Outpatient Management of COVID-19

Jason Bowling, MD
Associate Professor
Infectious Disease
University of Texas Health San Antonio

Disclosures

Dr. Jason Bowling is a NIH ACTT co- investigator and sub-investigator for the Novavax SARS-CoV-2 vaccine trial and is a consultant, advisor, and has an executive role with Eli Lilly.

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For more information, please visit https://minorityhealth.hhs.gov/

Learning Objectives

1. Name and compare the 4 targeted COVID-19 therapies that can be used for treating outpatients with mild COVID-19 disease

2. Identify at least 2 credible online resources for updated treatment guidelines.

Daily Update for the United States

Cases
New Cases (Daily Avg)
89,698

Case Trends

Jul 2022 Aug 2022

Deaths
New Deaths (Daily Avg)
390

Death Trends

Jul 2022 Aug 2022

Hospitalizations
New Admissions (Daily Avg)
5,581

Admission Trends

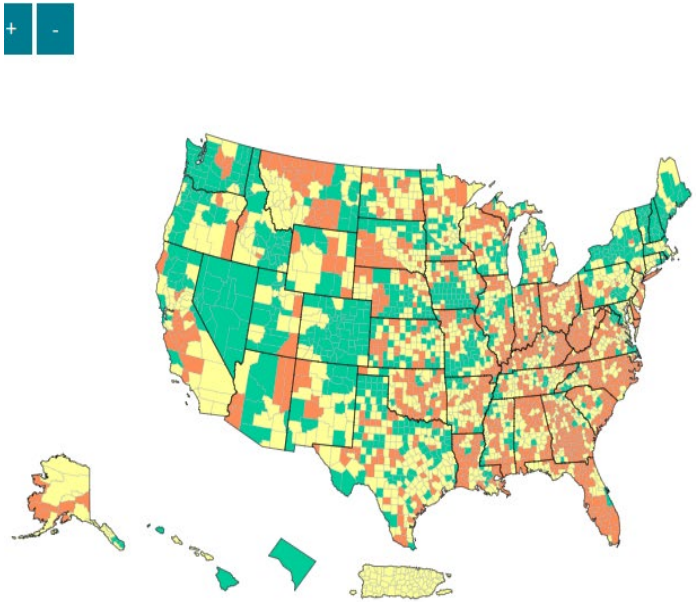
Jul 2022 Aug 2022

Vaccinations
% First Booster Dose
34.6%

People Age 5+

Total Cases	Total Deaths	Current Hospitalizations	Total First Booster Dose
93,647,250	1,036,604	32,512	108,217,633

CDC | Data as of: August 24, 2022 1:18 PM ET. Posted: August 24, 2022 2:41 PM ET



COVID-19 Community Levels in US by County

	Total	Percent	% Change
High	1092	33.88%	– 5.77%
Medium	1326	41.14%	0.59%
Low	805	24.98%	5.18%

How are COVID-19 Community Levels calculated?

CDC COVID Data Tracker: Home
Accessed 8-25-22

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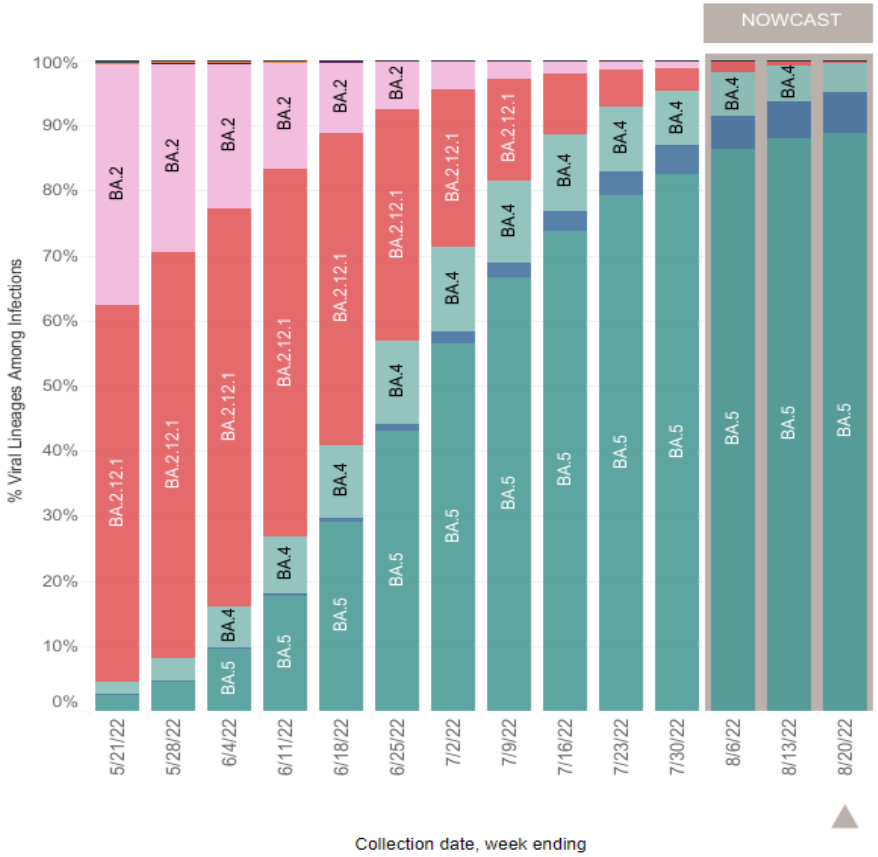
SARS-CoV-2 Variant Surveillance

