COVID-19 Outpatient Therapeutics

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UW Medicine

Disclosure Statement

No financial relationships or conflicts of interest to disclose.

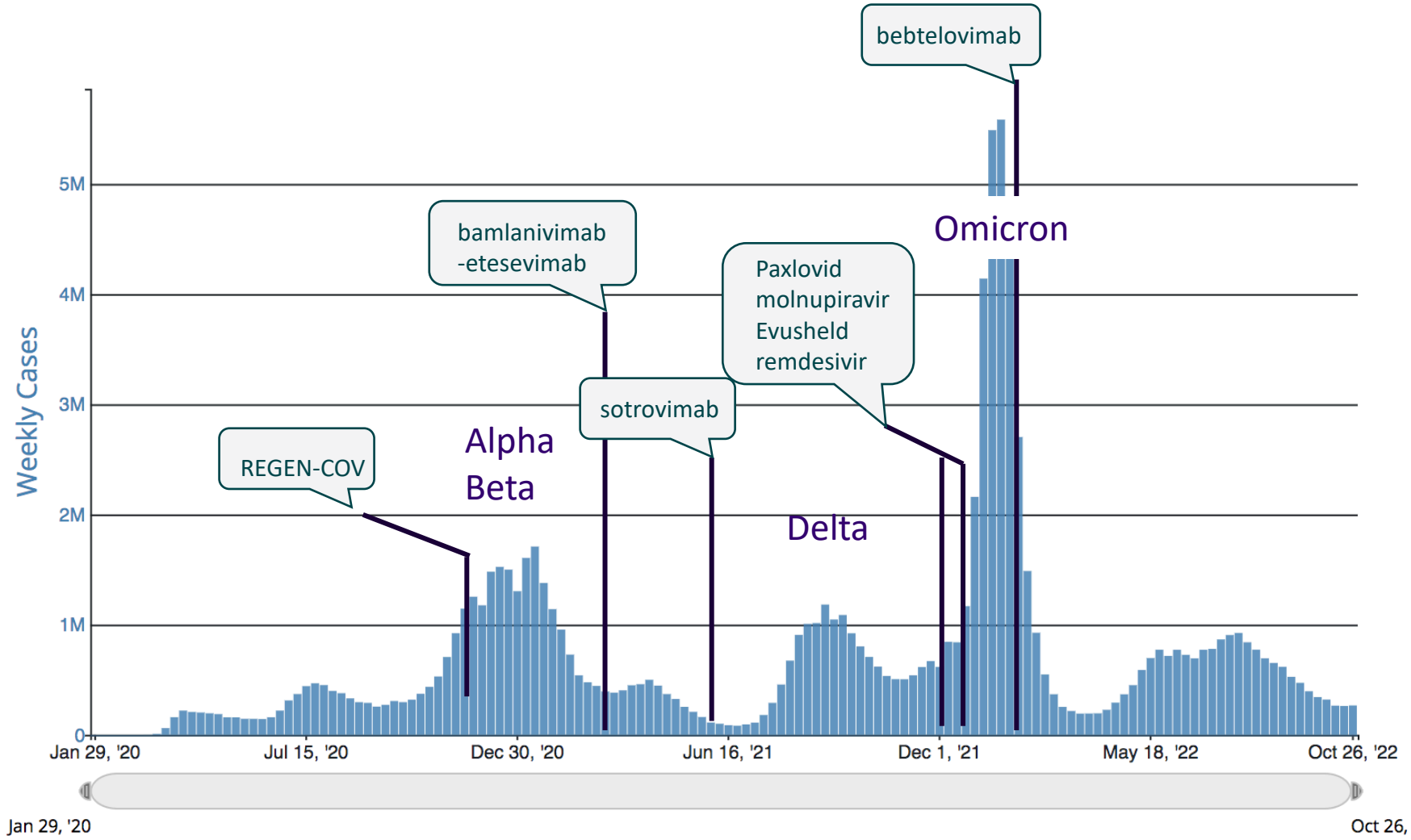
Learning Objectives

- Review available outpatient therapeutics for COVID-19 disease
- Review eligibility and contraindications to therapy
- Review treatment for preventing COVID-19 disease

