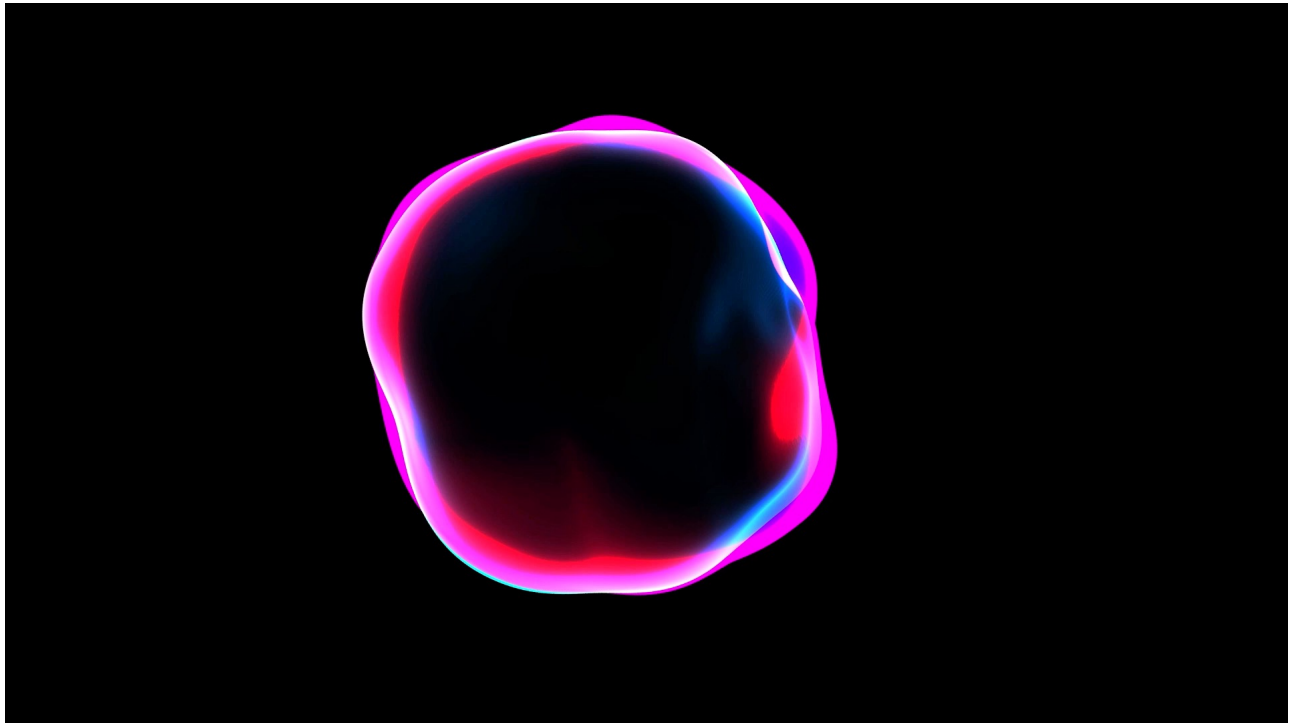
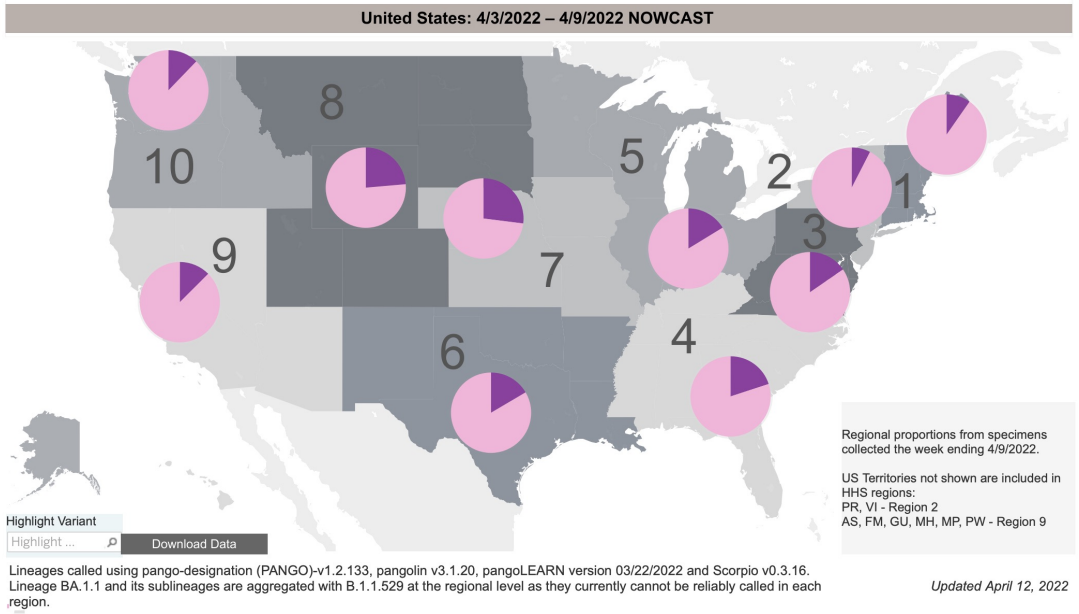
COVID-19 Updates
April, 2022