United States: 5/15/2022 – 8/20/2022



United States: 8/14/2022 – 8/20/2022 NOWCAST

USA

WHO label	Lineage #	US Class	%Total	95%PI
Omicron	BA.5	VOC	88.9%	87.6-90.1%
	BA.4.6	VOC	6.3%	5.2-7.6%
	BA.4	VOC	4.3%	4.0-4.7%
	BA.2.12.1	VOC	0.5%	0.4-0.5%
	BA.2	VOC	0.0%	0.0-0.0%
	B.1.1.529	VOC	0.0%	0.0-0.0%
	BA.1.1	VOC	0.0%	0.0-0.0%
Delta	B.1.617.2	VBM	0.0%	0.0-0.0%
Other	Other*		0.0%	0.0-0.0%

* Enumerated lineages are US VOC and lineages circulating above 1% nationally in at least one week period. "Other" represents the aggregation of lineages which are circulating <1% nationally during all weeks displayed.
** These data include Nowcast estimates, which are modeled projections that may differ from weighted estimates generated at later dates
# AY.1-AY.133 and their sublineages are aggregated with B.1.617.2. BA.1, BA.3 and their sublineages (except BA.1.1 and its sublineages) are aggregated with B.1.1.529. For regional data, BA.1.1 and its sublineages are also aggregated with B.1.1.529, as they currently cannot be reliably called in each region. Except BA.2.12.1, BA.2 sublineages are aggregated with BA.2. Except BA.4.6, sublineages of BA.4 are aggregated to BA.4. Sublineages of BA.5 are aggregated to BA.5.

CDC COVID Data Tracker: Variant Proportions – accessed 8-25-22

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Prevention

Vaccination and Testing

Full vaccination with booster

- Best protection against severe disease, hospitalization, death

mRNA vaccine protection against omicron variant

- With booster
- 82% protective against urgent care/ER encounter
- 90% protective against hospitalization

Stay up to date on vaccination

Test if you have symptoms

https://www.cdc.gov/mmwr/volumes/71/wr/mm7104e3.htm

https://www.cdc.gov/coronavirus/2019-ncov/your-health/covid-by-county.html

Monoclonal Antibodies

Pre-exposure prophylaxis EUA

- Tixagevimab/cilgavimab (Evusheld)
- Monoclonal antibody with long half life (repeat q 6 months if needed)
- Two intramuscular injections
- EUA for
  - Immunocompromised
  - Hx of severe allergy to COVID-19 vaccine
  - **NOT** a substitute for vaccination in those eligible
  - Can receive Evusheld 2 weeks after vaccination
- Warnings
  - Hypersensitivity, including anaphylaxis
  - Bleeding disorders (IM injection)
  - Cardiovascular events – prior hx cardiac disease
- Supply available

Treatment

What should all outpatients diagnosed with COVID-19 receive?

Supportive care – hydration, sleep, anti-pyretics or analgesics as needed if safe to do so

Evaluation for benefit from targeted COVID-19 therapies – are they at high risk for progression to severe disease?