COVID Data Tracker

Total Cases	Total Deaths	Current Hospitalizations
97,329,787	1,066,351	19,826

Daily Cases in the US



CDC. COVID Tracker 2022

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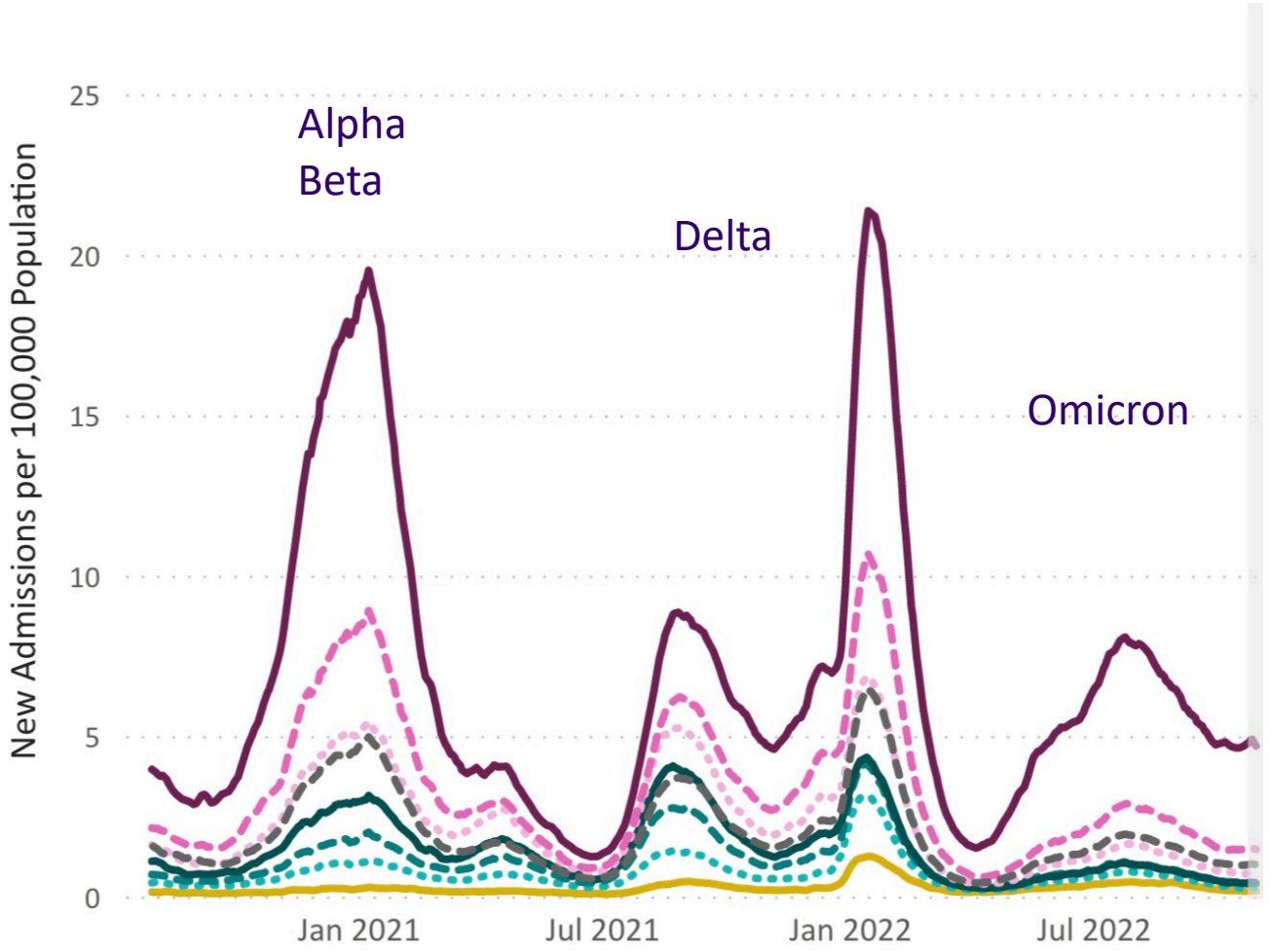
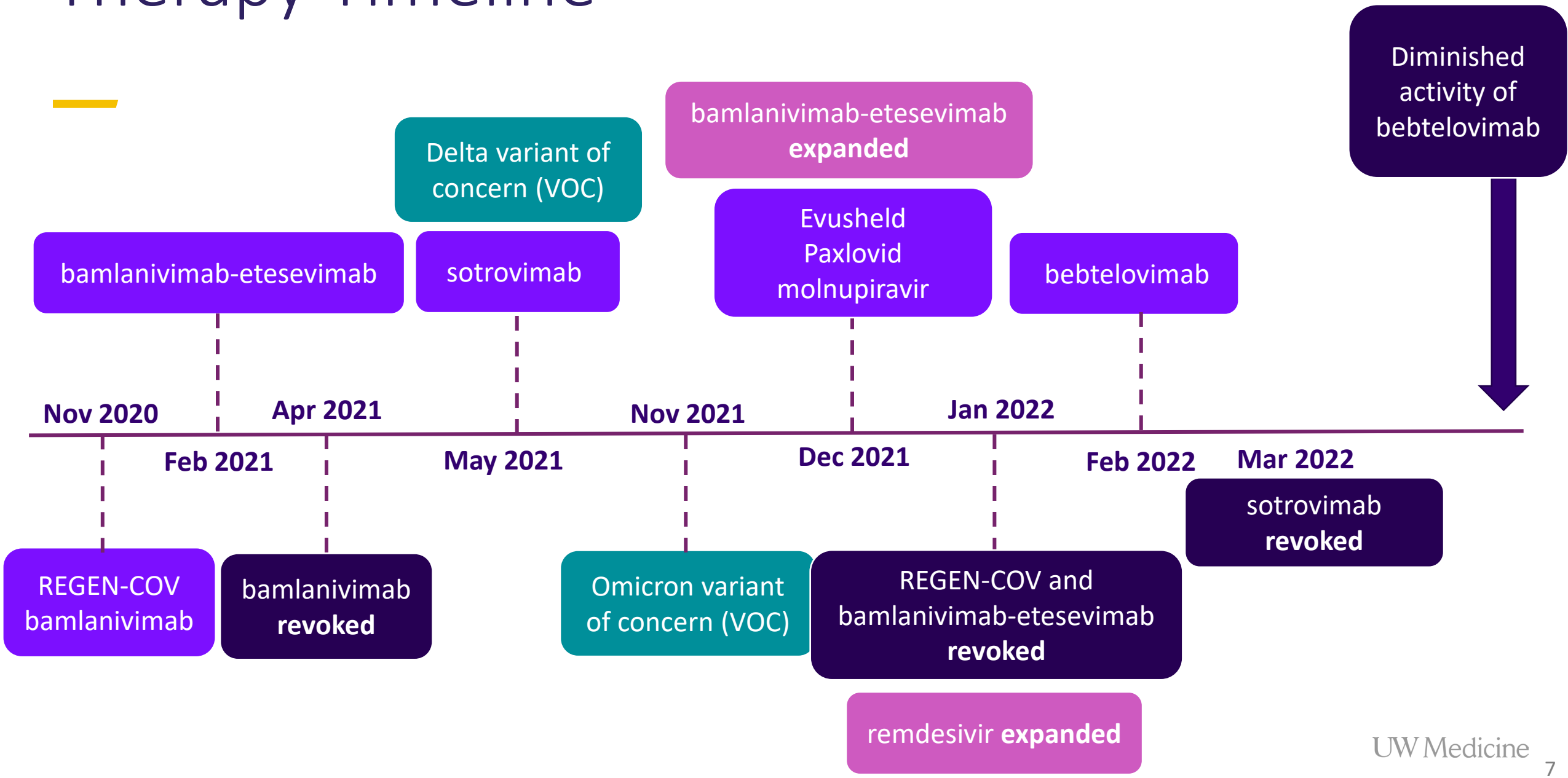
Epidemiology

Hospitalizations in the US



CDC. COVID Tracker 2022

Therapy Timeline



Case – a patient with no co-morbidities

PY is a 47-yr-old calls your office after testing positive for COVID-19. They endorse a new cough, fever, and headache and has been feeling short of breath when walking around their apartment.

Pulse Ox at home: 97%

COVID-19: vax and boosted

PMH: none; BMI = 25

Symptoms started 2 days ago

Medication list: none

What is this patient's disease severity at presentation?

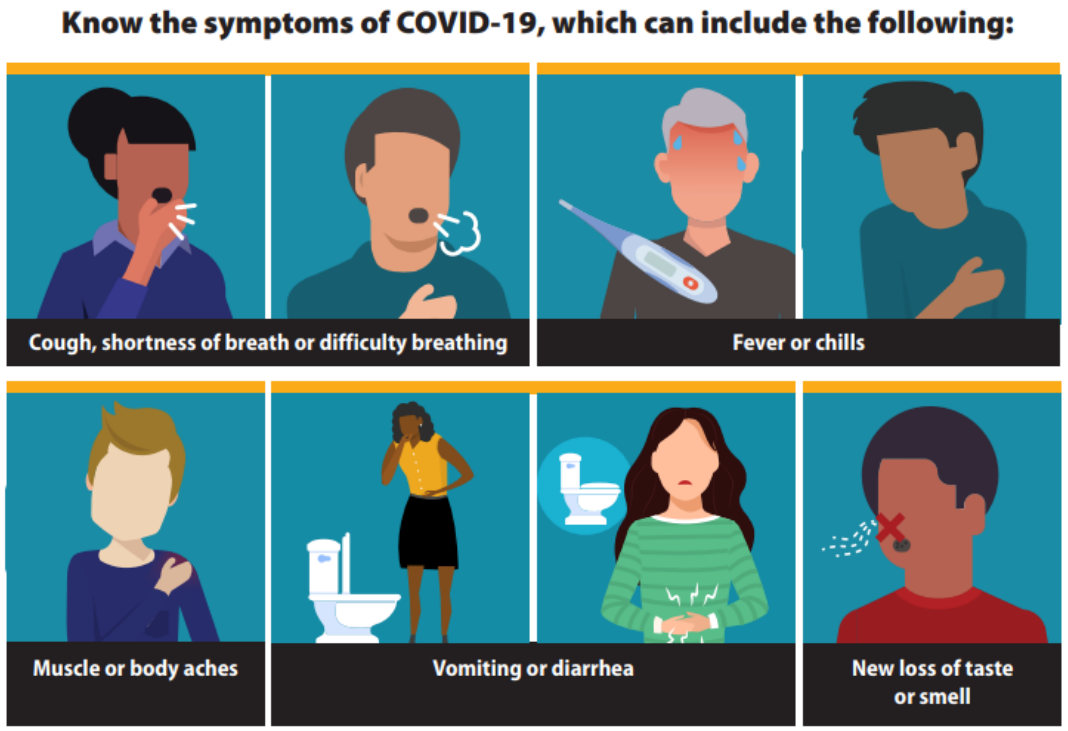
What are the risk factors for severe COVID-19 ?

Is this patient eligible for therapy?