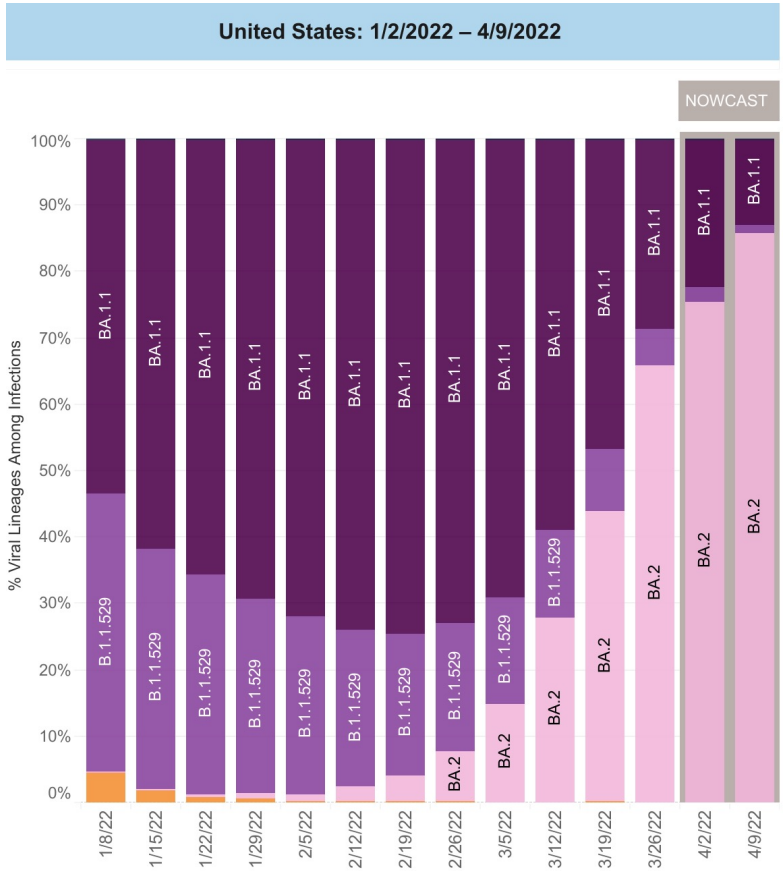
Jorge Mera, MD

Whitney Essex, APRN



COVID-19 Updates
Virology: BA.2 is, unfortunately, in the pink





https://covid.cdc.gov/covid-data-tracker/#variant-proportions

COVID-19 Outpatient Treatment: Who Qualifies?

Confirmed SARS-COV-2 test

- PCR, NAAT or Antigen

Symptomatic

- Mild or Moderate
- Not Hypoxic

Risk factor for progression of the disease

- Age, Comorbidities and Ethnicity

Timing

- Within 7 days of treatment

Variant shift therapeutic implications

Sotrovimab no longer authorized for use anywhere in the US

Preferred drugs of choice recommended by NIH 4/1/2022

- Nirmatrelvir/r for 5 days (≤ 5 days of symptom onset)
- Remdesivir daily for 3 days (≤ 7 days of symptom onset)

Alternate Rx: (only recommended if preferred options not available

- Bebtelovimab IV push x 1 (≤ 7 days of symptom onset)
- Molnupiravir (≤ 5 days of symptom onset)

https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/nonhospitalized-adults--therapeutic-management/

COVID-19 Treatment Guidelines

Figure 1. Therapeutic Management of Nonhospitalized Adults With COVID-19

PATIENT DISPOSITION	PANEL'S RECOMMENDATIONS
Does Not Require Hospitalization or Supplemental Oxygen	All patients should be offered symptomatic management **(AIII)**. For patients who are at high risk of progressing to severe COVID-19,[a] use 1 of the following treatment options: **Preferred Therapies** *Listed in order of preference:* • **Ritonavir-boosted nirmatrelvir (Paxlovid)[b,c] (AIIa)** • **Remdesivir[c,d] (BIIa)** **Alternative Therapies** *For use ONLY when neither of the preferred therapies are available, feasible to use, or clinically appropriate. Listed in alphabetical order:* • **Bebtelovimab[e] (CIII)** • **Molnupiravir[c,f] (CIIa)** For use **ONLY** in regions where the Omicron BA.2 subvariant is not the dominant subvariant and in situations where none of the preferred or alternative options are available, feasible to use, or clinically appropriate: • **Sotrovimab[g] (CIII)** The Panel **recommends against** the use of **dexamethasone** or **other systemic corticosteroids** in the absence of another indication **(AIII)**.[h]

https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/nonhospitalized-adults--therapeutic-management/