Instructions on how to reduce transmission (mask, isolation, etc)

Warning signs/symptoms to see further evaluation

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COVID-19 specific therapies

For Patients at high risk of progressing to severe COVID-19

NIH recommended prioritization:

Nirmatrelvir/ritonavir (Paxlovid)

Followed by Remdesivir

Alternative therapies:

- Bebtelovimab
- Molnupiravir

Both nirmatrelvir/ritonavir and remdesivir have high clinical efficacy in phase 3, randomized placebo-controlled trials

Factors impacting choice of therapy: clinical efficacy and availability, feasibility of IV administration, potential for drug-drug interactions, prevalence of variants of concern (especially for monoclonal Abs)

Oral antivirals

Nirmatrelvir/ritonavir (Paxlovid; Pfizer)

- 88% decrease in hospitalization/death (EPIC-HR trial)
- *If given within 5 days of symptoms*

EUA – for the treatment of mild to moderate disease

- 12 yo and older (and 40 kg or more)
  - + SARS-CoV-2 test
  - High risk of progress to severe COVID-19
- Should be started within 5 days of symptoms

Contraindications – on meds highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions

https://www.fda.gov/media/155050/download

Nirmatrelvir/ritonavir (Paxlovid)
Established and Potentially Significant Drug Interactions

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

- Alpha1-adrenoreceptor antagonist: alfuzosin
- Analgesics: pethidine, 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

Nirmatrelvir/ritonavir (Paxlovid)
Established and Potentially Significant Drug Interactions

Contraindicated with 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.

Cannot be started immediately after discontinuation of any of the following medications due to the delayed offset of the recently discontinued CYP3A inducer

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

https://www.fda.gov/media/155050/download

Other nirmatrelvir/ritonavir issues

"Paxlovid rebound"

Recurrence of mild symptoms and viremia

No indication to start a second course of nirmatrelvir/ritonavir

Patient should re-isolate for another 5 days

To date, reported cases have not progressed to severe disease

Other side effects:

Dysgeusia ("Paxlovid mouth"), diarrhea, elevated AST/ALT

Early Remdesivir in non-hospitalized patients

87% reduction in hospitalizations/death (PINETREE trial)

IV infusion daily X 3 days

Logistics currently difficult

Age 28 days and older (3 kg or more)

Consider when

- In setting of limited oral antiviral supply
- Nirmatrelvir/ritonavir contraindicated due to drug-drug interactions (ex. Solid organ transplant recipient pts)

Administer within 7 days of symptoms

https://www.nejm.org/doi/full/10.1056/NEJMoa2116846

Monoclonal Antibodies

Previous agents (Regeneron, Lilly)
- Not enough activity against Omicron variant

Not sufficiently active against Omicron BA.4 and BA.5 subvariants
- Sotrovimab (GSK)

Active against omicron and variants
- *Bebtelovimab* (Lilly) https://www.fda.gov/media/156152/download

Treatment for
- Mild to moderate COVID-19 disease
- >/= 18 yo
- At high risk of progression to severe COVID-19
- Within 7 days of symptom onset

Priority tiers by risk group
- Age, immune status, clinical risk factors
- https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-patient-prioritization-for-outpatient-therapies/

Oral antivirals

Molnupiravir (Lagevrio, Merck)

- 30% decrease in hospitalization/death (MOVe-OUT trial)
- *If given within 5 days of symptoms*

EUA – for the treatment of mild to moderate disease

- **18 yo and older**
  - + SARS-CoV-2 test
  - High risk of progress to severe COVID-19
- Should be started within 5 days of symptoms

Warnings –

- Embryo-fetal toxicity: not recommended in pregnancy.
- Bone and cartilage toxicity

https://www.fda.gov/media/155054/download

NIH Multicenter Outpatient Study

ACTIV6 Study

Criteria

- >/= 30 yo
- + SARS-CoV-2 test within 10 days
- At least 2 COVID-19 symptoms for 7 days or less

Treatment arms

- Fluvoxamine vs. placebo
- “Touchless” study – Medications shipped to patient with remote monitoring

https://activ6study.org

What should outpatients **NOT** receive for COVID-19?

NIH recommends against dexamethasone or other systemic glucocorticoids in patients who do not require hospital admit or O2

May cause harm

Also should **NOT** be used:

Hydroxychloroquine

Antibacterial therapy (azithromycin or doxycycline)

Ivermectin

August 18: N Engl J Med 2022;387:599-610

COVID-OUT Trial Phase 3, RCT: none of ivermectin, fluvoxamine, metformin reduced hypoxemia, ER visit, hospitalization, or death