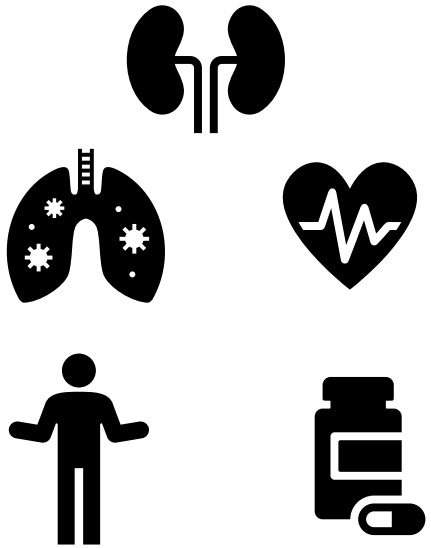
Checklist for Considering Treatment

Positive SARS CoV2 test (antigen or PCR)

Not hospitalized



Symptoms within 5-7 days

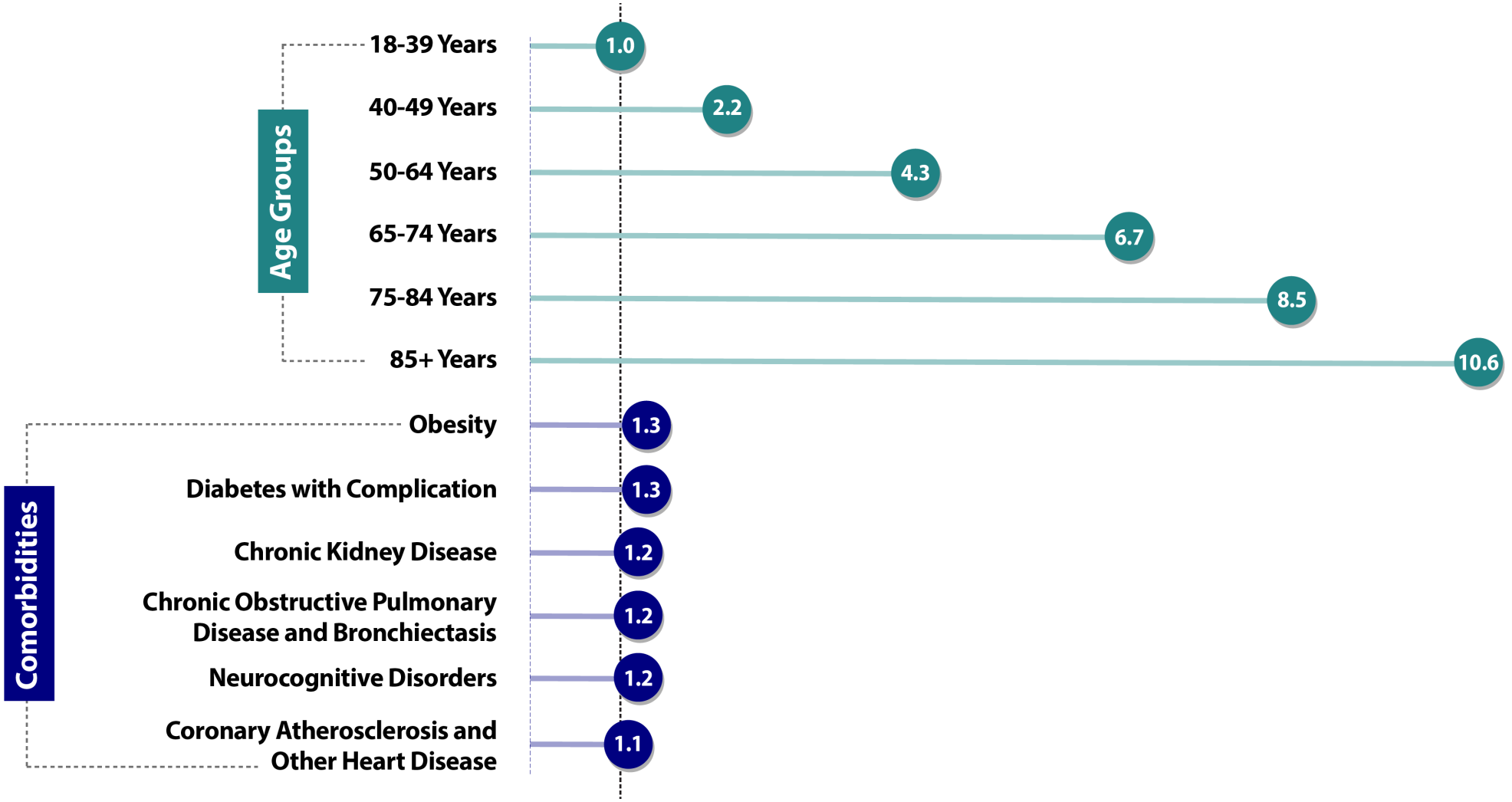


Risk Factors for Severe Disease

Disease Severity Classification

NIH Criteria

Risk Factors for Disease Progression

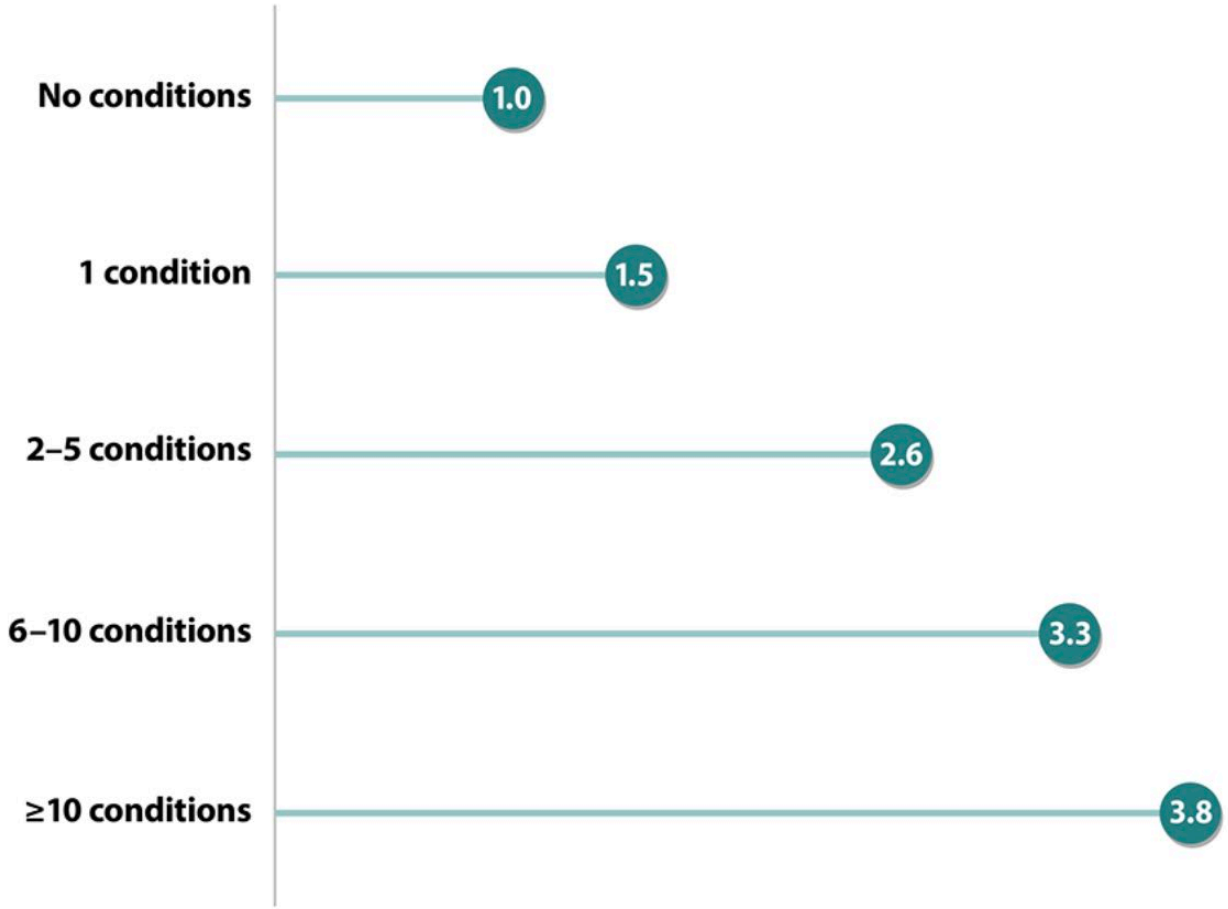


Underlying Medical Conditions. CDC 2022

Other factors

- Immunosuppression
- Cancer
- Pregnancy/ recent Pregnancy
- Polysubstance abuse
- Obesity (BMI $\geq$ 30)
- Chronic Liver Disease

See CDC website for complete list



https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

NIH COVID-19 Treatment Guidelines

Therapeutic Management of Non-hospitalized Adults With COVID-19

Does Not Require Hospitalization or Supplemental Oxygen

All patients should be offered symptomatic management **(AIII)**.