Treatment Options Depending on Age and Pregnancy Status

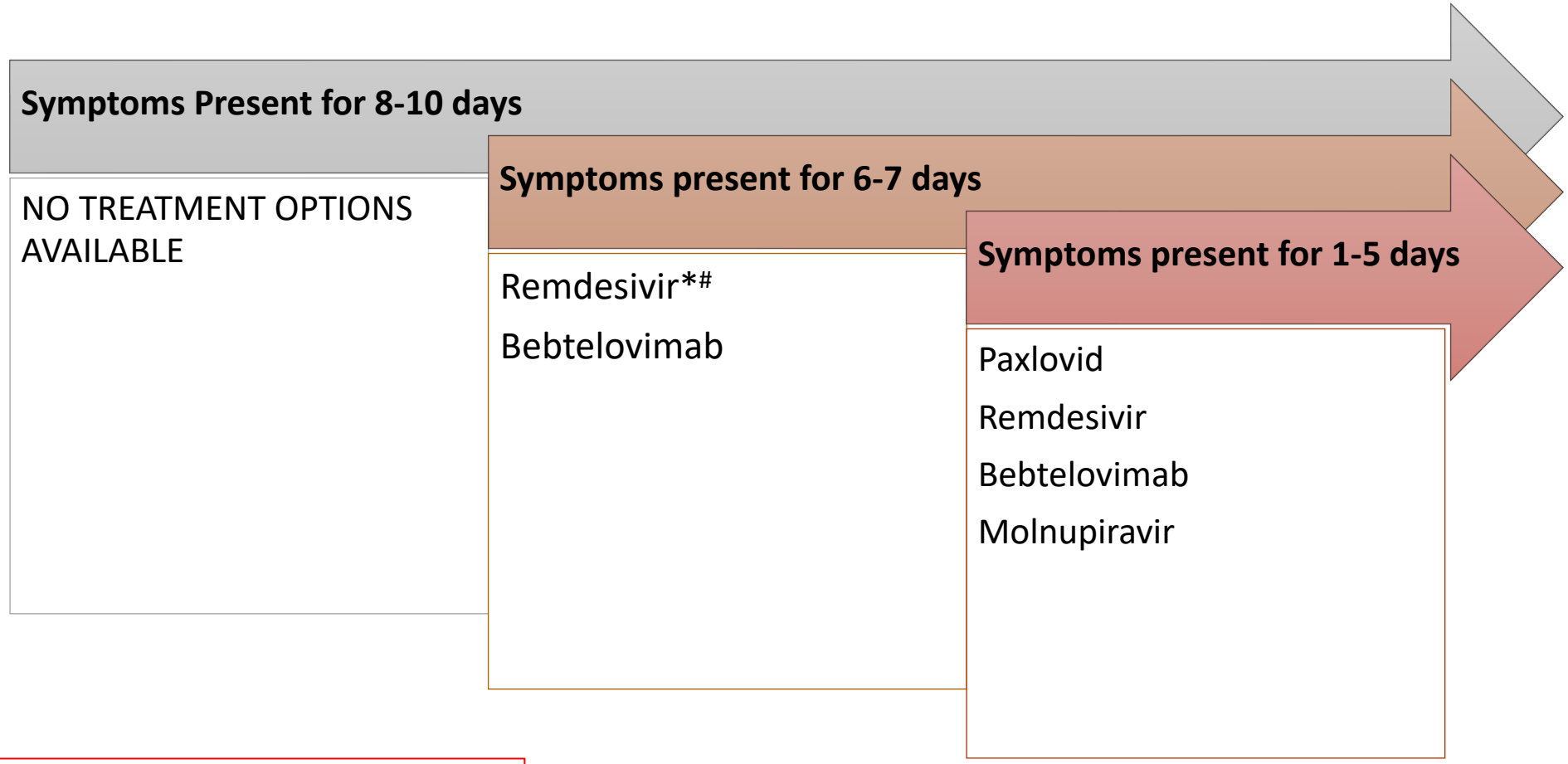
Age

- < 12 yo: Remdesivir
- > 12 yo and < 18 yo: Paxlovid, bebtelovimab, Remdesivir
- > 18 yo: Paxlovid, Sotrovimab, Remdesivir and Molnupiravir

Pregnancy

- Bebtelovimab, Remdesivir

Outpatient SARS-COV-2 Antiviral Options Based on Symptom Duration



* Only option for Children < 12 years of age or < 40 kg
\# Only option during pregnancy

NIH Guidelines recommendations for nonhospitalized patients with mild to moderate COVID-19 who are at high risk of disease progression (listed in order of preference)

Nirmatrelvir 300 mg/ritonavir 100 mg, orally (Paxlovid). **AIIa**

- Initiated ASAP **within 5 days** of symptom onset, orally twice daily in those aged ≥12 years and ≥40 kg
- Has significant and complex drug-drug interactions, primarily due to the ritonavir component.

Remdesivir 100 mg IV (Only FDA Approved Treatment) **BIIa**

- Initiate ASAP **within 7 days** of symptom onset. IV, in 3 consecutive days for ages ≥12 years and ≥40 kg
- NIH recommends 1 hour of observation, but this was not required in the clinical trial

