Anti viral in COVID ١٩

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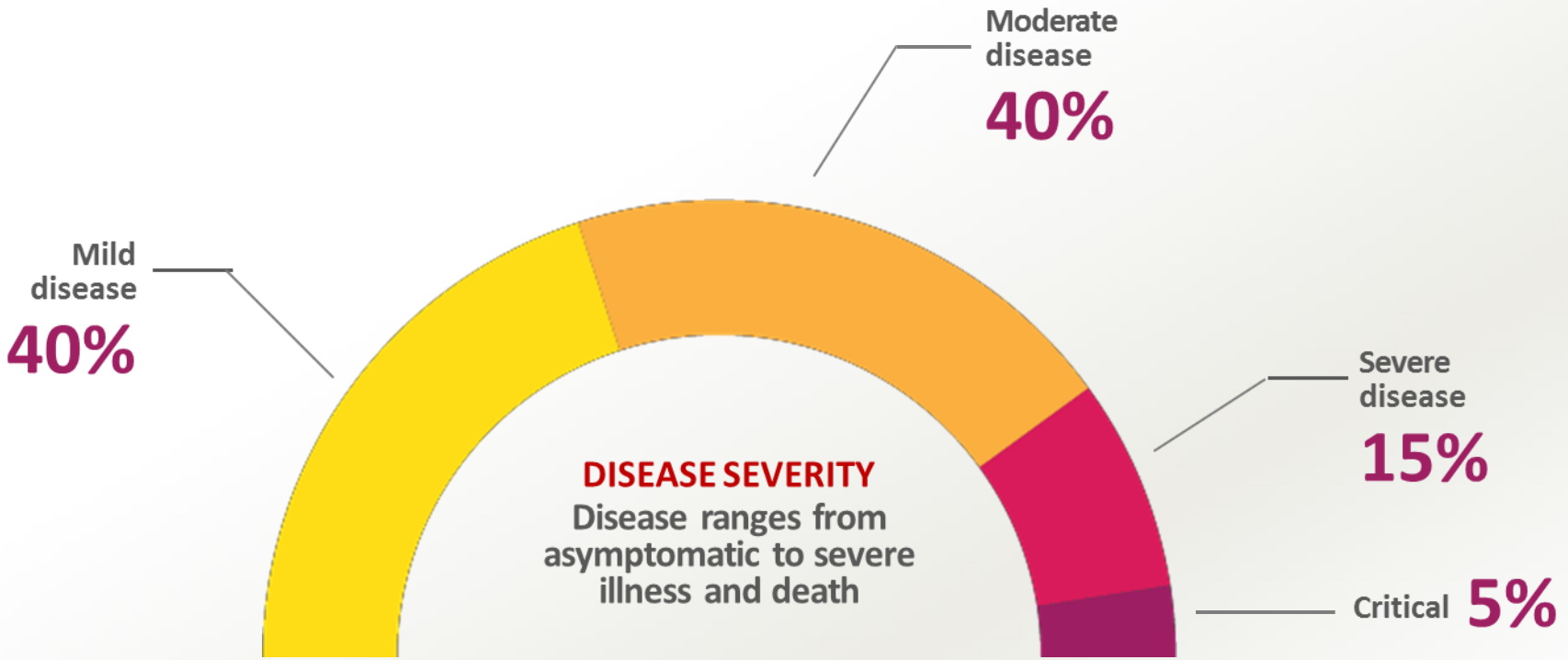
Most COVID-19 patients have mild to moderate disease



Severity of Disease

Severity	Indicators
Asymptomatic	No symptoms
Mild disease	Fever, cough, sore throat, N/V, diarrhea, loss of taste or smell but no dyspnea; normal O2 saturation and normal chest X-ray
Moderate disease	Symptoms of mild disease plus evidence of lower respiratory tract infection (exam and/or imaging), O2 saturation ≥94% on room air
Severe disease	Symptoms of moderate disease but O2 saturation <94%, PaO2/FiO2 <300 mmHg, respiratory frequency >30 breaths per minute, or lung infiltrates >50%
Critical disease	Symptoms of severe disease but intubated with respiratory failure, septic shock, and/or multiorgan dysfunction