Preferred therapies for patients who are at high risk of progressing to severe COVID-19 (listed in order of preference):

- **Ritonavir-boosted nirmatrelvir (Paxlovid) (AIIa)**
- **Remdesivir (BIIa)**

Alternative therapies: For use ONLY when neither of the preferred therapies are available, feasible to use, or clinical appropriate (in alphabetical order)

- **Bebtelovimab (CIII)**
- **Molnupiravir (CIIa)**

The panel **recommends against** the use of **dexamethasone** or **other systemic corticosteroids** in the absence of another indication **(AIIb)**.

Therapeutic goal: AVOID hospitalization and death

https://www.covid19treatmentguidelines.nih.gov/

Case – a patient with no co-morbidities

PY is a 47-yr-old calls your office after testing positive for COVID-19. They endors[illegible] a new cough, fever, and hea[illegible]he a[illegible] been feeling sho[illegible]und the[illegible]

CO[illegible]

PMH: non[illegible] BMI = 25

Symptoms started 2 days ago

Medication list: none

Does not meet EUA criteria

What is this patient's disease severity at presentation?

Mild-moderate

What are the risk factors for severe COVID-19 ?

NONE

Is this patient eligible for therapy?

Case – a patient with co-morbidities

PY is a 47-yr-old calls your office after testing positive for COVID-19. They endorse a new cough, fever, and headache and have been feeling short of breath when walking around their apartment. GI symptoms are well-controlled at this time.

Pulse Ox at home: 97%

COVID-19: vax and boosted

PMH: Crohn's disease ; BMI = 25

Symptoms started 2 days ago

Medication list: infliximab

What is this patient's disease severity at presentation?

Mild to Moderate

What are the risk factors for severe COVID-19 ?

Immunosuppression

Is this patient eligible for therapy?

Paxlovid™ (nirmatrelvir-ritonavir)

Indication	Non-hospitalized with mild-moderate COVID-19 at high risk for progression to severe COVID-19 ≥ 12-years-old and ≥ 40 kg Symptom onset ≤5 days
Mechanism of action	Nirmatrelvir: inhibits main protease (Mpro) Ritonavir: inhibits CYP3A4-mediated metabolism of nirmatrelvir
Dosing	300mg-100mg (3 tabs) PO BID x **5 days**

Patient information for Paxlovid 2022

Oral Nirmatrelvir for High Risk, Non-hospitalized Adults with COVID-19 (EPIC-HR)

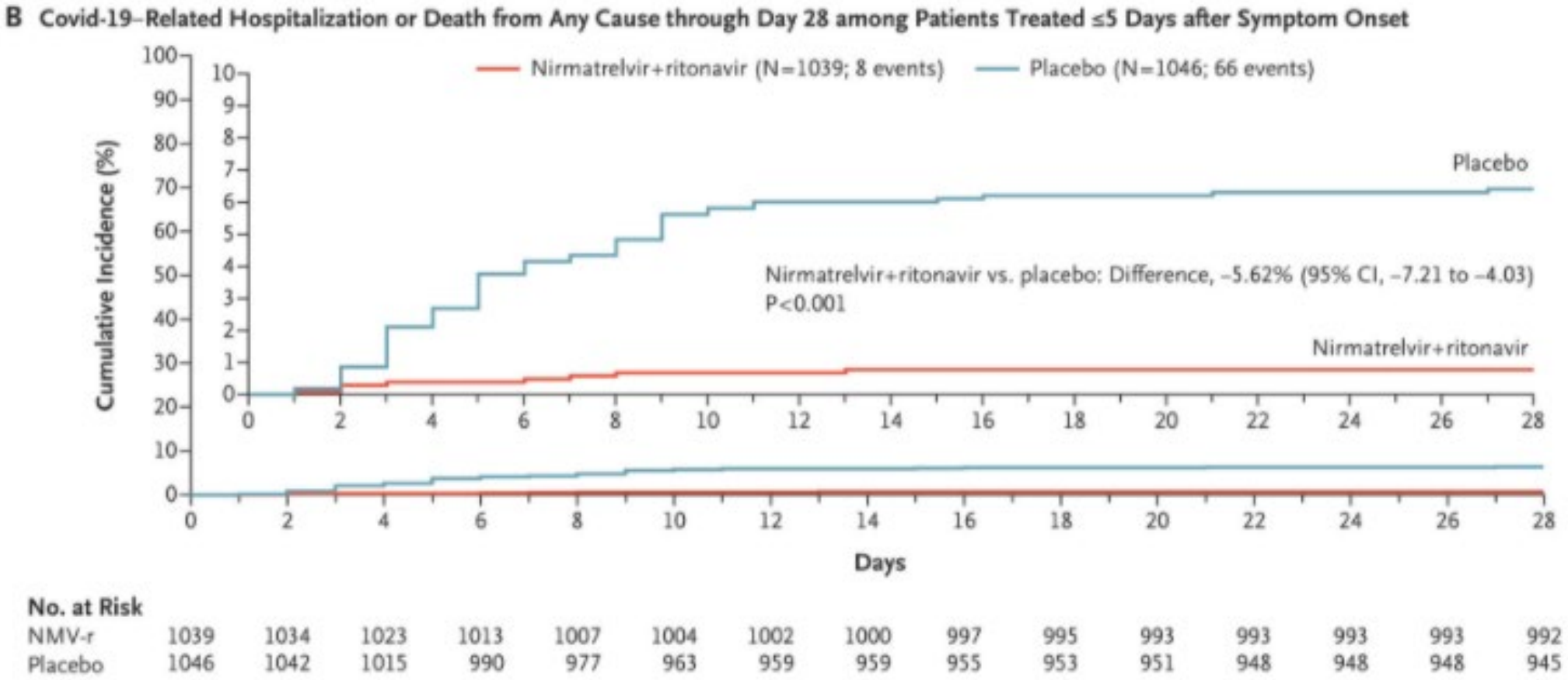
Population	Intervention	Outcome
• Non-hospitalized, mild to moderate disease • ≥ 1 risk factor for developing severe disease • Symptom onset within 5 days	• Paxlovid (n=1039) • Placebo (n=1046)	• Primary: COVID-19 related hospitalization or death from any cause by day 28

Key Exclusion Criteria

- Prior COVID-19 infection or hospitalization for COVID-19
- Anticipated need for hospitalization within 48 hours of randomization
- **Received COVID-19 vaccine** or convalescent COVID-19 plasma
- Pregnancy or breastfeeding

Hammond J, et al. NEJM 2022

Oral Nirmatrelvir for High Risk, Non-hospitalized Adults with COVID-19 (EPIC-HR)