Bebtelovimab 175 mg IV push **AIIa**

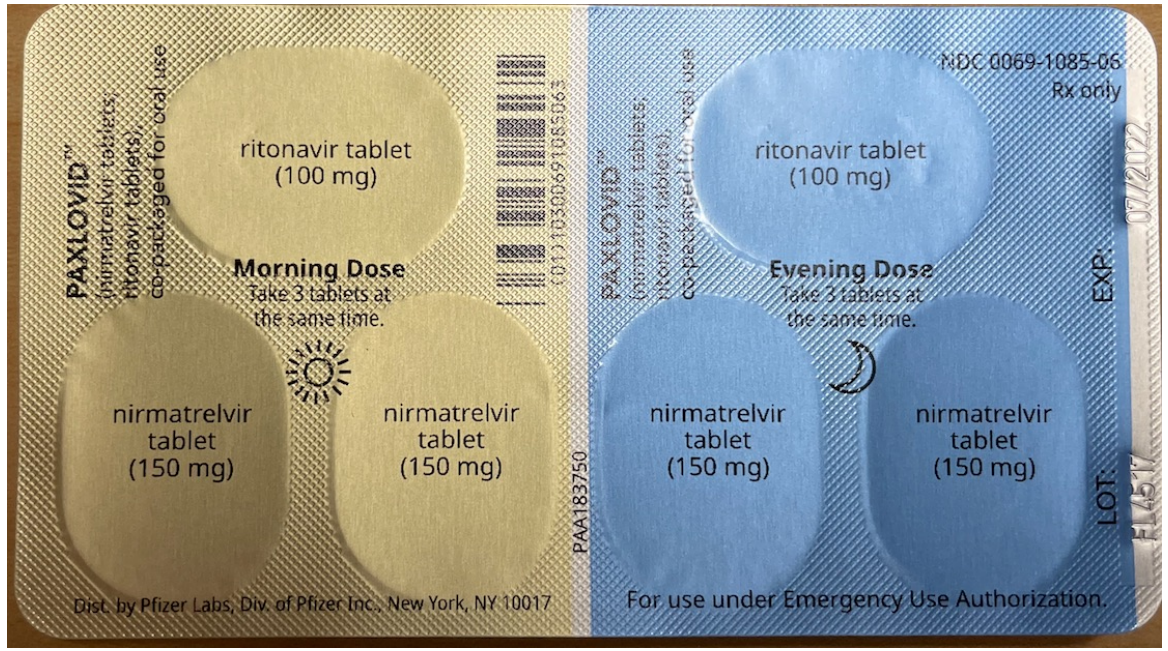
- Initiate ASAP **within 7days** of symptom onset, , single IV push for those aged ≥12 years and ≥40 kg,
- Patients should be observed for at least 1 hour after infusion.

Molnupiravir 800 mg, orally, ONLY when no other options can be used **CIIa**

- **Initiate ASAP within 5 days of symptom onset** on those aged ≥18 years
- **Not recommended for use in pregnant patients or in persons < 18 years of age**
  - Concerns about fetal toxicity observed during animal studies
  - Concerns for potential bone and cartilage toxicity

COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed [01/02/2021].

Nirmatrelvir 300 mg/ritonavir 100 mg, orally (Paxlovid).



First-line preferred regimen

Authorization:

- **Emergency use only, not FDA approved**
- **Mild to moderate illness only – not for hospitalized persons**
- **Treatment only – not for pre- or post-exposure**

Dosing:

- **300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all 3 tablets taken together twice daily for 5 days**
- **Dose reductions must be made for patients with moderate renal impairment**
- For those aged ≥12 years and weighing ≥40 kg.

Timing:

- **Start Paxlovid within 5 days of symptom onset**
- **Better outcomes if started within 3 days of symptom onset**
- **Reduces risk of hospitalization/death**
- Has significant/complex drug-drug interactions

AE

- Dysgeusia very common
- May cause nausea and vomiting due to ritonavir component
- **Take with food**

Medication Review: Ritonavir-boosted nirmatrelvir (Paxlovid)

First-line preferred regimen

Authorization:

- **Emergency use only, not FDA approved**
- **Mild to moderate illness only – not for hospitalized persons**
- **Treatment only – not for pre- or post-exposure**

Dosing:

- **300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all 3 tablets taken together twice daily for 5 days**
- **Dose reductions must be made for patients with moderate renal impairment**

Timing:

- **Start Paxlovid within 5 days of symptom onset**
- **Better outcomes if started within 3 days of symptom onset**

Ritonavir-boosted nirmatrelvir (Paxlovid): Data from the EPIC-HR Study

2,246 subjects were randomized to receive either PAXLOVID or placebo

	PAXLOVID (N=1,039)	**Placebo** (N=1,046)
COVID-19 related hospitalization or death from any cause through Day 28		
n (%)	8 (0.8%)	66 (6.3%)
Reduction relative to placebo[a] [95% CI], %	-5.62 (-7.21, -4.03)	
All-cause mortality through Day 28, %	0	12 (1.1%)

Abbreviations: CI=confidence interval.

