Welcome & Introductions

Dana Wollins, DrPH, MGC
Vice President
Clinical Affairs & Guidelines
Infectious Diseases Society of America

- 93rd in a series of calls, initiated in 2020 as a forum for information sharing among frontline clinicians caring for patients with COVID-19.

- The views and opinions expressed here are those of the presenters and do not necessarily reflect the official policy or position of the CDC or IDSA. Involvement of CDC and IDSA should not be viewed as endorsement of any entity or individual involved.

- This webinar is being recorded and can be found online at www.idsociety.org/cliniciancalls.
1. COVID-19: Situation Update, Emerging Variants & Implications for Therapeutics

**Update on COVID-19 Epidemiology**
Pragna Patel, MD, MPH
Captain, U.S. Public Health Service
Chief Medical Officer (acting)
Coronavirus and Other Respiratory Diseases Division (proposed)
National Center for Immunization and Respiratory Diseases
U.S. Centers for Disease Control & Prevention

**COVID-19 Therapeutics Update**
Meghan E. Pennini, PhD
Director, Therapeutics
HHS Coordination Operations and Response Element (H-CORE)/
Administration for Strategic Preparedness and Response
U.S. Department of Health and Human Services

2. Monkeypox: Clinical Characteristics and Treatment Options for Severe Disease

**Introduction**
Agam Rao, MD, MPH
Captain, U.S. Public Health Service
Poxvirus Subject Matter Expert
Multinational Monkeypox Response
U.S. Centers for Disease Control and Prevention

**Encephalitis in a Patient With Severe Monkeypox**
Matthew J. Copeland, DO
Assist. Professor of Medicine, Georgetown University Medical Center
Attending Physician, Division of Infectious Diseases, Medstar Georgetown
University Hospital

**Ocular Monkeypox**
Vivian Huang, MD, MPH
Assist. Medical Director, Office of Epidemiology and Data Services
Maricopa County Department of Public Health

**Severe Monkeypox in a Patient With Newly Diagnosed HIV**
Robert L. Atmar, MD, FIDSA
Chief, Infectious Diseases, Ben Taub Hospital
Professor, Medicine-Infectious Disease
Baylor College of Medicine

**Nelson Nicolasora, MD**
Clinical Assist. Professor, Division of Infectious Disease
Banner University Medical Center – Phoenix
University of Arizona
Question?
Use the “Q&A” Button

Comment?
Use the “Chat” Button
Update on COVID-19 Epidemiology

Pragna Patel, MD MPH
Acting Chief Medical Officer
Coronavirus and Other Respiratory Viruses Division (proposed), NCIRD, CDC

CDC/IDSA Clinician Call
September 24, 2022
Omicron variant

- Unusually large number of mutations across the SARS-CoV-2 genome
  - 45-52 amino acid changes, deletions, or insertions:
    - 15 within receptor binding domain
- More infectious and transmissible than the Delta variant
- Resist neutralization by vaccine- and infection-induced antibodies
- Evade innate immunity
- Resistance to some therapeutics

Daily Change in COVID-19 Cases, United States

January 22, 2020* - September 22, 2022

95,795,378
Total Cases Reported

95,014
New Cases Reported**

53,377
Current 7-Day Average**
Sep 16, 2022 - Sep 22, 2022

62,578
Prior 7-Day Average**
Sep 09, 2022 - Sep 15, 2022

-14.7%
Change in 7-Day Average

Peaks in Single Day and 7-Day Average of New Cases**

<table>
<thead>
<tr>
<th>Peak</th>
<th>Single Day</th>
<th>7-Day Average</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Date</td>
</tr>
<tr>
<td>1st Peak</td>
<td>34,809</td>
<td>24-Apr-20</td>
</tr>
<tr>
<td>2nd Peak</td>
<td>77,215</td>
<td>17-Jul-20</td>
</tr>
<tr>
<td>3rd Peak</td>
<td>292,566</td>
<td>08-Jan-21</td>
</tr>
<tr>
<td>4th Peak</td>
<td>78,525</td>
<td>17-Apr-21</td>
</tr>
<tr>
<td>5th Peak</td>
<td>198,035</td>
<td>01-Sep-21</td>
</tr>
<tr>
<td>Latest</td>
<td>1,272,900</td>
<td>10-Jan-22</td>
</tr>
</tbody>
</table>

*Graph displays data for Mar 01, 2020, to date. The totals include cases reported since Jan 22, 2020.
**The histogram, total of new cases in the last 24 hours, and 7-day averages do not include historical cases retrospectively that are not yet attributed to the correct date of report. Of 658,910 historical cases reported retrospectively, none were reported on Sep 22, 2022; none in the current week; and 8 in the prior week.