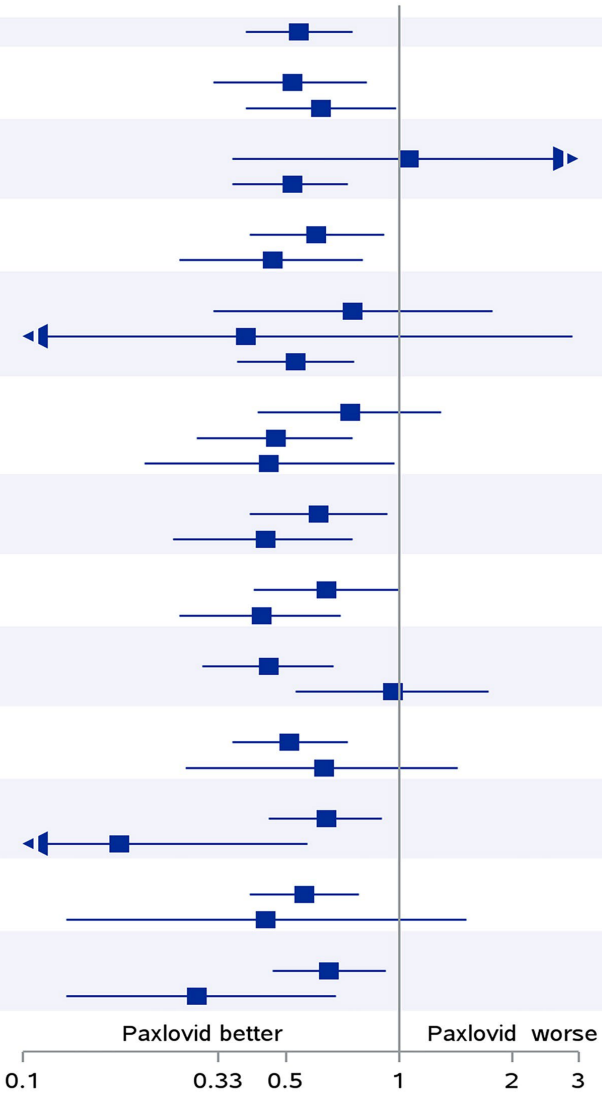


- 88% lower risk of COVID-19 related hospitalizations or death
- Adverse effects of altered taste, diarrhea, hypertension, myalgia

Hammond J, et al. NEJM 2022

The effectiveness of Paxlovid in reducing the risk of severe coronavirus disease 2019 or mortality

Subgroup	Paxlovid No.	Non-Paxlovid No.	Hazard Ratio (95% CI)	Interaction *P* Value
Overall	4737	175 614	0.54 (.39, .75)	
Adequate COVID-19 vaccination				.129
No	1051	43 818	0.52 (.32, .82)	
Yes	3686	131 796	0.62 (.39, .98)	
Age category				.039
<60 years	973	102 040	1.06 (.36, 3.15)	
≥60 years	3764	73 574	0.52 (.36, .73)	
Sex				.514
Males	1992	71967	0.60 (.40, .91)	
Females	2745	103 647	0.46 (.26, .80)	
Population sector				.708
Arab	300	32 758	0.75 (.32, 1.77)	
Ultra-Orthodox Jewish	202	6835	0.39 (.05, 2.89)	
General Jewish	4234	135 464	0.53 (.37, .76)	
Socioeconomic status				.846
Low	1120	62 618	0.74 (.42, 1.29)	
Middle	2090	74 928	0.47 (.29, .75)	
High	1517	37 022	0.45 (.21, .97)	
Diabetes				.257
No	2911	139 767	0.61 (.40, .93)	
Yes	1826	35 487	0.44 (.25, .75)	
Cardiovascular disease				.028
No	3231	152 121	0.64 (.41, 1.00)	
Yes	1506	23 493	0.43 (.26, .70)	
Chronic lung disease				.114
No	4238	169 385	0.45 (.30, .67)	
Yes	499	6229	0.96 (.53, 1.73)	
Chronic kidney disease				.965
No	4506	170 949	0.51 (.36, .73)	
Yes	231	4665	0.63 (.27, 1.43)	
Neurological disease				.016
No	4410	164 650	0.64 (.45, .90)	
Yes	327	10 964	0.18 (.06, .57)	
Malignancy in the prior year				.387
No	4559	174 090	0.56 (.40, .78)	
Yes	178	1524	0.44 (.13, 1.51)	
Immunosuppression				.042
No	4421	174 400	0.65 (.46, .92)	
Yes	316	1214	0.29 (.13, .68)	



Clin Infect Dis, ciac443, https://doi.org/10.1093/cid/ciac443

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Check the medication list

- ✓ Use COVID-19 interaction checker to review medication list
- ✓ If drug interactions, evaluate whether medication can be held (i.e. statins) or dose reduced
- ✓ AVOID Paxlovid in patients who are taking :
  - ✓ Anti-rejection medications for transplant (tacrolimus, cyclosporine or sirolimus)
  - ✓ DOAC (apixaban, etc)
- ✓ Oral contraceptives: additional method recommended while on paxlovid

Drugs that are contraindicated	
Cardiac	Ranolazine amiodarone, dronedarone, flecainide, propafenone, quinidine lovastatin, simvastatin
Anti-convulsants	Carbamazepine, clonazepam Phenobarbital Phenytoin Primidone
Antimicrobial	Rifampin Rifapentine
Herbal	St John's Wort
Misc **and many more**	Alfuzosin Colchicine Sildenafil (PAH) Ergotamine

Ritonavir-boosted nirmatrelvir (Paxlovid). NIH COVID-19 treatment guidelines 2022
https://www.covid19-druginteractions.org/checker

Counsel About Potential For Rebound

- 2-8 days after completion of 5-day course of nirmatrelvir/ritonavir
- Recurrence of symptoms after resolution/improvement
- No additional treatment needed
- Restart isolation period for 5 days from recurrence of symptoms

Rebound rates 3.5% at 7 days (5.4% at 30 days)

Wang L et al. medRxiv 2022. Preprint

Case – a patient with co-morbidities

PY is a 47-yr-old who calls your office after testing positive for COVID-19. They endorse a new cough, f… r, a… adache and have bee… …oon walkin… …oms are w…

Pulse O…

COVID-19: v… …nd boosted

PMH: Crohn's disease ; BMI = 25

Symptoms started 2 days ago

Medication list: infliximab

Are there any drug interactions?

What is this patient's disease severity at presentation?

Mild to Moderate

What are the risk factors for severe COVID-19 ?