88% Relative Risk Reduction in Hospitalization or Death

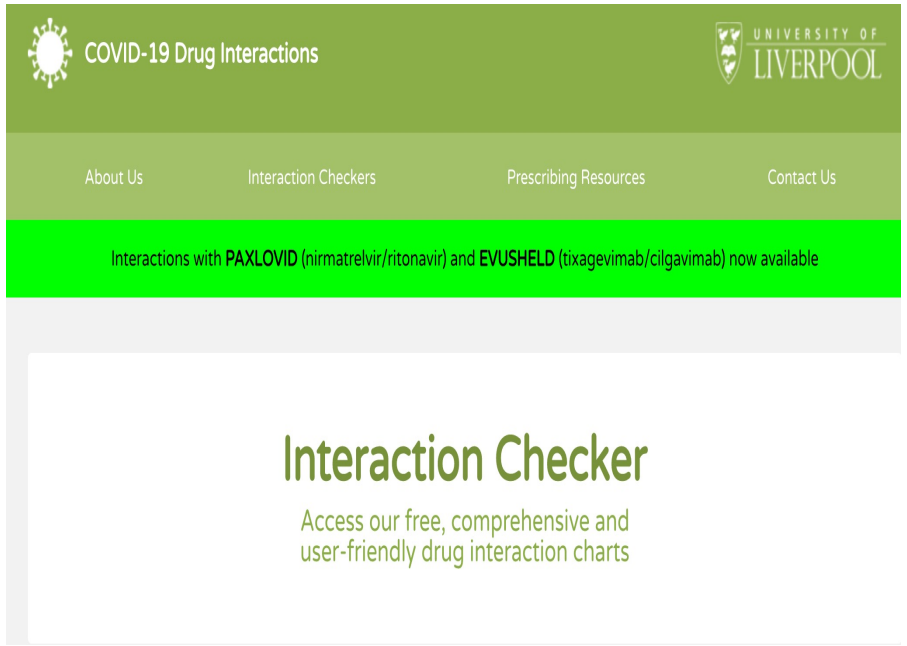
https://www.covid19oralrx-patient.com/files/Fact_Sheet_HCP.pdf

Paxlovid – Drug-Drug Interactions

Clinicians should carefully review a patient's concomitant medications and evaluate potential drug-drug interactions

Paxlovid 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

Link here: Liverpool COVID-19 Drug Interaction Checker



Prescribe an alternative COVID-19 therapy for patients who are receiving any of the medications listed.		If the patient is receiving any of these medications, withhold the medication if clinically appropriate or use an alternative concomitant medication or COVID-19 therapy.[a]	
Amiodarone	Lumateperone	Alfuzosin	Piroxicam
Apalutamide	Lurasidone	Alprazolam	Propoxyphene
Bosentan	Mexiletine	Atorvastatin	Rosuvastatin
Carbamazepine	Phenobarbital	Avanafil	Salmeterol
Cisapride	Phenytoin	Clonazepam	Sildenafil for erectile dysfunction
Clopidogrel	Pimozide	Codeine	Silodosin
Clozapine	Propafenone	Cyclosporine[b]	Simvastatin
Colchicine in patients with renal and/or hepatic impairment	Quinidine	Diazepam	Sirolimus[b]
Disopyramide	Ranolazine	Everolimus[b]	Suvorexant
Dofetilide	Rifampin	Fentanyl	Tacrolimus[b]
Dronedarone	Rifapentine	Hydrocodone	Tadalafil for erectile dysfunction
Eplerenone	Rivaroxaban	Lomitapide	Tamsulosin
Ergot derivatives	Sildenafil for pulmonary hypertension	Lovastatin	Tramadol
FlecainideFlibanserin	St. John's wort	Meperidine (pethidine)	Triazolam
Glecaprevir/pibrentasvir	Tadalafil for pulmonary hypertension	Midazolam (oral)	Vardenafil
Ivabradine	Ticagrelor	Oxycodone	
	Vorapaxar		

- [a] Expert consultation may be considered. In some cases, dose reduction of the concomitant medication may be an appropriate management strategy
- [b] Before prescribing ritonavir-boosted nirmatrelvir (Paxlovid) for a patient receiving this immunosuppressant, the patient's specialist provider(s) should be consulted, given the significant drug-drug interaction potential between ritonavir and the narrow therapeutic index agent and because close monitoring may not be feasible.

Remdesivir

- Reduces hospitalization and death by 87%
- When given within 7 days of symptom onset.
  - 200 mg on day 1 and 100 mg on day 2 and 3
- IV treatment: 30-minute infusion
- Contraindicated in patients with:
  - GFR < 30
  - Decompensated cirrhosis

Molnupiravir

- **Reduces hospitalization**
  - By 30%
- **Initiate within 5 days of symptom onset**
  - 800mg twice a day
  - Patients aged ≥18 years only
- **Not recommended for use in pregnant patients**
  - Discretion in females with childbearing potential
- Reliable, correct, and consistent contraception
  - **Women:** during treatment and for 4 days after the last dose of molnupiravir
  - **Men:** during treatment and for at least 3 months after the last dose of molnupiravir

AI/AN Mortality Disparities

In-Hospital Mortality Disparities among AI/AN, Black and White patients with COVID-19

Retrospective analysis of the Mississippi Inpatient Outpatient Data System:

- 18,731 adult patients (≥ 18 years old), hospitalized with COVID 3/1/2020-12/31/2020
- 1.2% AI/AN, 49.1% Black, 48.7% White

Mortality

- Black patients had a 75% lower odds of in-hospital mortality compared with AI/AN (OR 0.25)
- White patients had a 77% lower odds of in-hospital mortality compared with AI/AN (OR 0.23)
- AI/AN with COVID-19 had lower co-morbidity risk scores that Black or white patients