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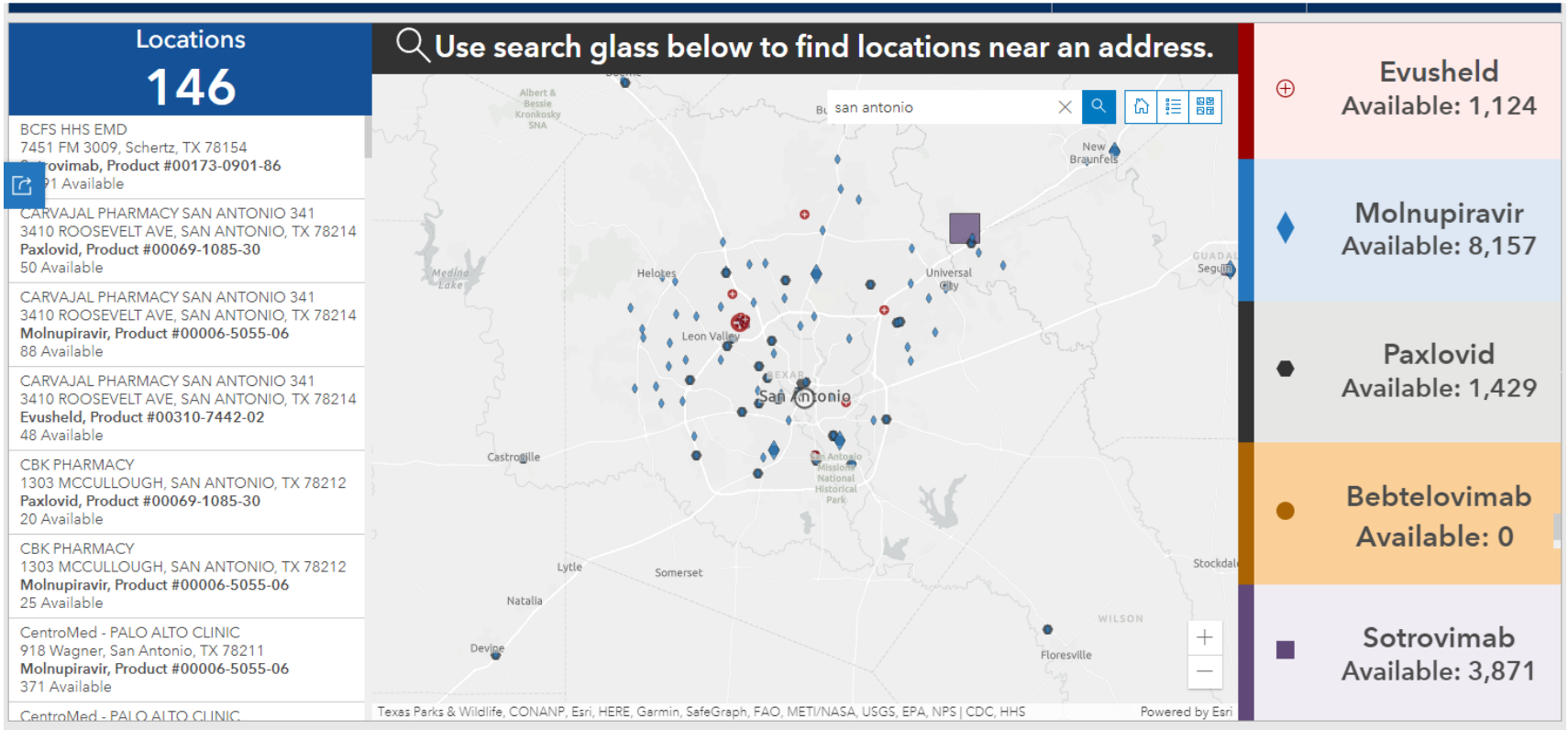
Summary of targeted therapies

Agent	Considerations
Nirmatrelvir/ritonavir	ASAP and within 5 days of symptom onset WATCH: drug-drug interaction; rebound possible
Remdesivir	ASAP and within 7 days of symptom onset WATCH: requires IV administration
Bebtelovimab	ASAP and within 7 days of symptom onset WATCH: alternative – not as effective, requires IV
Molnupiravir	ASAP and within 5 days of symptom onset WATCH: mutagenic – not for pregnant or children; not as effective

COVID-19 Therapeutics Locator (arcgis.com)



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

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Outpatient Treatment

NIH guidelines

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

IDSA guidelines

https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

STRAC.org, Outpatient Strategies by ID Leads

Outpt_Strategies_ID_Leads_REV2_14Jul2271_Final.pdf (strac.org)

Practice Takeaways

Vaccines remain an important method of decreasing risk of severe disease and death.

- Patients should be up-to-date and don't forget about Tixagevimab/cilgavimab (Evusheld) for highly immunocompromised patients

All patients diagnosed with COVID-19 should be instructed on how to reduce transmission to others and have risk assessment to determine benefit from targeted COVID-19 therapies

Nirmatrelvir/ritonavir and remdesivir are preferred therapies and are highly effective in high risk patients.

- Good to be familiar with how to use these agents and available supply in your local area.

Questions?