Recommendations for therapeutics may differ based on the severity of COVID-19

Figure. Three disease severity groups and key characteristics

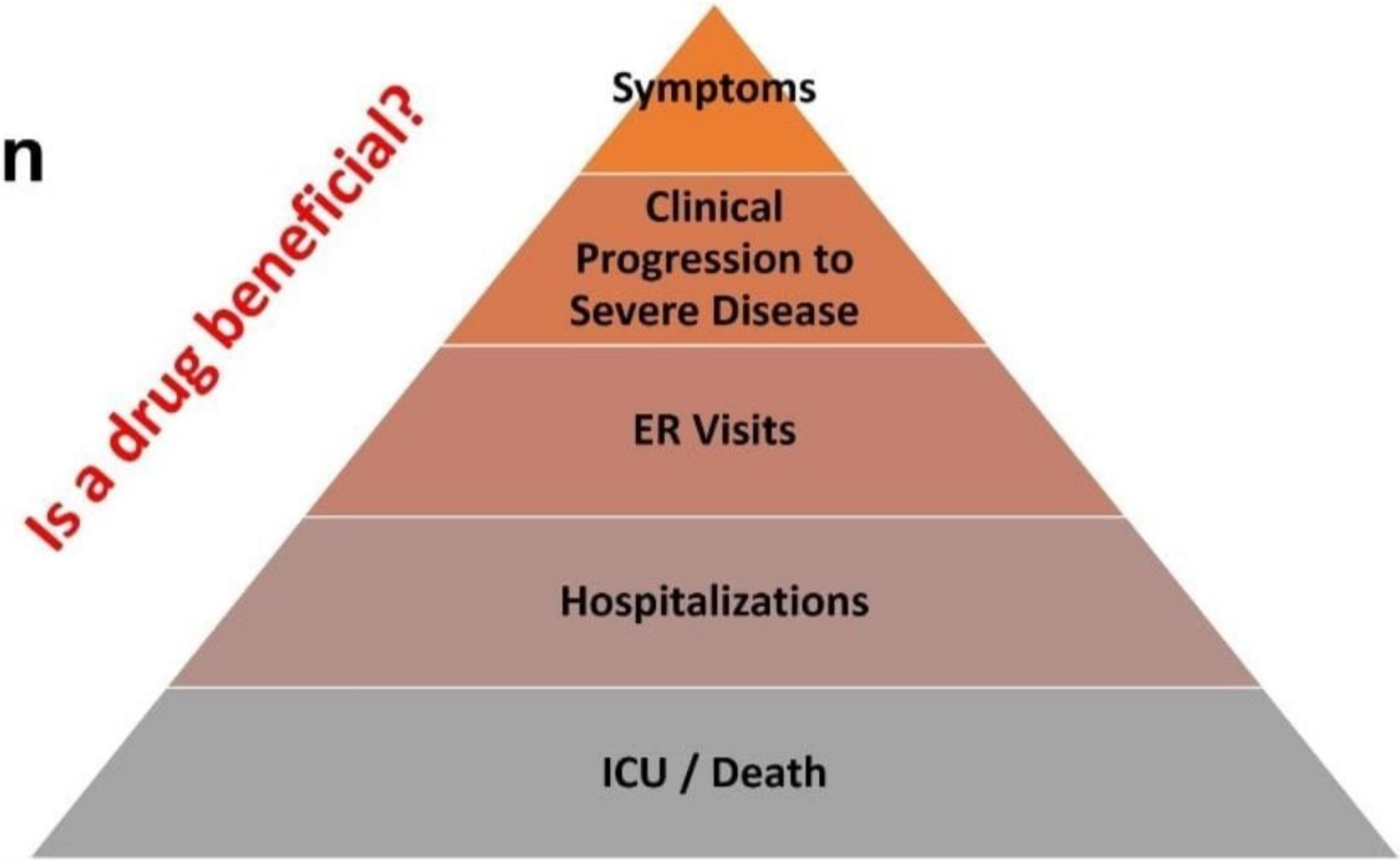
DISEASE SEVERITY & DEFINITIONS

NON-SEVERE	SEVERE	CRITICAL
Absence of signs of severe or critical disease	SpO_2<90% on room air	Requires life sustaining treatment
	Respiratory rate >30 in adults	Acute respiratory distress syndrome
	Raised respiratory rate in children	Sepsis
	Signs of severe respiratory distress	Septic shock