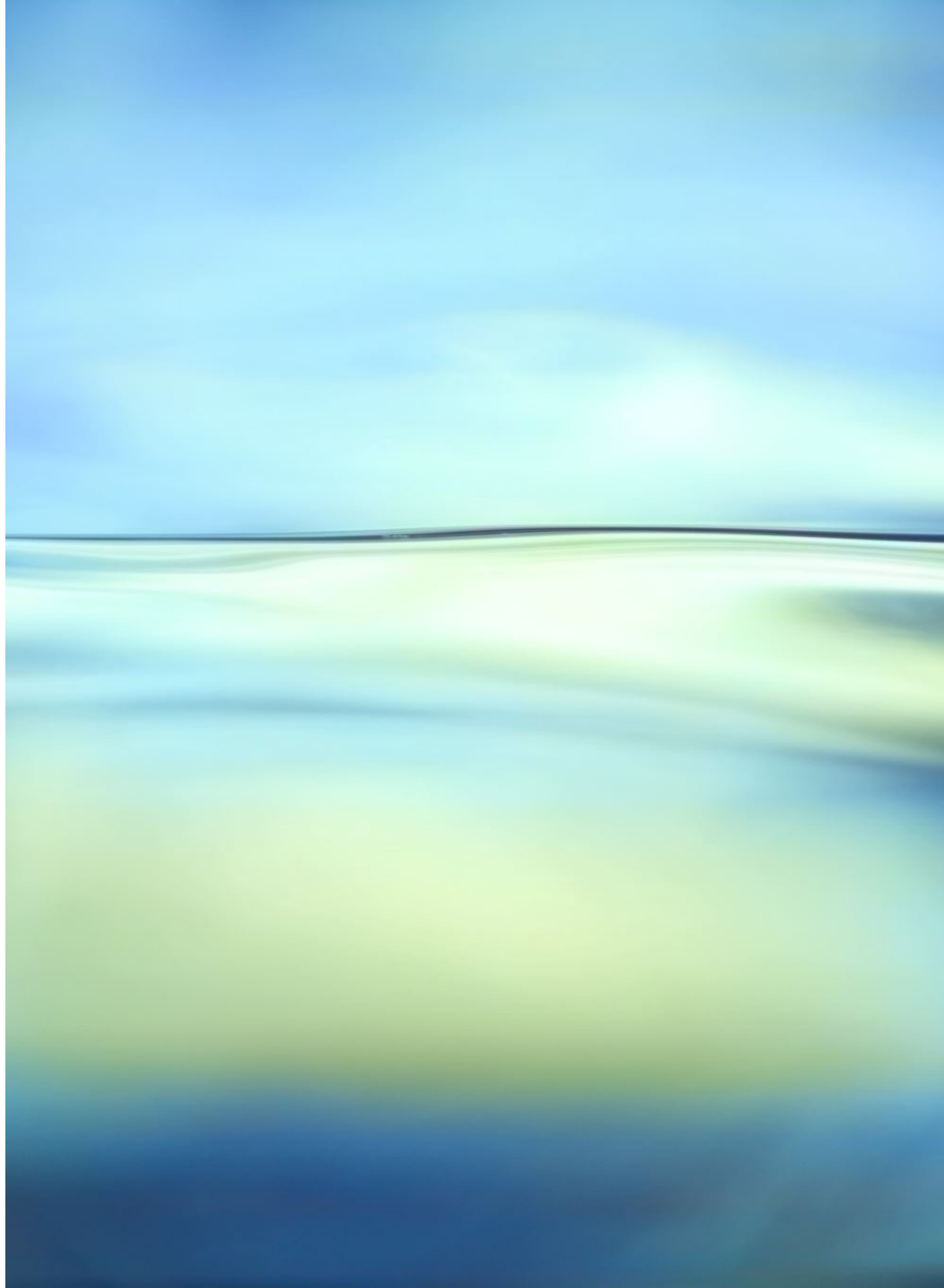
“Despite empirical associations between reduced comorbidity risk scores and reduced odds of inpatient mortality, AI/AN patients were significantly more likely to die in the hospital of COVID-19 than Black or White patients at every level of comorbidity risk”

Musshafen et al, Jama Network Open, 3/30/2022

Vaccine Update
Update March 29, 2022

Second mRNA booster allowed for certain immunocompromised individuals and people over the age of 50 who received an initial booster dose at least 4 months ago

- Adults who received a primary vaccine and booster dose of Johnson & Johnson's Janssen COVID-19 vaccine at least 4 months ago may now receive a second booster dose using an mRNA COVID-19 vaccine.



The Landscape of Candidemia During the Coronavirus Disease 2019 (COVID-19) Pandemic

Seagle EE, Jackson BR, Lockhart SR, Georgacopoulos O, Nunnally NS, Roland J, Barter DM, Johnston HL, Czaja CA, Kayalioglu H, Clogher P, Revis A, Farley MM, Harrison LH, Davis SS, Phipps EC, Tesini BL, Schaffner W, Markus TM, Lyman MM. Clin Infect Dis. 2022 Mar 9;74(5):802-811.