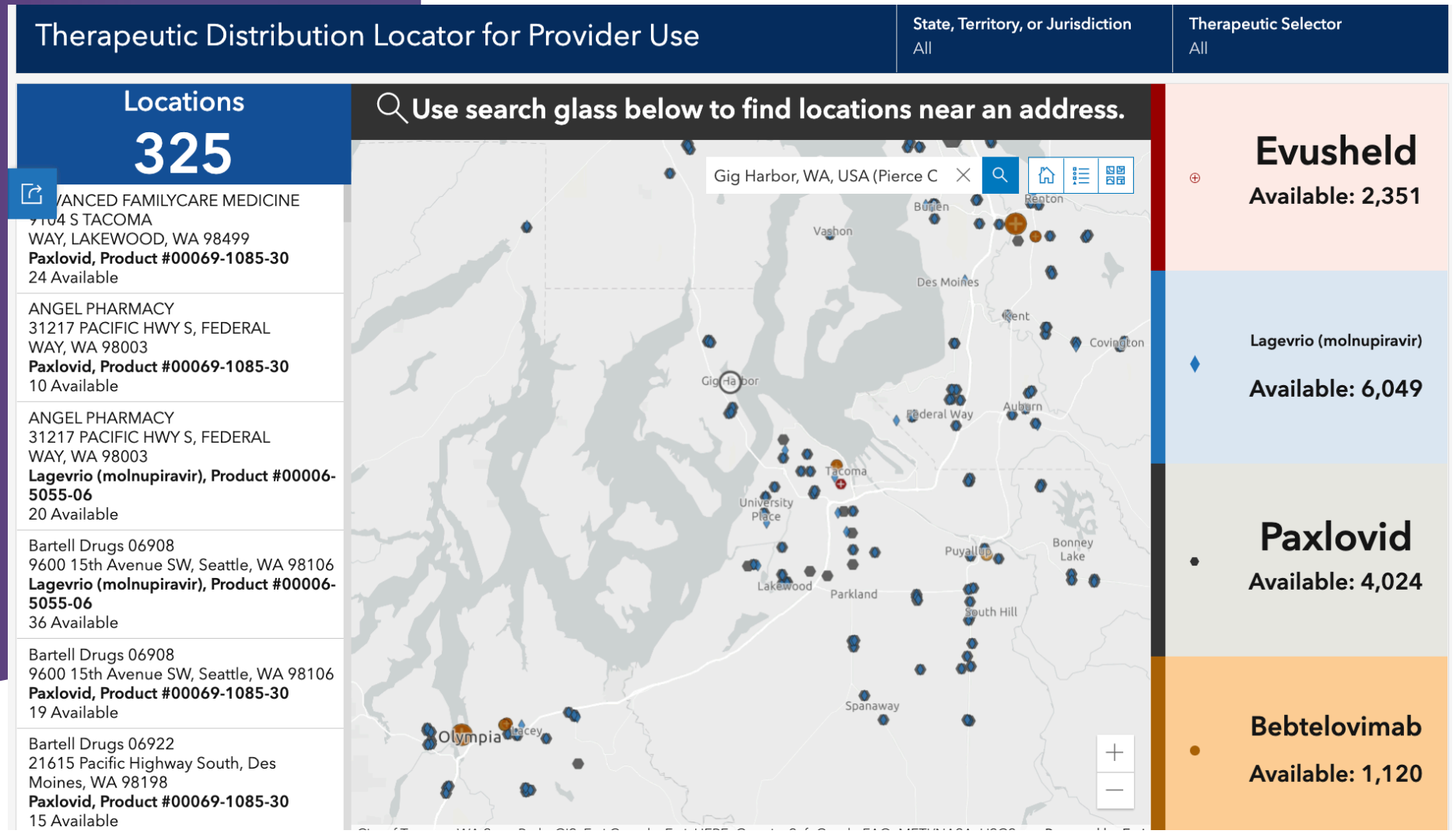
Immunosuppression

Is this patient eligible for therapy?

☑

WHERE SHOULD I SEND THE PRESCRIPTION?

Go to locator



https://covid-19-therapeutics-locator-dhhs.hub.arcgis.com/

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Case – a patient with co-morbidities

PY is a 47-yr-old who calls your office after testing positive for COVID-19. They endorse a new cough, f… r, a… adache and have bee… …oor walkin… …oms are w…

Pulse O…

COVID-19: v… …nd boosted

PMH: Crohn's disease ; BMI = 25

Symptoms started 2 days ago

Medication list: infliximab

PAXLOVID

What is this patient's disease severity at presentation?

Mild to Moderate

What are the risk factors for severe COVID-19 ?

Immunosuppression

Is this patient eligible for therapy?

☑

Case – a pregnant patient

PY is a 27-yr-old who calls your office after testing positive for COVID-1[illegible]. **They are 24 weeks p[illegible]gnant**; t[illegible] a nev[illegible]
cough, feve[illegible]
feeling[illegible]nd
th[illegible]
COV[illegible]
PMH: none, BMI = 25
Symptoms started 2 days ago
Medication list: prenatal vitamins

PAXLOVID

What is this patient's disease severity at presentation?

Mild to Moderate

What are the risk factors for severe COVID-19 ?

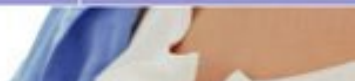
Pregnancy

Is this patient eligible for therapy?

☑

Society for Maternal-Fetal Medicine

ABOUT US | CLINICAL GUIDANCE | ADVOCACY | FOR WOMEN & FAMILIES | EDUCATION | PRACTICE MANAGEMENT



FDA Issues EUA for the Treatment of Mild-to-Moderate COVID-19

Maternal-Fetal Medicine Subspecialists Support Use in Pregnant Patients

Public

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- Management Considerations for Pregnant Patients With COVID-19 (February 2, 2021; updated from earlier versions on January 7, 2021 and July 2, June 16, and April 30, 2020). *As we make updates to this document, we will highlight new/different content in yellow.*

December 22, 2021 – Today the U.S. Food and Drug Administration issued an Emergency Use Authorization (EUA) for Paxlovid for the treatment of mild-to-moderate COVID-19 in adults and some pediatric patients. In response, the Society for Maternal-Fetal Medicine (SMFM) issued the following statement.

"SMFM supports the use of Paxlovid (nirmatrelvir [PF-07321332] tablets and ritonavir tablets) for treatment of pregnant patients with COVID-19 who meet clinical qualifications. Any therapy that would otherwise be given should not be withheld specifically due to pregnancy or lactation."

https://www.smfm.org/covidclinical;
https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/

Case – an organ transplant patient

PY is a 57-yr-old who calls your office after testing positive for COVID-19. They endorse a new cough, fever, and headache and have been feeling short of breath when walking around their apartment.

Pulse Ox at home: 97%

COVID-19: vax and boosted

PMH: Liver transplant 2012; BMI = 25

Symptoms started 2 days ago

Medication list: tacrolimus, aspirin, losartan, rosuvastatin, mycophenolate

What is this patient's disease severity at presentation?

Mild to moderate

What are the risk factors for severe COVID-19 ?

Immunosuppression

Is this patient eligible for therapy?

Bebtelovimab

Indication	Non-hospitalized with mild-moderate COVID-19 at high risk for progression to severe COVID-19 ≥ 12-years-old and ≥ 40kg Symptom onset ≤7 days
Mechanism of action	Binds to spike protein of SARS-CoV-2
Dosing	175mg IV once
Not authorized for	• hospitalized due to COVID-19 • require oxygen therapy and/or respiratory support due to COVID-19, • require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19

Bebtelovimab fact sheet. FDA 2022

BLAZE-4 Trial for Bebtelovimab

Phase 2 Data from the Randomized, Open-Label Portion

Outcome	BEB	BAM-ETE-BEB*
Hospitalization or death from any cause	3%	4%

*bamlanivimab + etesevimab + bebtelovimab combination therapy

Conclusions

- Insufficient outcome data for patients at high risk for progression to severe disease
- Efficacy based on other therapeutics with similar mechanism and demonstrated benefit
- Potent activity against Omicron *in vitro* (BA.1 & BA.2 subvariants included)

Bebtelovimab fact sheet. FDA 2022

Case – a transplant patient

PY is a 57-yr-old who calls your office after testing positive for COVID-19 [illegible] endorse a [illegible] cough, [illegible] dache and have be[illegible] wa[illegible]

Pulse O[illegible]

COVID[illegible]

PM[illegible] [illegible]M [illegible]5

Symptoms started 2 days ago

Medication list: tacrolimus

IV REMDESIVIR x 3 days
vs
Bebtlovimab

What is this patient's disease severity at presentation?

Mild to Moderate

What are the risk factors for severe COVID-19 ?

Immunosuppression

Is this patient eligible for therapy?

☑

Case – a patient on interacting medications

PY is a 67-yr-old who calls your office after testing positive for COVID-19. They endorse a new cough, fever, and headache and have been feeling short of breath when walking around their apartment.

Pulse Ox at home: 97%

COVID-19: vax and boosted

PMH: htn, afib, hyperlipidemia, stroke 6 months ago; BMI = 25

Symptoms started 2 days ago

Medication list: apixaban, losartan, amlodipine, aspirin

What is this patient's disease severity at presentation?

