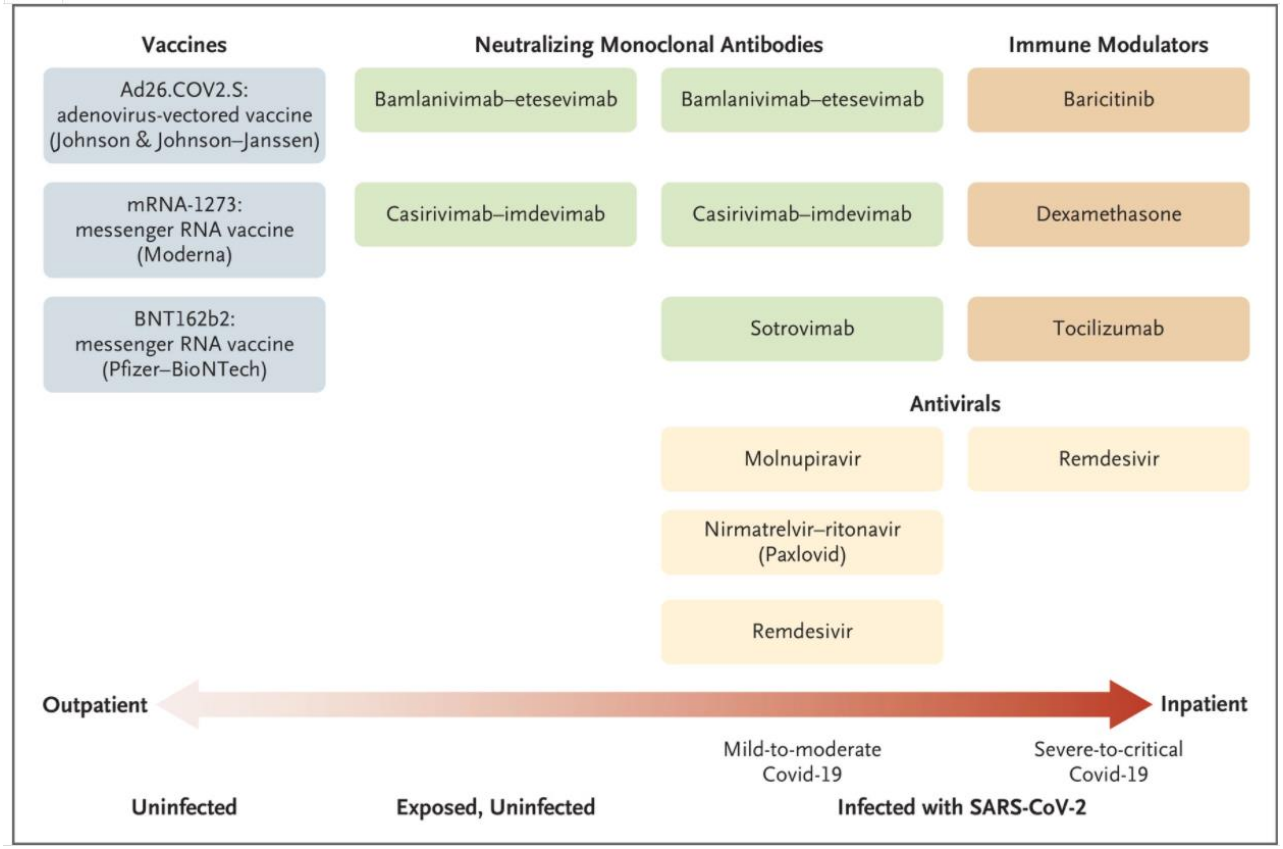
COVID-19 therapies for patients in an ambulatory setting

KAREN KINNEY, MD

THANKS TO EMILY SIEGRIST, PHARM D AND BRYAN WHITE, PHARM D WHO PROVIDED MANY OF THE SLIDES

Covid therapeutics



Monoclonal antibodies for treatment

Bamlanivimab-etesesvimab

Casirivimab-Imdevimab

- No activity against omicron
- Not recommended for use when prevalence over 80%
- Our region is at 86.5% omicron per 12/28 CDC data