Background

Candidemia is associated with high morbidity, prolonged hospital stay, and substantial healthcare costs

In the US

- The estimated incidence of candidemia is 9 cases per 100 000 population
- The estimated case fatality ratio of candidemia is 25–30% [1,2,3]

Most cases are healthcare-associated, and common risk factors include

- Presence of central venous catheters (CVCs) or other indwelling medical devices
- Abdominal surgeries
- Malignancies
- Hemodialysis
- Diabetes
- Receipt of immunosuppressive medications (including corticosteroids), total parenteral nutrition, and systemic antibacterial medications
- Injection drug use (non–healthcare-associated risk factor)

1. Toda M, Williams SR, BerkowEL, et al. Population-based active surveillance for culture-confirmed candidemia—four sites, United States, 2012-201. *MMWR Surveill Summ* 2019; 68:1–15.
2. Strollo S, Lionakis MS, Adjemian J, Steiner CA, PrevotsDR. Epidemiology of Hospitalizations associated with invasive candidiasis, United States, 2002 *Emerg Infect Dis* 2016; 23:7 **3**. Pappas PG, Lionakis M , Arendrup MC , Ostrosky-ZeichnerL, Kullberg. Invasive candidiasis. *Nat Rev Dis Primers*2018; 4 :18026

Background

The recent emergence of COVID-19 has resulted in an unprecedented public health crisis and brought about new healthcare challenges, including the development of fungal coinfections, such as candidemia.

Risk factors for developing severe COVID-19 (many of which are also risk factors for candidemia) include:

- Older age
- Malignancies
- Obesity
- Immunocompromised conditions
- Chronic diseases including diabetes

Patients hospitalized for COVID-19 have greater exposure to known healthcare-associated candidemia risk factors such as:

- Indwelling medical devices
- Antibacterial medications

Background

Candidemia coinfection in patients with COVID-19 has been increasingly described in the literature.

Among patients with COVID-19 admitted to the ICU in 1 US hospital, 8.9% developed candidemia, which resulted in longer ICU stays compared with patients with COVID-19 without candidemia.

Higher overall incidence of candidemia incidence during the pandemic has been reported as well as higher frequency among patients hospitalized for COVID-19 receiving corticosteroids compared with patients without COVID-19.

Prior analyses have been limited by small sample sizes and geographic scope.

This study used available data from a nationally representative US candidemia surveillance system to describe characteristics among patients with candidemia during the COVID-19 pandemic.

The Landscape of Candidemia During the Coronavirus Disease 2019 (COVID-19) Pandemic

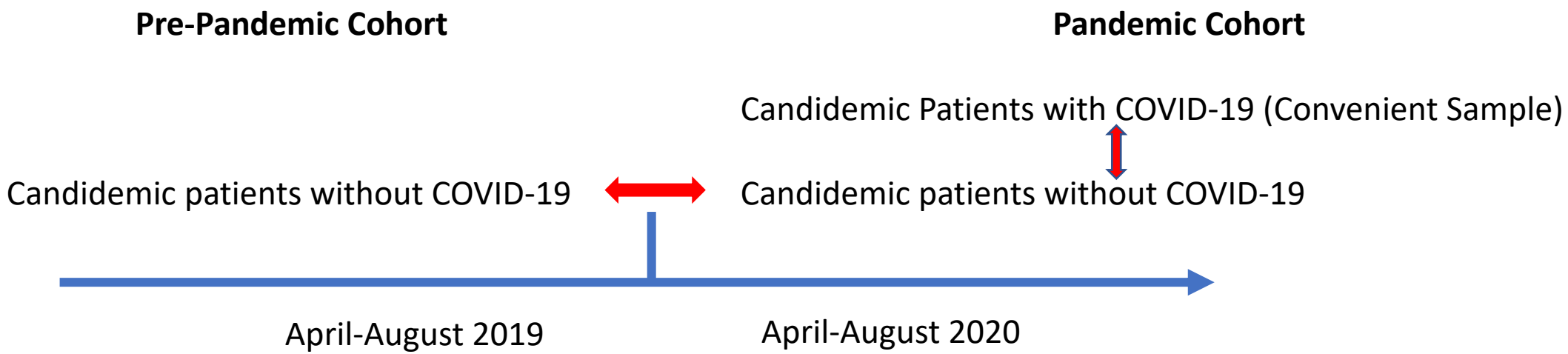
Methods

- Case-level analysis using population-based candidemia surveillance data collected through the CDC Emerging Infections Program during April–August 2020

Objective

- To compare characteristics of candidemia patients with and without a positive test for COVID-19 in the 30 days before their *Candida* culture using chi-square or Fisher's exact tests.

Methods: Data and Definition of Analysis



Cohort's demographics, underlying conditions history of smoking, alcohol abuse, and IDU, *Candida* spp. and microbiological factors, clinical characteristics, healthcare exposures; time between *Candida* culture, SARS-CoV-2 positive test, and hospital admission and discharge; and case fatality rate were compared.