Mild to Moderate

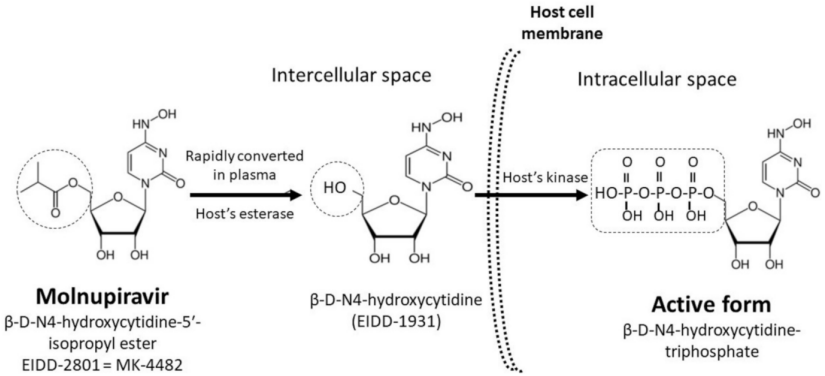
What are the risk factors for severe COVID-19 ?

HTN, hyperlipidemia, age > 65

Is this patient eligible for therapy?

Molnupiravir

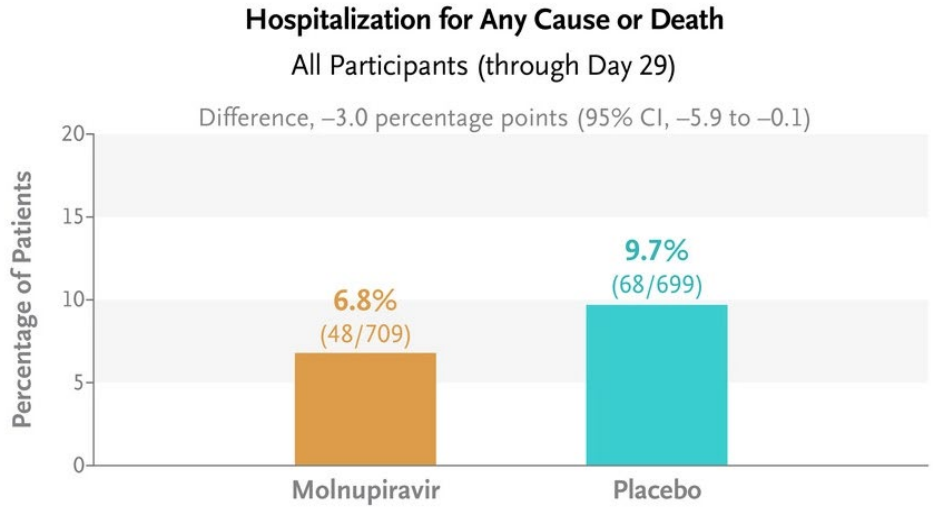
Indication	Non-hospitalized with mild-moderate COVID-19 at high risk for progression to severe COVID-19 ≥ 18-years-old Symptom onset ≤5 days **When alternative treatments are not accessible or clinically appropriate**
Mechanism of action	Nucleoside analog prodrug of NHC
Dosing	800mg (4 caps) PO BID x5 days
Precaution	is not recommended during pregnancy

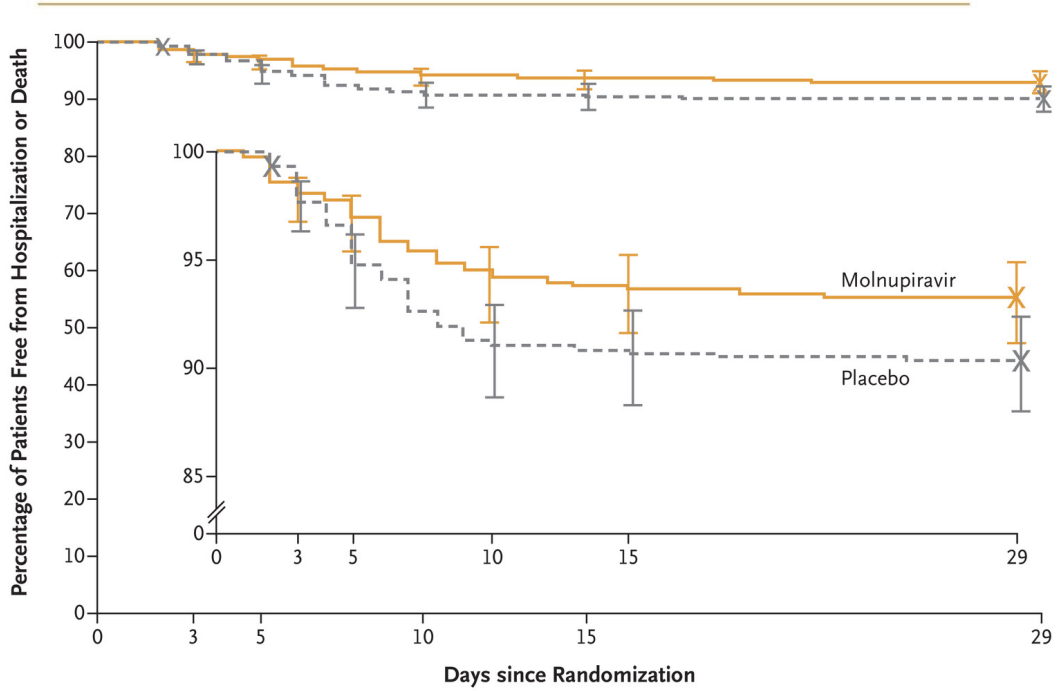


https://www.mdpi.com/2079-6382/10/11/1294/htm

Molnupiravir

Population	Non-hospitalized, mild to moderate disease ≥ 1 risk factor for developing severe disease Symptom onset within 5 days
Intervention	Molnupiravir (n=716) Placebo (n=717)
Primary outcome	Primary: hospitalization or death by day 29



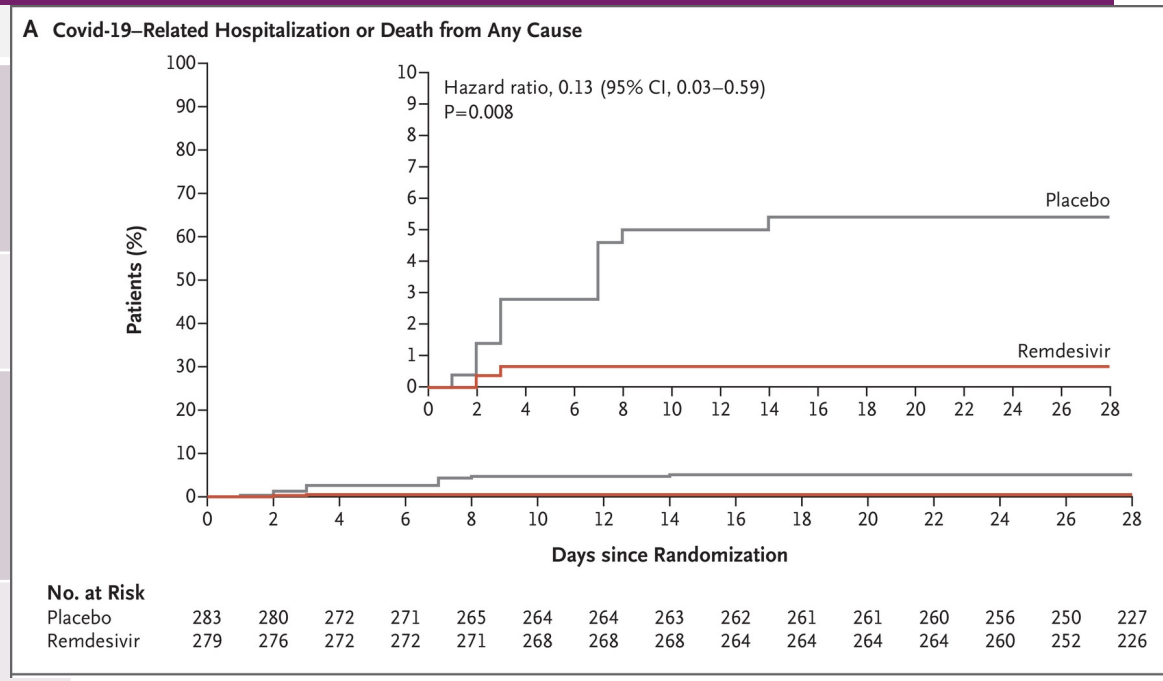


N Engl J Med 2022; 386:509-520
DOI: 10.1056/NEJMoa2116044

Remdesivir

- 87% lower risk of COVID-19-related hospitalization or death
- 81% lower risk of COVID-19-related medical visits
- Acceptable safety profile