Sotrovimab

- Activity against omicron
- Limited supply
- Health department has stated that there will not enough

Sotrovimab

Sotrovimab Efficacy Against Omicron

WHO Virus Label	BAM + ETE		CAS + IMD		SOT	
	In vitro efficacy	Anticipated clinical activity	In vitro efficacy	Anticipated clinical activity	In vitro efficacy	Anticipated clinical activity
Alpha	No change	Active	No change	Active	No change	Active
Gamma	Marked reduction	Unlikely to be active	No change	Active	No change	Active
Delta	No change	Active	No change	Active	No change	Active
Omicron	Anticipated marked reduction	Unlikely to be active	Anticipated marked reduction	Unlikely to be active	Anticipated no change	Active

Sotrovimab Indication

Indication:

- Treatment of mild-to-moderate COVID-19 in adults and pediatric patients (patients 12 years and older weighing at least 40 kg) with positive COVID-19 viral testing at high risk of progression to severe COVID-19. Patients must be within 10 days of symptom onset

High risk for progression:

- Age ≥ 65 years
- Obesity or overweight
- Pregnancy
- CKD
- Diabetes
- Immunosuppressive disease or treatment
- Cardiovascular disease or hypertension

Limitations of authorization

Sotrovimab has NOT been authorized for use in patients who:

- Are hospitalized due to COVID-19
- Require oxygen therapy due to COVID-19
- Require increase in baseline oxygen flow rate due to COVID-19

Sotrovimab Dosing and Administration

- 500 mg Sotrovimab by IV infusion over 30 minutes
- Should only be administered in healthcare settings with access to medications to treat severe infusion reaction such as anaphylaxis
- Must diluted in 50 or 100 mL of NS and administered by IV infusion over 30 minutes
- Administered as soon as possible after a positive viral test for COVID-19 and within 10 days of symptom onset
- Patients must be monitored for at least 1 hour after infusion is complete

Sotrovimab Pharmacology

Class: recombinant human IgG1-Kappa mAb that binds to conserved epitope on the SARS-CoV-2 spike protein receptor

Mechanism of action:

- Does not compete with human ACE2 receptor. Inhibits undefined step after viral attachment and prior to fusion of viral/cell membranes
- In-vitro activity is anticipated with Omicron variant

Sotrovimab Contraindications

Patients with previous severe hypersensitivity reactions including anaphylaxis to any component

Sotrovimab Warnings & Precautions

Hypersensitivity including anaphylaxis and infusion-related reactions have been observed

- These may occur > 24 hours after infusion and may be life-threatening
- Patients must be monitored for 1 hour after end of infusion

Clinical worsening after administration has been reported and may include fever, hypoxia, respiratory difficulty, arrhythmia, fatigue, and altered mental status

No benefit has been seen in patients hospitalized due to COVID-19 and may be associated with worse clinical outcomes

Sotrovimab Adverse Events

Most frequent (>10%):

- none

Less frequent (1-10%):

- hypersensitivity reactions (2%)
- infusion site extravasation
- rash (1%)
- diarrhea (2%)

Rare (<1%)

- anaphylaxis

Sotrovimab Clinical Evidence

Citation	Methods	Patient population	Intervention	Outcome
COMET-ICE	N = 1049 Phase I/II/III	Adults ≥ 18yrs with mild/mod COVID-19 within 5 days of symptom onset: • Age > 55 • Obesity • Heart failure • COPD • Mod/severe asthma • CKD Excluded: • Hospitalized patients • Severely immunocompromised • Requiring oxygen	Single dose of sotrovimab 500 mg IV x 1 vs placebo	Progression of COVID-19 at day 29 Sotrovimab: 6 (1%) Placebo: 30 (6%) NNT: 20 RRR: 79% (95% CI 50,91)

Sotrovimab Pricing

Purchased by HHS and distributed through OSDH at no cost at this time

Tixagevimab Cilgavimab Indication

Indication:

- Pre-exposure prophylaxis of COVID-19 in adults and pediatrics (>12 years and > 40 kg) who:
  - Are not currently infected with SARS-CoV-2 AND
  - Have no known recent SARS-CoV-2 exposure AND
    - Have moderate to severe immune compromise due to medical condition* or iatrogenic immunosuppression* and may not mount adequate response to COVID-19 vaccination OR
    - Cannot receive vaccination with any available COVID-19 vaccine due to history of severe allergic reaction to COVID-19 vaccine and/or one of the vaccine components

Outpatient Remdesivir

Remdesivir

An adenosine analog that acts an inhibitor of RNA-dependent RNA polymerase

Indicated for treatment of hospitalized patients with COVID-19
- Showed decreased length of stay but no mortality difference

New outpatient data was recently published

Remdesivir outpatient data

Randomized unvaccinated, outpatients (n=584) with COVID-19 within 7 days of symptoms with a risk factor to progression to IV remdesivir or placebo

- Remdesivir 3 day regimen: 200 mg IV on day 1, 100 mg on days 2 and 3

Primary endpoint: composite of hospitalization to due COVID and all cause 28 day mortality

GOTTLIEB RL, VACA CE, PAREDES R, ET AL. NEW ENGLAND JOURNAL OF MEDICINE. 2021;

Remdesivir outpatient data: Demographics

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Remdesivir (N=279)	Placebo (N=283)	Total (N=562)
Race or ethnic group — no. (%)†			
White	228 (81.7)	224 (79.2)	452 (80.4)
Black	20 (7.2)	22 (7.8)	42 (7.5)
American Indian or Alaska Native	15 (5.4)	21 (7.4)	36 (6.4)
Asian, Native Hawaiian, or Pacific Islander	7 (2.5)	7 (2.5)	14 (2.5)
Hispanic or Latinx	123 (44.1)	112 (39.6)	235 (41.8)
Other	3 (1.1)	2 (0.7)	5 (0.9)
Body-mass index	31.2±6.7	30.8±5.8	31.0±6.2
Coexisting conditions — no. (%)			
Diabetes mellitus	173 (62.0)	173 (61.1)	346 (61.6)
Obesity	154 (55.2)	156 (55.1)	310 (55.2)
Hypertension	138 (49.5)	130 (45.9)	268 (47.7)
Chronic lung disease	67 (24.0)	68 (24.0)	135 (24.0)
Current cancer	12 (4.3)	18 (6.4)	30 (5.3)
Cardiovascular or cerebrovascular disease	20 (7.2)	24 (8.5)	44 (7.8)
Immune compromise	14 (5.0)	9 (3.2)	23 (4.1)
Chronic kidney disease, mild or moderate	7 (2.5)	11 (3.9)	18 (3.2)
Chronic liver disease	1 (0.4)	1 (0.4)	2 (0.4)
Residence in skilled nursing facility — no. (%)	8 (2.9)	7 (2.5)	15 (2.7)

GOTTLIEB RL, VACA CE, PAREDES R, ET AL. NEW ENGLAND JOURNAL OF MEDICINE. 2021;

Remdesivir outpatient data

Median duration of symptoms to infusion was 5 days

Primary endpoint: composite of hospitalization to due COVID and all cause 28 day mortality

- 0.7 vs 5.3 % (p= 0.008)
- NNT: 22
- No deaths in either group

Safety

- Any adverse events : 42.3% vs 46.3%

GOTTLIEB RL, VACA CE, PAREDES R, ET AL. NEW ENGLAND JOURNAL OF MEDICINE. 2021;

National guidelines

IDSA

- Suggests use in patients with mild to moderate COVID-19 initiated within 7 days of symptom onset (conditional recommendation, low certainty of evidence)

NIH

- Use 3 day course outpatient remdesivir in areas with high rates of omicron (BIIa)

Oral therapies

Molnipravir

- Limited supply
- NNT of 35 to prevent a hospitalization or death

Nirmatrelvir-ritonavir (Paxolvid)

- Better data (NNT 19)
- Multiple drug interactions
- Not able to be used in patients with severe renal or hepatic failure
- Limited supply
- Initial 2 week shipment to Oklahoma is 620 courses