SpO_2 = oxygen saturation

Caution: The guideline panel noted that the oxygen saturation threshold of 90% to define severe COVID-19 was arbitrary and should be interpreted cautiously when used to define disease severity. For example, clinicians must use their judgment to determine whether a low oxygen saturation is a sign of severity or is normal for a given patient with chronic lung disease. Similarly, a saturation between 90–94% in room air may be abnormal (in patient with normal lungs) and can be an early sign of severe disease, if patient is on a downward trend. Generally, if there is any doubt, the panel suggested erring on the side of considering the illness as severe

Outpatient Disease Progression



Risk factor for development of severe illness from Covid-19

1 - Age >60 years

2 - Active cancer

3 - Chronic kidney disease

4 - Chronic obstructive pulmonary disease

5 – Obesity

6 - Heart failure

7 - Coronary artery disease

8 - Cardiomyopathies

9 - Diabetes mellitus

- Panel has prioritized the risk groups for anti-SARS-CoV-2 therapy based on 4 key elements: **age**, **vaccination status**, **immune status**, and the presence of **risk factors for clinical progression.**

Outpatient COVID-19 Treatment Algorithm

Scoring Tool Criteria and Points Subject to Change

Patient Risk Scoring Tool

Due to supply shortage of COVID-19 therapeutic agents, patients with a risk score of ≥ 7 are prioritized. Factors included in the calculator are: age, diabetes, BMI (≥ 35), hypertension, pregnancy, vaccination (unvaccinated or partially vaccinated) status, and immunocompromised status (see page 2 for details).

Patient Risk Scoring Tool

A risk score of ≥ 7 is prioritized.

Note: Scoring Tool Criteria and Points Subject to Change

Factor	Score
Age *(e.g. 50 years old = 5)*	1 point for every 10 years
BMI ≥ 35	1
Diabetes	1
Hypertension	1
Unvaccinated or partially vaccinated (not boosted)	2
Pregnancy	4
Immunocompromised status (see below for defintion)	4

- Immunocompromised (any of the following):
- -Receiving active cancer treatment for tumors or cancers of the blood
- -Received an organ transplant and are taking medicine to suppress the immune system
- -Graft-versus-host-disease (GVHD)
- -Received a stem cell transplant or Chimeric Antigen Receptor T-cell therapy (CAR-T) within the last 2 years or are taking medicine to suppress the immune system
- -Moderate or severe primary immunodeficiency (such as DiGeorge syndrome, Wiskott-Aldrich syndrome, Immunodeficiency with increased immunoglobulin M, hyperimmunoglobulin E syndrome, Common Variable Immunodeficiency, functional disorders of polymorphonuclear neutrophils, nonfamilial hypogammaglobulinemia, hereditary hypogammaglobulinemia, severe combined immunodeficiency with retircular dysgenesis, etc.)
- -Advanced or untreated HIV infection (CD4 count <200)
- -Active treatment with high-dose corticosteroids (? prednisone 20 mg per day x 4 weeks) or other drugs that may suppress your immune response (B and T-cell depleting therapies, monoclonal antibodies therapy used in rheumatology and neurology, etc.)

- Patients who are within 1 year of receiving B cell-depleting therapies (e.g., rituximab, ocrelizumab, ofatumumab, alemtuzumab)
- Patients who are receiving Bruton tyrosine kinase inhibitors
- Chimeric antigen receptor T cell recipients
- Post-hematopoietic cell transplant recipients who have chronic graft versus host disease or who are taking immunosuppressive medications for another indication
- Patients with hematologic malignancies who are on active therapy
- Lung transplant recipients
- Patients who are within 1 year of receiving a solid organ transplant (other than a lung transplant)
- Solid organ transplant recipients with recent treatment for acute rejection with T cell- or B cell-depleting agents
- Patients with severe combined immunodeficiencies
- Patients with untreated HIV who have a CD4 T lymphocyte cell count <50 cells/mm^3

START

Age ≥ 12 years **AND** ≥ 40 kg
AND
Mild-moderate COVID-19 withOUT supplemental oxygen (or increase in baseline if on O2) **AND** symptom onset ≤5 days (remdesivir ≤7 days)

Key for gray: Remdesivir not available at all sites due to staffing and scheduling logistics.

Pregnant or breastfeeding?

