or death from any cause by Day 29: 2 (4%) in BAM plus ETE plus BEB arm vs. 3 (3%) in BEB arm
- Mean decline in VL greater in BAM plus ETE plus BEB arm vs. BEB arm at Day 5 but not at Days 3, 7, or 11

Efficacy Endpoints:
- COVID-19-related hospitalization or death from any cause by Day 29
- Mean change in VL from baseline to Days 3, 5, 7, and 11

Key Limitations:
- Open-label study
- No placebo arm
- Not powered to assess hospitalizations and deaths
- Conducted before widespread circulation of the Omicron VOC

Interpretation:
- There was no difference in the proportion of patients who were hospitalized or who died between the arms.
Remdesivir

- Nucleotide prodrug of an adenosine analog
- Binds to the viral RNA-dependent RNA polymerase, inhibiting viral replication through premature termination of RNA transcription
- Repurposed drug
- IV only
- Once daily (200 mg on day 1, 100 mg on day 2-3) x 3 days

Barlow A et al, Pharmacotherapy 2020
## Methods

**PINETREE**: Double-Blind, RCT of remdsevir 3-day course in Nonhospitalized Patients With Mild to Moderate COVID-19

### Key Inclusion Criteria:
- Aged ≥12 years
- SARS-CoV-2 +
- Symptom onset within 7 days
- ≥1 risk factor for severe COVID-19
- unvaccinated

### Interventions:
- 3-day course:
  - REM 200 mg day 1, 100 mg days 2-3 (n=279) vs. placebo (n=283)

### Primary Endpoint:
- Composite of COVID-19-related hospitalization or death from any cause by day 28

### Secondary Endpoint:
- Composite of COVID-19-related medically attended visit or death from any cause by day 28

## Results

### Participant Characteristics:
- Median age 50 years; 41.8% Hispanic/Latinx, 7.5% Black/African American
- Median duration of symptoms prior to enrollment was 5 days

### Primary Outcomes:
- COVID-19-related hospitalizations or all-cause deaths through Day 28:
  - 2 (0.7%) REM vs. 15 (5.3%) placebo ($P = 0.008$)

### Secondary Outcomes:
- COVID-19-related medically attended visit or all-cause deaths through Day 28:
  - 4 (1.6%) REM vs. 21 (8.3%) placebo

## Interpretation

- Compared to placebo in COVID-19-related hospitalizations or all-cause death
  - REM 3-day course
  - 87% relative risk reduction

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Molnupiravir

- Molnupiravir incorporates into viral RNA
  - Creates errors, leading to inability of SARS-CoV-2 to replicate
- Not for use in pregnancy - teratogenic
- Repurposed drug
- Oral only
- 800 mg (4x 200 mg tabs) twice daily x 5 days

https://www.science.org/content/article/pfizer-antiviral-slashes-covid-19-hospitalizations
Molnupiravir

<table>
<thead>
<tr>
<th>Key Inclusion Criteria:</th>
<th>Participant Characteristics:</th>
<th>Interpretation:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Aged ≥18 years</td>
<td>• Median age 42 years; 17% over 60; 49% male; 57% White; 5% Black; 50% Hispanic/Latinx</td>
<td>• Compared to placebo in COVID-19-related hospitalizations or all-cause death</td>
</tr>
<tr>
<td>• SARS-CoV-2 +</td>
<td>• Median duration of symptoms prior to enrollment was 3 days</td>
<td>• MOL 5 day course</td>
</tr>
<tr>
<td>• Symptom onset within 5 days</td>
<td>• Secondary Outcome:</td>
<td>• 30% risk reduction</td>
</tr>
<tr>
<td>• ≥1 risk factor for severe COVID-19</td>
<td>• All-cause mortality through Day 29</td>
<td></td>
</tr>
<tr>
<td>• Unvaccinated</td>
<td>• 0.1% (1) MOL vs 1.3% (9) placebo</td>
<td></td>
</tr>
</tbody>
</table>