Nirmatrelvir/Ritonavir (Paxlovid)

- Authorized for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 yrs or older, weighing at least 40 kg) with positive results of direct SARS-CoV-2 testing and who are at high risk for progression to severe COVID-19, including hospitalization or death
- Screen patient's medications for serious drug interactions
- Nirmatrelvir 150 mg, ritonavir 100 mg
- Dosing based on renal function
  - -eGFR≥60 ml/min:300 mg nirmatrelvir/100 mg ritonavir q 12 hrs for 5 days
  - -eGFR ≥30 ml/min:150 mg nirmatrelvir/100 mg ritonavir q 12 hrs for 5 days
  - -eGFR<30 ml/min: not recommended

Nirmatrelvir/Ritonavir (Paxlovid)

- Nirmatrelvir is an inhibitor to the main protease (Mpro) of SARS-CoV-2)----- inhibition of the enzyme blocks viral replication
- Nirmatrelvir is a substrate of the cytochrome P450 3A4 isoenzyme system and is co-packaged with ritonavir, a potent inhibitor of cytochrome P450 3A4 resulting in higher concentrations and a longer half-life of nirmatrelvir allowing for q 12 hour dosing

Nirmatrelvir/Ritonavir (Paxlovid)

Figure 8. Nirmatrelvir/ritonavir is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions [1]

- Alpha1-adrenoreceptor antagonist: alfuzosin
- Analgesics: pethidine, piroxicam, propoxyphene
- Antianginal: ranolazine
- Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
- Anti-gout: colchicine
- Antipsychotics: lurasidone, pimozide, clozapine
- Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
- HMG-CoA reductase inhibitors: lovastatin, simvastatin
- PDE5 inhibitor: sildenafil (Revatio®) when used for pulmonary arterial hypertension (PAH)
- Sedative/hypnotics: triazolam, oral midazolam

Reference

1. U.S. Food and Drug Administration. Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) for Paxlovid™ Available at: https://www.fda.gov/media/155050/download. Accessed 22 December 2021.

Figure 9. Nirmatrelvir/ritonavir is contraindicated with drugs that are potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance [1]

- Anticancer drugs: apalutamide
- Anticonvulsant: carbamazepine, phenobarbital, phenytoin
- Antimycobacterials: rifampin
- Herbal products: St. John's Wort (*Hypericum perforatum*)

Reference

1. U.S. Food and Drug Administration. Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) for Paxlovid™ Available at: https://www.fda.gov/media/155050/download. Accessed 22 December 2021.

Molnupiravir

- Molnupiravir may be used for the treatment of mild-to-moderate COVID-19 in adults (≥18 yo) with positive results of direct SARS-CoV-2 testing and who are at high risk for progression to severe COVID, including hospitalization and death, and for whom alternative COVID-19 options authorized by the FDA are not accessible or clinically appropriate.
- molupiraver is available in 200 mg tables
- Dosage: Molnupiravir 800 mg po q 12 hours for 5 days
- Mechanism: Molnupiravir is an oral pro-drug that is converted to ß-D-N4-hydroxcytidine which acts as a substrate for RNA-dependent RNA polymerase. After it is incorporated into the viral RNA, serial mutations develop resulting in a virus less fit for ongoing viral replication.

Molnupiravir: some considerations

- Patients who put a higher value on the putative mutagenesis, adverse events or reproductive concerns, and a lower value on the uncertain benefits, would reasonably decline molnupiravir.
- Molnupiravir 800 mg for five days.
- Patients with mild to moderate COVID-19 who are at high risk of progression to severe disease admitted to the hospital for reasons other than COVID-19 may also receive molnupiravir.
- Molnupiravir is not authorized under the FDA EUA for use in patients <18 years, because it may affect bone and cartilage growth.
- Molnupiravir is not recommended under the FDA EUA for use during pregnancy.
- Molnupiravir is not authorized under the FDA EUA for pre-exposure or post-exposure prevention of COVID-19 or for initiation of treatment in patients hospitalized due to COVID-19, because benefit of treatment has not been observed in individuals when treatment is started after hospitalization due to COVID-19.

Questions?