No

Does patient have any **one** of the following:
1) Severe liver disease Child Pugh C
2) eGFR <30 mL/min
3) Drug-drug interaction list (see next page)

Yes

Which outpatient pharmacy has it? Link:
https://covid-19-therapeutics-locator-dhhs.hub.arcgis.com/
SSM Inventory Link

Yes

Sotrovimab*
Click drug name for fact sheet

*Patient cannot get sotrovimab on same day as another monoclonal antibody

No

Paxlovid
Click drug name for fact sheet

Pregnancy consideration: no human data, only animal studies performed (see fact sheet for more details)

Does patient have ALT ≥ 5 ULN

Yes

Does patient have any **one** of the following:
1) Pregnant or breastfeeding
2) Age < 18 years old

Yes

Patient does not qualify for available COVID-19 therapy

No

Remdesivir
Click drug name for fact sheet

Limited data suggest the risk of toxicity with a short course of remdesivir is low in patients with eGFR<30 mL/min

No

Molnupiravir
Click drug name for fact sheet

Rank	Agent	Timing of Administration from Symptom Onset	Efficacy *Note: Studies were performed prior to omicron variant*
1	**Nirmatrelvir/ritonavir (Paxlovid)** 300mg/100mg BID PO x 5 days	≤5 days	EPIC-HR study (n = 2,246): Paxlovid **reduced** risk of hospitalization or death by **89%** (within 3 days of symptom onset) and **88%** (within 5 days of symptom onset) vs. placebo.[1]
2	**Sotrovimab (Xevudy)** 500mg IV x 1	≤5 days	COMET-ICE study interim analysis: **relative risk reduction of 85%** in hospitalization or death vs. placebo.[2]
3	Remdesivir (Veklury) 200mg IV x 1, then 100mg daily on days 2 and 3	≤7 days	PINETREE study (n = 562): Three day outpatient remdesivir course had a **87% lower risk** of hospitalization or death than placebo.[3]
4	**Molnupiravir (Lagevrio)** 800mg PO BID x 5 days	≤5 days	MOVe-OUT study (n = 1,433): Molnupiravir **~ 31% lower** rate of hospitalization or death through day 29 vs. placebo (hazard ratio, 0.69; 95% CI, 0.48 to 1.01).[4]

Paxlovid Drug-Drug Interactions

Contraindications

1. Drugs **highly dependent on CYP3A for clearance** and for which elevated concentrations are associated with serious and/or life-threatening reactions. Examples include:

Alfuzosin, pethidine, piroxicam, propoxyphene, ranolazine, amiodarone, dronedarone, flecainide, propafenone, quinidine, colchicine, lurasidone, pimozide, clozapine, dihydroergotamine, methylergonovine, lovastatin, simvastatin, sildenafil, triazolam, oral midazolam

OR

2. Drugs that are **potent CYP3A inducers** (causes significantly reduced nirmatrelvir or ritonavir plasma concentrations; thus, may be associated with potential for loss of virologic response and possible resistance). **Note**: Paxlovid cannot be started immediately after discontinuation of any of the following medications due to the delayed offset of the recently discontinued CYP3A inducer:

Apalutamide, carbamazepine, phenobarbital, phenytoin, rifampin, St. John's Wort

Use with Caution: Commonly Used Medications

- Ethinyl estradiol *(Consider non-hormonal contraception)*
- Rivaroxaban
- Warfarin

Recommend holding these drugs for 5 days while on Paxlovid:

- Cyclosporine
- Dasatinib
- Ibrutinib
- Nilotinib
- Sirolimus
- Tacrolimus
- Venetoclax

For a Complete List of Potential Drug-Drug Interactions: EUA Table 1:

Link: Paxlovid EUA

Liverpool COVID-19 Drug Interaction Checker:
https://www.covid19-druginteractions.org/checker

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ORIGINAL ARTICLE

Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients

Key exclusion criteria

1 - Anticipated need for hospitalization for Covid-19 within the next 48 hours

2 - Dialysis or estimated glomerular filtration rate less than 30 ml per minute per 1.73 m2

3 - Pregnancy

4 - Unwillingness to use contraception during the intervention period and for at least 4 days after completion of the regimen.