**Interventions:**

- 5 day course:
  - MOL 800 mg BID (n=716) vs. placebo (n=717)

**Primary Endpoint:**

- Composite of COVID-19-related hospitalization or death from any cause by day 29

**Primary Outcomes:**

- COVID-19-related hospitalizations or all-cause deaths through Day 29:
  - 6.8% MOL vs. 9.7% placebo, -3.0% [CI -5.9 - -0.1]
  - 48 vs. 68 -3% [CI -5.9 - -0.1]

Other Investigated Outpatient COVID Treatment Options

• Inhaled corticosteroids
• Fluvoxamine
Inhaled Corticosteroids

- Inhaled budesonide (800 mcg BID x14 days) and ciclesonide (320 mcg BID x30 days) have been studied in non-hospitalized adults with mild-moderate symptoms of COVID-19
- Results across studies are not consistent for:
  - Time to recovery of COVID-related symptoms
  - Reduction of COVID-related ED visits or hospitalizations
- Not recommended as routine therapy
- They may be considered on a case-by-case basis given some potential for benefit and a low risk of harm.
- Studies to date have not identified an optimal product or dose.
- Consider DDI
Fluvoxamine

• Fluvoxamine has been studied in non-hospitalized adults with mild-moderate symptoms of COVID-19
  – **TOGETHER**: Double-Blind, Adaptive RCT of Fluvoxamine in Nonhospitalized Patients With COVID-19 in Brazil
  – **STOP COVID**: Double-Blind RCT of Fluvoxamine in Nonhospitalized Patients With COVID-19 in the United States
  – **STOP COVID 2**: Double-Blind RCT of Fluvoxamine in Nonhospitalized Patients With COVID-19 in the United States

• Results across studies are not consistent: different endpoints
• STOP COVID 2 just stopped for futility
• Not recommended as routine therapy
• May be considered on a case-by-case basis given some potential for benefit, but significant DDI would need to be taken into account
• Studies to date have not identified an optimal dose or duration
## Treatment Comparison

<table>
<thead>
<tr>
<th></th>
<th>Paxlovid (nirmatrelvir-ritonavir)</th>
<th>molnupiravir</th>
<th>bebtelovimab (monoclonal antibody)</th>
<th>3-day remdesivir</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Route</strong></td>
<td>Oral</td>
<td>Oral</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td><strong>Efficacy (risk reduction)</strong></td>
<td>Very high (88%)</td>
<td>Marginal (30%)</td>
<td>Very high (85%)</td>
<td>Very high (87%)</td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
<td>Yes, must assess and act</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Dose adjustment for renal dysfunction</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Use in pregnancy</strong></td>
<td>Yes (no human data but not teratogenic in preclinical)</td>
<td>No (teratogenic), requires pregnancy testing if clinically applicable</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>Inhibitor of SARS-CoV-2 protease; prevents viral replication</td>
<td>Incorporates into viral RNA leading to viral error catastrophe</td>
<td>Binds directly to spike protein and neutralizes cellular fusion</td>
<td>inhibits viral replication via premature termination of RNA transcription</td>
</tr>
<tr>
<td><strong>Additional drug considerations</strong></td>
<td>Combination product and must take all components; Contraindicated in Child-Pugh Class C liver disease</td>
<td>Second line agent ONLY if bebtelovimab/Paxlovid unavailable or absolutely contraindicated</td>
<td>Limited capacity in infusion center; well tolerated; delays vaccine administration</td>
<td>3 consecutive days of infusion limit ability for outpatient administration; not currently an outpatient option at MM</td>
</tr>
</tbody>
</table>
The Nuts and Bolts of Outpatient COVID-19 Therapeutic Prescribing at Michigan Medicine
COVID Testing/Resulting Flows