Date Source: CDC Case Surveillance, state-level aggregated COVID-19 Cases; HHS Protect; Visualization: CC CPR DEO Situational Awareness Public Health Science Team

Last Updated: Sep 23, 2022, 09:50
Weekly Trends in COVID-19 Associated Hospitalization Rates by Age group

Since April, hospitalization rates in older age increased relative to other age groups.
Hospitalization Rate Ratios by Age Group
COVID-NET, June 2021 – May 31, 2022

Adults aged 18-49 years are the reference group for all periods

Havers et al. MMWR 2022; 71(34);1085-1091. https://www.cdc.gov/mmwr/volumes/71/wr/mm7134a3.htm?s_cid=mm7134a3_w
# Characteristics of hospitalized adults ≥18 years
COVID-NET, June 20, 2021 – May 31, 2022

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Delta</th>
<th>Omicron BA.1</th>
<th>Omicron BA.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Median (years)</td>
<td>59.9</td>
<td>63.8</td>
<td>70.5</td>
</tr>
<tr>
<td>Likely COVID-19-related*</td>
<td>95.5</td>
<td>87.8</td>
<td>85.4</td>
</tr>
<tr>
<td><strong>Risk Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any underlying medical condition</td>
<td>89.3</td>
<td>91.7</td>
<td>95.1</td>
</tr>
<tr>
<td>Immunosuppressive condition</td>
<td>11.0</td>
<td>16.0</td>
<td>19.2</td>
</tr>
<tr>
<td>Long-term care facility</td>
<td>5.7</td>
<td>9.0</td>
<td>14.2</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of stay (days, median)</td>
<td>4.8</td>
<td>3.9</td>
<td>3.3</td>
</tr>
<tr>
<td>ICU admission</td>
<td>24.3</td>
<td>17.9</td>
<td>13.2</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>13.5</td>
<td>7.6</td>
<td>5.7</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>12.4</td>
<td>7.5</td>
<td>5.1</td>
</tr>
</tbody>
</table>

### Trends during BA.1 & BA.2
- Median age increased
- Underlying conditions more prevalent
- Clinical outcomes less severe

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* COVID-19–related illness as a likely reason for admission is indicated by COVID-19 diagnosis or symptoms consistent with COVID-19 as the chief complaint or reason for admission in the history of present illness. Non-COVID-19 reasons for admission included planned inpatient surgery or procedures, psychiatric admission needing acute medical care, trauma, other, and unknown. Havers et al. MMWR 2022; 71(34):1085–1091. [https://www.cdc.gov/mmwr/volumes/71/wr/mm7134a3.htm?s_cid=mm7134a3_w](https://www.cdc.gov/mmwr/volumes/71/wr/mm7134a3.htm?s_cid=mm7134a3_w)
Factors Associated with Severe Outcomes Among Immunocompromised Adults Hospitalized for COVID-19 — COVID-NET, 10 States, March 2020–February 2022

SUPPLEMENTARY TABLE 2. Association of immunocompromise and vaccination status* with in-hospital death among patients hospitalized for COVID-19, by SARS-CoV-2 variant predominant period† — COVID-NET, 10 States, 5 March 1, 2020–February 28, 2022

<table>
<thead>
<tr>
<th>Comparison groups</th>
<th>Pre-Delta</th>
<th>Delta</th>
<th>Omicron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunocompromised versus nonimmunocompromised</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>1.37 (1.02-1.82)**</td>
<td>1.31 (0.74-2.30)</td>
<td>1.04 (0.57-1.91)</td>
</tr>
<tr>
<td>Vaccinated*</td>
<td>2.91 (1.69-5.02)$^{55}$</td>
<td>2.51 (1.30-4.83)$^{55}$</td>
<td>0.99 (0.61-1.63)</td>
</tr>
<tr>
<td>Vaccinated versus unvaccinated*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>1.76 (0.82-3.75)</td>
<td>1.23 (0.57-2.64)</td>
<td>1.09 (0.44-2.72)</td>
</tr>
<tr>
<td>Nonimmunocompromised**</td>
<td>0.44 (0.23-0.84)**</td>
<td>0.42 (0.28-0.64)$^{55}$</td>
<td>0.84 (0.46-1.57)</td>
</tr>
</tbody>
</table>

Abbreviations: aOR, adjusted odds ratio; COVID-NET = COVID-19–Associated Hospitalization Surveillance Network.