5 -Severe neutropenia

6 - Platelet count below 100,000 per microliter

٧- Use of therapies intended as Covid-19 treatments (including any monoclonal antibodies and remdesivir)

Version 1. medRxiv. Preprint. 2021 Jun 17.
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Molnupiravir, an Oral Antiviral Treatment for COVID-19

William Fischer, Joseph J. Eron, Wayne Holman, Myron S. Cohen, Lei Fang, Laura J. Szewczyk, Timothy P Sheahan, Ralph Baric, Katie R. Mollan, Cameron R. Wolfe, Elizabeth R. Duke, Masoud M. Azizad, Katyna Borroto-Esoda, David A. Wohl, Amy James Loftis, Paul Alabanza, Felicia Lipansky, and Wendy P. Painter

In the EPIC-HR trial, ritonavir-boosted nirmatrelvir (Paxlovid) reduced the risk of hospitalization or death by 88% compared to placebo in nonhospitalized adults with laboratory-confirmed SARS-CoV-2 infection.[8] This efficacy is comparable to the efficacies reported for sotrovimab (i.e., 85% relative reduction),[9] and remdesivir (i.e., 87% relative reduction)[10] and greater than the efficacy reported for molnupiravir (i.e., 30% relative reduction).[11]

Ritonavir-boosted nirmatrelvir (Paxlovid) is expected to be active against the Omicron VOC, although in vitro and in vivo data are currently limited.[12] Because of the potential for significant drug-drug interactions with concomitant medications, this regimen may not be a safe choice for all patients (see the

Merck and Ridgeback's Investigational Oral Antiviral Molnupiravir Reduced the Risk of Hospitalization or Death by Approximately 50 Percent Compared to Placebo for Patients with Mild or Moderate COVID-19 in Positive Interim Analysis of Phase 3 Study

Sotrovimab

Several anti-SARS-CoV-2 mAb products (i.e., bamlanivimab plus etesevimab, casirivimab plus imdevimab, and sotrovimab) have received EUAs from the FDA for the treatment of nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease. In the clinical trials for these agents, anti-SARS-CoV-2 mAbs reduced the risk of hospitalization or death by 70% to 85% compared to placebo.

The Omicron VOC has become the dominant variant in the United States[1] and is predicted to have markedly reduced susceptibility to bamlanivimab plus etesevimab and casirivimab plus imdevimab. In vitro studies indicate that sotrovimab remains active against the Omicron VOC.[13,14]

Remdesivir

Remdesivir has been studied in nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease. The PINETREE trial showed that 3 consecutive days of IV remdesivir resulted in an 87% relative reduction in the risk of hospitalization or death compared to placebo.[10]

Remdesivir is expected to be active against the Omicron VOC, although in vitro and in vivo data are currently limited.[12] Because remdesivir requires IV infusion for 3 consecutive days, there may be logistical constraints to administering remdesivir in many settings, but it is an option if ritonavir-boosted nirmatrelvir (Paxlovid) and sotrovimab are not available.

Molnupiravir

In the MOVe-OUT trial, molnupiravir reduced the rate of hospitalization or death by 30% compared to placebo.[6] Even though the different treatment options have not been directly compared in clinical trials, the Panel recommends using molnupiravir only when ritonavir-boosted nirmatrelvir (Paxlovid), sotrovimab, and remdesivir are not available or cannot be given, because molnupiravir has lower efficacy than the other options.

Molnupiravir is expected to be active against the Omicron VOC, although in vitro and in vivo data are currently limited.[12]

(Paxlovid)

In the EPIC-HR trial, ritonavir-boosted nirmatrelvir reduced the risk of hospitalization or death by 88% compared to placebo in nonhospitalized adults with laboratory-confirmed SARS-CoV-2 infection.[5] This efficacy is comparable to the efficacies reported in similar patient populations for sotrovimab (85% relative reduction),[6] and remdesivir (87% relative reduction)[7], and greater than the efficacy reported for molnupiravir in this setting (30% relative reduction).[8]

Pre-Exposure Prophylaxis (PrEP):

- This includes the Panel's recommendation on using these mAbs as PrEP in certain patients who do not have SARS-CoV-2 infection but who are at risk of progressing to severe COVID-19 if infected.
- The Panel emphasizes that **tixagevimab** plus **cilgavimab** is not a substitute for COVID-19 vaccination and should not be used in unvaccinated individuals for whom COVID-19 vaccination is recommended and who are anticipated to have an adequate response.

Post-Exposure Prophylaxis (PEP):

- The Panel **recommends against** the use of the anti-SARS-CoV-2 mAbs bamlanivimab plus etesevimab and casirivimab plus imdevimab as PEP because they have markedly reduced susceptibility to the B.1.1.529 (Omicron) variant of concern (VOC), which is currently the dominant SARS-CoV-2 variant in the United States.

Thank you for your attention