Internal Testing Flows

- Patient calls COVID Hotline with symptoms (PCP is auth MD or hotline APP if no MM PCP)
- Patient calls clinic with symptoms (PCP or Specialist managing the call is auth MD)
- Patient is seen in clinic (Clinic provider is auth MD)
- Patient tested for pre-procedure purposes (Procedure area designated MD is auth MD)
- Patient is seen in Virtual Urgent Care (eVisits/urgently scheduled video visits) (APP is auth provider)

Positive Result

1. POS TEST in in-basket of auth MD
2. Infection Flag automatically applied in MiChart
3. Silent BPA screening performed for patients with MM PCP

External Testing Flows (Majority)

Patient tests positive anywhere outside of MM

1. Patient messages us or calls provider with positive result (symptoms or not)
2. We happen upon the info (urgent care faxes, HIE, etc.)
3. We never know (no opportunity to treat)

Staff contacts patient:
- Acknowledge results, confirm date of test
- Inquire about sx/ triage and send message according to standard recs
- Enter ‘Outside Reported COVID-19 Pos Status’ order

1. Infection Flag automatically applied in MiChart
2. Silent BPA screening performed for patients with MM PCP
Primary Care Silent BPA for MM-PCP patients

**Positive COVID test**
- MM internal
- Outside reported COVID-19 pos order

**Silent BPA triggered**
- Identifies high-risk patients
- Accounts for age, comorbidities, inpatient status, medications, immunization, past procedures
- Still requires additional screening (in particular immunosuppression categorization)

**In-basket message**
- Tier 1a, 1b and 2 routed to panel managers in basket folder titled **COVID-19 High Risk Therapy Candidates**.

**Screening performed**
- Tier 1a, 1b, and 2- Panel Managers will perform screening utilizing **.AMBCOVIDTXSCREENING** 8am-8pm M-F
- Other Tiers that come to attention of clinic will be forwarded to on-site support (RN, LPN, MA) to perform screening
- Screening is sent to Urgent PCP pool for review and treatment decisions

**Provider**
- Provider uses **.AMBCOVIDTXPROVIDER** smartphrase to walk through the steps needed to evaluate appropriateness, including DDI. This documents thoughts/actions in the note at the same time.
- Provider sends Rx
- Provider sends encounter to RN staff for education

**RNs**
- RN provides patient education and sends EUA Info Sheet to patient
Non-MM Primary Care Patients

- Tier 1a, 1b, and 2, patients that do not have a MM PCP are managed through the specialist RN and MD (or outside PCP). Tier 3a, 3b, and 4 patients will only be considered if they reach out (MM-PCP or not)
- The specialist will be only notified of a possible need for treatment by:
  - A positive MM COVID test result they ordered in their in-basket results folder
  - A patient calling with a positive test or desire for treatment
- There will be no silent BPA functionality for this group

- IMPORTANT! Staff entering ‘Outside Reported COVID-19 Pos Status’
  - Must document the date of positive date. We do not need to see the test or scan the result into MiChart. Any positive test is acceptable, including home tests – they do not need repeat PCR testing

- For specialist patients who have MM PCP, the specialist can see progress of treatment/plan in the telephone encounter in chart review. The encounter department will be under the PCP department
- Specialty staff can now use .AMBSPECIALTYCOVIDTXSCREENING to collect information from patients prior to evaluation by provider/pharmacist for Rx
- Providers can now use a smartphrase to walk them through decision making and document appropriateness of therapy in their note with .AMBCOVIDTXPROVIDER
- Tier 3a, 3b, and 4 will not get addressed proactively, but patients who qualify may be treated if they contact the provider
### Antimicrobial Stewardship COVID-19 Outpatient Treatment Guidelines