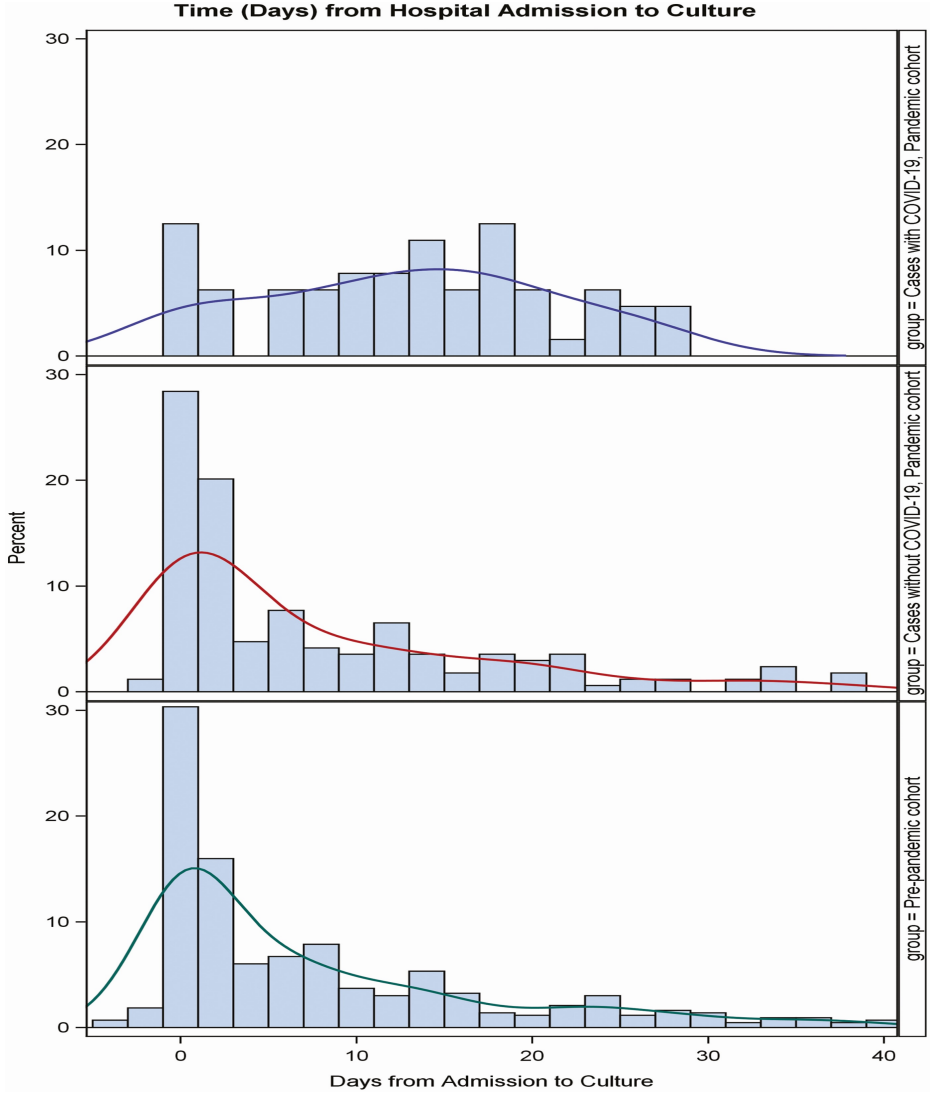
Differences in these characteristics between those with and without COVID-19 were assessed using chi-square or Fisher's exact tests ($\alpha < 0.05$).

The Landscape of Candidemia During the Coronavirus Disease 2019 (COVID-19) Pandemic: *Results*

Of the 251 candidemia patients included, 64 (25.5%) were positive for SARS-CoV-2

- Liver disease, solid-organ malignancies, and prior surgeries were each >3 times more common in patients **without** COVID-19 coinfection
- ICU–level care, mechanical ventilation, having a central venous catheter, and receipt of corticosteroids and immunosuppressants were each >1.3 times more common in patients with COVID-19.
- All-cause in-hospital fatality was 2 times higher among those with COVID-19 (62.5%) than without (32.1%).

Figure 1. Histogram of time (days) between candidemia-associated hospital admission and initial Candida culture among ...



- The median number of days between hospital admission and.
  initial *Candida* blood culture differed between those
  - With COVID-19 (14 days [IQR = 7–18 days])
  - Without (4 days [IQR: 0–14 days]) COVID-19
- Additionally, patients with COVID-19 were significantly more likely to have had the specimen collected within the ICU (78.1% vs 38.0% without COVID-19; $P \leq .0001$).

Clin Infect Dis, Volume 74, Issue 5, 1 March 2022, Pages 802–811, https://doi.org/10.1093/cid/ciab562

The Landscape of Candidemia During the Coronavirus Disease 2019 (COVID-19) Pandemic: *Conclusions*

One-quarter of candidemia patients had COVID-19.

- These patients were:
  - Less likely to have certain underlying conditions and recent surgery commonly associated with candidemia
  - More likely to have acute risk factors linked to COVID-19 care, including immunosuppressive medications.

Given the high mortality, it is important for clinicians to remain vigilant and take proactive measures to prevent candidemia in patients with COVID-19.

Questions that are still unanswered

Candidemia incidence in patients with COVID-19
Incidence of systemic candidiasis in patients with COVID-19
Determining risk factors for Candidemia in patients with COVID-19 by comparing patients with COVID-19 with and without Candidemia
Determining if COVID-19 is an independent risk factor for candidemia
Determining coinfection risk factors and mortality in patients with C. auris infection
Determining Incidence and mortality of Candidemia in AI/AN patients with COVID-19
Determining role of antifungal therapy as preventive or preemptive treatment
Determining role of Infection Control Intervention as prevention