Pre-Delta period, March 1, 2020–June 26, 2021; Delta period, June 27–December 18, 2021; Omicron period December 19, 2021–February 28, 2022. ** p-value <0.05. Singson et al. MMWR 2022 71 (27) https://www.cdc.gov/mmwr/volumes/71/wr/pdfs/mm7127a3-H.pdf
In July 2022, compared to people who are up to date with COVID-19 vaccination, monthly rates of COVID-19-associated hospitalizations were 4.8x higher in Unvaccinated Adults Ages 18 Years and older.
COVID-19 Weekly Deaths per 100,000 Population

https://covid.cdc.gov/covid-data-tracker/#demographicsovertime

In June 2022, unvaccinated people ages ≥5 years had 8X higher COVID-19-associated death rates compared to those with at least one booster dose.

This was a decrease from ~20X during January-March 2022.
Immunogenicity: Moderna bivalent booster

- Met superiority criteria* in participants ≥18 years with or without evidence of infection on day 29

*Superiority criterion: the lower bound of the 95% CI for GMR is >1.0

https://www.medrxiv.org/content/10.1101/2022.06.24.22276703v1.full.pdf
Surveillance for Variants of Concern - NOWCAST

- **BA.5**
  - Predominant in all regions

- **BA.4.6**
  - More prevalent in east and southeast, and HHS Region 7

- **BF.7**
  - Most prevalent in HHS Region 1

- **BA 2.75.2**

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Variants of Concern: Spike Protein R346T Mutation

- Evusheld is expected to have reduced potency against lineages with R346T substitutions (BA.4.6, BF.7, BA.2.75.2)
- Bebtelovimab retains potency

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
COVID-19 Therapeutics Update

Meghan Pennini, PhD
Director, Therapeutics
HHS Coordination Operations and Response Element (H-CORE)/ASPR

September 24, 2022

https://aspr.hhs.gov/COVID-19/Therapeutics/Pages/default.aspx

Unclassified/For Public Distribution
CDC NOWCAST for the week ending 17 Sep 22:

- **BA.5** – 84.8%
  - Predominant all regions
- **BA.4.6** – 10.3%
  - Highest in R7 (17.8%)
  - R346T spike RBD substitution + N658S
- **BF.7** (1.7%) separated from BA.5
  - R346T
- **BA.2.75** (1.3%) separated from BA.2
  - Some with R346T (BA.2.75.2)
### Efficacy of COVID-19 Therapeutics against Variants

#### Bebtelovimab (treatment)

<table>
<thead>
<tr>
<th>Lineage</th>
<th>Country First Identified</th>
<th>WHO Nomenclature</th>
<th>Key Substitutions Tested</th>
<th>Fold Reduction (Pseudotyped VLPS)</th>
<th>Fold Reduction (Authentic Virus)</th>
<th>Country of Origin</th>
<th>WHO Nomenclature</th>
<th>Key Substitutions Tested</th>
<th>Fold Reduction in Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>BA.1.1</td>
<td>Botswana</td>
<td>Omicron (BA.1)</td>
<td>+S373P+S375F+K417N+N440K+G446S+S477N+T478K+E484A+Q493R+G496S+Q498R+N501Y+Y505H</td>
<td>132- to 183-fold#</td>
<td>12- to 30-fold</td>
<td>USA</td>
<td>Omicron [BA.2]+L452Q</td>
<td>+S373F+S375F+K417N+N440K+G446S+S477N+T478K+E484A+Q493R+G496S+Q498R+N501Y+Y505H</td>
<td>ND</td>
</tr>
<tr>
<td>BA.2</td>
<td>Multiple country origin</td>
<td>Omicron (BA.2)</td>
<td>+S373P+S375F+K417N+N440K+S477N+T478K+E484A+Q493R+G496S+Q498R+N501Y+Y505H</td>
<td>5-fold</td>
<td>ND</td>
<td>USA</td>
<td>Omicron [BA.2]+L452Q</td>
<td>+S373F+S375F+K417N+N440K+S477N+T478K+E484A+Q493R+G496S+Q498R+N501Y+Y505H</td>
<td>ND</td>
</tr>
<tr>
<td>BA.3</td>
<td>Multiple country origin</td>
<td>Omicron (BA.3)</td>
<td>+S373P+S375F+K417N+N440K+S477N+T478K+E484A+Q493R+G496S+Q498R+N501Y+Y505H</td>
<td>16-fold</td>
<td>ND</td>
<td>USA</td>
<td>Omicron [BA.4]+L452Q</td>
<td>+S373F+S375F+K417N+N440K+S477N+T478K+E484A+Q493R+G496S+Q498R+N501Y+Y505H</td>
<td>ND</td>
</tr>
</tbody>
</table>