<table>
<thead>
<tr>
<th>Patient demographics</th>
<th>Paxlovid (oral)</th>
<th>molnupiravir (oral)</th>
<th>bebtelovimab (IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>age ≥12, ≥40 kg</td>
<td></td>
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<tr>
<td>age ≥18</td>
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<td></td>
</tr>
<tr>
<td>age ≥12, ≥40 kg</td>
<td></td>
<td></td>
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<tr>
<td>Symptom onset range</td>
<td>Sx ≤5 days¹</td>
<td>Sx ≤5 days¹</td>
<td>Sx ≤7 days¹</td>
</tr>
<tr>
<td>(to start therapy)</td>
<td></td>
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<tr>
<td>Relative risk</td>
<td>88%</td>
<td>30%</td>
<td>85%</td>
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<tr>
<td>reduction in</td>
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<tr>
<td>hospitalization or</td>
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<td></td>
</tr>
<tr>
<td>death</td>
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### Criteria

**Mild-moderate COVID in a patient at high risk for progression to severe COVID-19²**

Alternative ONLY if patient cannot get Paxlovid nor mAb

Regardless of vaccination status with one of the following:
- Severe³ immunocompromise
- Absolute drug contraindication to Paxlovid AND moderate⁴ immunocompromise

Not up-to-date⁵ on vaccines with one of the following:
- Pregnant
- Absolute drug contraindication to Paxlovid AND additional CDC risk factor for severe disease³

### Notes

Evaluate for DDI

Not for use in pregnancy

Preferred in pregnancy and severe immunocompromise⁴

*Otherwise, only if Paxlovid is contraindicated, or if not available

¹First day of symptoms counts as day 0 (i.e., if symptoms started on Monday (day 0), Saturday would be day 5)

²CDC risk factors include (not all inclusive): Age ≥65 years, immunosuppression, chronic lung disease, chronic kidney disease, chronic liver disease, neurological conditions, diabetes, down syndrome, heart conditions, mental health conditions, BMI ≥25, sickle cell disease or thalassemia, smoking, cerebrovascular disease, substance use disorders, tuberculosis

³Severe immunocompromise: solid organ transplant, bone marrow transplant, hematologic malignancy, on b-cell depleting therapy (i.e., on rituximab)

⁴Moderate immunocompromise: Primary immunodeficiency, active malignancy and receiving chemotherapy, autoimmune diseases requiring immunosuppressive therapy (hydroxychloroquine or sulfasalazine alone is not sufficient), advanced or untreated HIV infection

⁵Up-to-date w/vaccines = a person has received all recommended COVID-19 vaccines, including any booster dose(s) when eligible (5 months after primary series)
MD decision-making process (Cont’d)

• up-to-date w/vaccines = means a person has received all recommended COVID-19 vaccines, including any booster dose(s) when eligible (5 months after primary series)
  – E.g., 1 J&J + booster, or 2 mRNA vaccine + booster
  – “Up-to-date” is the same definition as the previous “maximally vaccinated”

• CDC/MDHHS Moderate or Severe Immunocompromise Criteria:
  – Moderate or Severe Primary immunodeficiency
  – SOT on immunosuppressive medications
  – Active malignancy and receiving chemotherapy
  – Hematopoietic stem cell transplant in last 2 years or receiving immunosuppressive therapy
  – Autoimmune diseases requiring immunosuppressive therapy**
  – Advanced or untreated HIV infection

**hydroxychloroquine or sulfasalazine alone not indicated
Paxlovid (ritonavir boosted nirmatrelvir) MD Decision-Making Process

- Peds considerations - age ≥12 years of age, ≥40 kg
- Restrictions/adjustments:
  - eGFR <30 contraindicated, eGFR 30-59 dose reduced, eGFR ≥60 no adjustment
  - Contraindicated in Child-Pugh Class C liver disease
- Interactions with many medications. Contraindications for some, adjustments needed for others:
  - [https://www.med.umich.edu/asp/pdf/outpatient_guidelines/Paxlovid-DDI.pdf](https://www.med.umich.edu/asp/pdf/outpatient_guidelines/Paxlovid-DDI.pdf)
  - Liverpool Drug Interactions Website
- Review the following with the patient:
  - Potential adverse events (dysgeusia, diarrhea, myalgia, hypertension, hepatic injury) and pertinent drug interactions
  - FDA has authorized emergency use of Paxlovid but Paxlovid is not FDA approved
- Provide electronically the FDA Fact Sheet for Patients/Caregivers via email or patient portal:
  - Fact Sheet Paxlovid
  - MiChart Patient Instructions: Paxlovid For Coronavirus Disease 2019 (COVID-19) (FDA EUA)-UMHS
- Availability of drug? ALL Meijer and select non-Meijer pharmacies. Updated link with active drug availability here:
  - [https://rx.meijer.com/covid19/therapeuticprogram](https://rx.meijer.com/covid19/therapeuticprogram)
- Send eRx in MiChart to one of those select Meijer pharmacies
  - You MUST complete the wildcards in the sig in order for it to be filled. You do NOT need to also do the online form provided by the state if you eRx the medication.
- $0 co-pay to patients
Paxlovid MiChart Order