Indication	No at ≥ 1 Symptom onset ≤7 days
Mechanism of action	Direct acting nucleotide inhibitor of RNA-dependent polymerase
Dosing	200mg IV on day 1, then 100mg IV on day 2, 3
Population	Non-hospitalized, mild to moderate disease ≥ 1 risk factor for developing severe disease Symptom onset within 7 days
Outcome	Primary: COVID-19 related hospitalization or death Secondary: COVID-19 related medical visits or death



Gottlieb RL, et al. NEJM 2022; 386(4):305-315

FRED HUTCH CURES START HERE

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Pre-Exposure Prophylaxis

Evusheld™ (tixagevimab-cilgavimab)

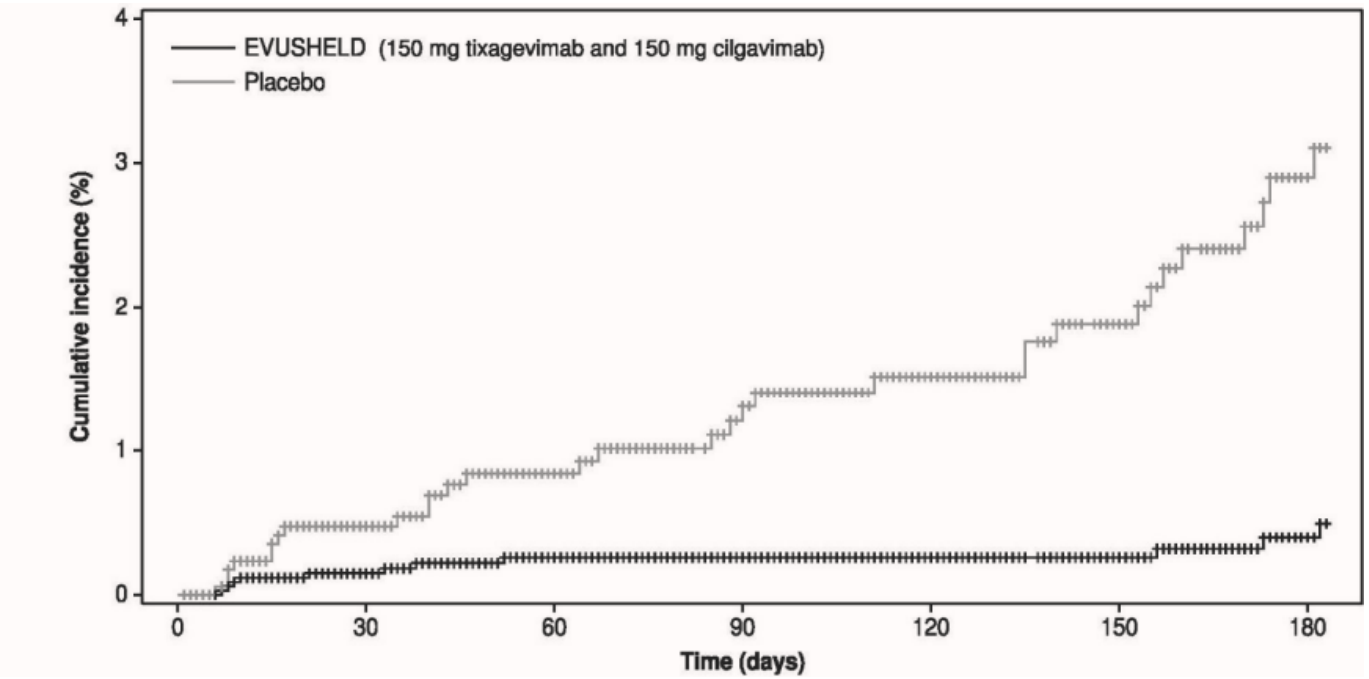
Indication	No known COVID-19 exposure and COVID-19 negative AND Immunocompromised or unable to receive vaccination ≥ 12-years-old and ≥ 40kg
Mechanism of action	Neutralizing mAbs targeting spike protein of SARS-CoV-2 at non-overlapping epitopes Passive immunity
Dosing	300mg-300mg IM x1 (previously 150-150mg) Two separate injections 3mL
Duration of protection	Unknown, depends on circulating variant

Provider FACT sheet: https://www.fda.gov/media/154701/download

Evusheld™ (tixagevimab-cilgavimab)

	PROVENT **Pre-exposure prophylaxis**
Population	**No known exposure** and unvaccinated Would benefit from prevention ≥ 18 years old
Intervention	Placebo (n=1,731) Evusheld 150mg-150mg IM x1 (n=3,441)
Outcomes	Primary: incidence of COVID-19 positive cases by day 183 (6 month)
Results	**77% reduction in symptomatic COVID-19 disease** **69% reduction in COVID-19 disease or death from any cause**

Cumulative Incidence of Symptomatic COVID-19



JAMA 2022;327(4):384-385

https://www.biospace.com/article/releases/evusheld-formerly-azd7442-long-acting-antibody-combination-authorized-for-emergency-use-in-the-us-for-pre-exposure-prophylaxis-prevention-of-covid-19/

EUA Outpatient Therapies for COVID-19

Drug	Mechanism of Action	Population	Efficacy
Evusheld (Tixagevimab/ cilgavimab)	Long-acting monoclonal antibody (spike)	Pre-exposure prophylaxis • Immunocompromised, may not mount response OR • Unable to vaccinate	77% reduction in symptomatic COVID-19
Bebtelovimab	Monoclonal antibody (spike)	Early treatment*, high risk (NIH Tier 1 and Tier 2)	79% reduction in risk of hosp/death**
Paxlovid	SARS-CoV-2 protease inhibitor	Early treatment*, high risk (NIH Tier 1- 4)	88% reduction in risk of hosp/death
Molnupiravir	Nucleoside analogue	Early Treatment*, high risk	30% reduction in risk of hosp/death
Remdesivir	Inhibits viral RNA polymerase	Early Treatment*, high risk (NIH Tier 1-3)	87% reduction in hospitalization

*within 7 days of symptom onset **based on other monoclonal therapies not bebtelovimab

Checklist for Considering Treatment

- ✓Positive Test (PCR or Ag, Lab or Home)
- ✓Symptom onset (within 5 days for orals, within 7 days for IV monoclonal antibody or remdesivir therapy)
- ✓Risk factors for severe disease
- ✓Review medication list (to review for drug-drug interactions)
- ✓Counsel regarding potential for rebound
- ✓Prescribe therapy (or refer to facility that offers IV remdesivir or bebtelovimab)

Know Your Resources!

Resources

NIH | COVID-19 Treatment Guidelines

FDA Fact Sheet

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

UW Medicine

COVID-19

COVID-19 Treatments and Therapeutics

https://one.uwmedicine.org/coronavirus

Acknowledgements!

Rupali Jain, PharmD
UW Medicine COVID-19 Therapeutics Team
Kate Bialick, PharmD (Pharmacy Resident

QUESTIONS?