Note: There are two different orders dependent upon the patient's eGFR.

Select Meijer stores with Paxlovid availability

Drug-Drug Interaction info

REQUIRED: Complete wildcards
Paxlovid Drug-Drug Interactions

• Nirmatrelvir and ritonavir = CYP3A inhibitor
• Drugs metabolized by CYP3A can be increased
• Drugs that induce CYP3A may decrease Pax and decrease PAXLOVID therapeutic effect
• Each DDI needs to be evaluated for severity and options for avoidance
  – Many DDIs can be accommodated with simple adjustments
  – E.g., statins, calcium channel blockers, alpha-1 blockers, etc.
Quality of Evidence: Very Low

Summary:
Coadministration of simvastatin and potent CYP3A4 inhibitors, such as ritonavir, is contraindicated due to potential for serious reactions such as risk of myopathy including rhabdomyolysis. Given the duration of nirmatrelvir/ritonavir treatment, simvastatin should be stopped. Restart simvastatin 3 days after the last dose of nirmatrelvir/ritonavir. After stopping nirmatrelvir/ritonavir, the CYP3A4 inhibitory effect of nirmatrelvir/ritonavir is predicted to mostly disappear after 3 days.

Description:
Coadministration is contraindicated due to increased plasma concentrations of simvastatin; thereby, increasing the risk of myopathy including rhabdomyolysis. HMG-CoA reductase inhibitors which are highly dependent on CYP3A metabolism, such as simvastatin, are expected to have markedly increased plasma concentrations when coadministered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer. Since increased concentrations of simvastatin may predispose patients to myopathies, including rhabdomyolysis, the combination of these medicinal products with ritonavir is contraindicated.


Do Not Coadminister

Nirmatrelvir/ritonavir [Paxlovid] (Please read the interaction details as management of these interactions may be complex.)

Simvastatin

Co-administration may increase simvastatin concentrations. Co-administration contraindicated due to potential for myopathy including rhabdomyolysis. Discontinue use of simvastatin at least 12 hours prior to initiation of Paxlovid.


• https://www.med.umich.edu/asp/pdf/outpatient_guidelines/Paxlovid-DDI.pdf

• https://www.covid19-druginteractions.org/
Paxlovid Drug-Drug Interactions (cont.)

• For more complex DDIs or narrow therapeutic index interactions, contact clinical pharmacy for further assistance

• Solid Organ Transplant Patients: Follow workflow developed by Tx PharmDs

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Appendix B
Contact methods for pharmacists

Coverage:
0700 – 1600 Monday-Friday, except institutional holidays

Non-transplant patients:
For questions regarding drug-drug interactions that cannot be addressed by this guidance or the Liverpool website, please contact the pharmacist in your patient care area or the pharmacist involved in the care of that patient regarding the specific drug interaction. Please consider the timing of this medication as the response back from the clinical pharmacist may not be immediate. If no pharmacist is in the given patient care area, contact the Antimicrobial Stewardship Pharmacist (pg#31888).

Hematopoietic Cell Transplant Recipients:
Page David Frame, PharmD, Denise Markstrom, PharmD, or Gianni Scappaticci, PharmD

Solid Organ Transplant Recipients:

<table>
<thead>
<tr>
<th>Transplant Program</th>
<th>Pharmacist Contact (mChart In-basket Pool)</th>
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<tbody>
<tr>
<td>Adult Kidney</td>
<td>TC TXP PHARMACIST KP</td>
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<tr>
<td>Pediatric Kidney</td>
<td>TC TXP PHARMACIST KP</td>
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<tr>
<td>Adult Liver</td>
<td>TC TXP PHARMACIST LV</td>
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<tr>
<td>Pediatric Liver</td>
<td>TC TXP PHARMACIST LV</td>
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<tr>
<td>Lung</td>
<td>TC TXP PHARMACIST LUNG</td>
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<tr>
<td>Pharmacist Contact via Email</td>
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<tr>
<td>Adult Heart</td>
<td>Sarah Hanigan, Kristin Pogue, or Claire Walter</td>
</tr>
<tr>
<td>Pediatric Heart</td>
<td>Audrey Jarosz or Ashley Huebchman</td>
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<tr>
<td>Common Absolute Contraindications:</td>
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<tr>
<td>• St John’s Wort</td>
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<td>• Amiodorone</td>
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<tr>
<td>• Rivaroxaban</td>
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<td>• Carbamazepine</td>
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<table>
<thead>
<tr>
<th>Common holding or dose adjustments needed:</th>
</tr>
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<tbody>
<tr>
<td>• Simvastatin (hold)</td>
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<tr>
<td>• Oxycodone (reduce)</td>
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<tr>
<td>• Amlodipine (reduce)</td>
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<tr>
<td>• Sildenafil (hold if used for ED)</td>
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</table>
Molnupiravir MD Decision-Making Process

- Peds considerations - ≥18 years of age
- Pregnancy is contraindicated
- Less efficacious—second-line alternative agent
  - 30% risk reduction in hospitalization and death
- Review potential adverse events, pregnancy contraindication, and EUA status with patient (details in guideline)
- Provide electronically the FDA Fact Sheet for Patients/Caregivers via email or patient portal:
  - Fact Sheet molnupiravir
  - MiChart Patient Instructions: molnupiravir For Coronavirus Disease 2019 (COVID-19) (FDA EUA)-UMHS
- Available at ALL Meijer pharmacies and some select other pharmacies
  - https://rx.meijer.com/covid19/therapeuticprogram
- Send eRx in MiChart to any Meijer pharmacy. You MUST complete the wildcards in the sig in order for it to be filled. You do NOT need to also do the online form provided by the state if you eRx the medication.
- $0 co-pay to patients
Molnupiravir MiChart Order

Select pharmacies with medication availability
Drug-Drug Interaction info

REQUIRED: Complete wildcards
mAb (bebtelovimab) MD Decision-Making Process

• Paxlovid is the preferred agent, if appropriate for the patient, given the scarcity of mAb
• We are ONLY using bebtelovimab at MM as this is the only one shown to be active against Omicron BA.2 subvariant
• MD or staff can order “Referral for COVID-19 Monoclonal Antibody Infusion (mAb)”
• This referral order goes directly to a MiChart work queue that is worked by the mAb pharmacy team
  – Do not need to send the encounter to your referral person for processing
• The pharmacy/infusion teams will contact patient, give info, solicit interest/consent, arrange for insurance coverage/authorization, schedule infusion
• Given limited supplies, a referral does not guarantee an infusion
• The patient may qualify for mAb at other facilities and can be given instructions on trying to find a location for this
  – https://covid.infusioncenter.org/
  – Google “COVID infusion sites” – it’s the first hit
Summary

• **When possible, prescribe Paxlovid**
  – Review table for DDI. Can also use Liverpool, but don’t let MiChart scare you. Statins can be held!

• If your patient is eligible and able to get Paxlovid, advise them to take it as soon as possible. They should NOT WAIT for a call for mAb.

• Moving targets as eligibility expands when supply expands, we will continue to update the posted guidelines, and the smartphrases to help guide you