https://www.fda.gov/media/156152/download

- Preliminary reports showing retained activity against BA.4/5 for Veklury® & oral antivirals (Paxlovid, Lagevrio®)
- Evusheld activity against BA.4.6 is likely diminished

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#### Evusheld (PrEP)

<table>
<thead>
<tr>
<th>Lineage</th>
<th>Country First Identified</th>
<th>WHO Nomenclature</th>
<th>Key Substitutions Tested</th>
<th>Fold Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>BA.1.1</td>
<td>Botswana</td>
<td>Omicron (BA.1)</td>
<td>+S373P+S375F+K417N+N440K+G446S+S477N+T478K+E484A+Q493R+G496S+Q498R+N501Y+Y505H</td>
<td>424-fold</td>
</tr>
<tr>
<td>BA.2</td>
<td>Multiple country origin</td>
<td>Omicron (BA.2)</td>
<td>+S373P+S375F+K417N+N440K+S477N+T478K+E484A+Q493R+G496S+Q498R+N501Y+Y505H</td>
<td>176-fold</td>
</tr>
<tr>
<td>BA.2.12.1</td>
<td>United States</td>
<td>Omicron (BA.2.12.1)</td>
<td>+S373P+S375F+K417N+N440K+S477N+T478K+E484A+Q493R+G496S+Q498R+N501Y+Y505H</td>
<td>5-fold</td>
</tr>
<tr>
<td>BA.3</td>
<td>Multiple country origin</td>
<td>Omicron (BA.3)</td>
<td>+S373P+S375F+K417N+N440K+S477N+T478K+E484A+Q493R+G496S+Q498R+N501Y+Y505H</td>
<td>16-fold</td>
</tr>
<tr>
<td>BA.4/5</td>
<td>Multiple country origin</td>
<td>Omicron (BA.4/5)</td>
<td>+S373P+S375F+K417N+N440K+S477N+T478K+E484A+Q493R+G496S+Q498R+N501Y+Y505H</td>
<td>33- to 65-fold</td>
</tr>
</tbody>
</table>

https://www.fda.gov/media/154701/download

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### Unclassified/For Public Distribution

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### Unclassified/For Public Use

### Unclassified/For Public Distribution
# Efficacy of COVID-19 Therapeutics against Variants

**Table 1. Efficacy of Monoclonal Antibodies and Antiviral Drugs against Omicron Subvariants in Vitro.**

<table>
<thead>
<tr>
<th>Subvariant</th>
<th>Mean Neutralization Activity of Monoclonal Antibody†</th>
<th>Susceptibility to Antiviral Drugs‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Imdevimab</td>
<td>Casirivimab</td>
</tr>
<tr>
<td>Reference‡</td>
<td>ng per milliliter</td>
<td>μmol</td>
</tr>
<tr>
<td>BA.1</td>
<td>&gt;50,000</td>
<td>&gt;50,000</td>
</tr>
<tr>
<td>BA.1.1</td>
<td>&gt;50,000</td>
<td>&gt;50,000</td>
</tr>
<tr>
<td>BA.2</td>
<td>329.0</td>
<td>&gt;50,000</td>
</tr>
<tr>
<td>BA.2.12.1</td>
<td>238.1</td>
<td>&gt;50,000</td>
</tr>
<tr>
<td>BA.4</td>
<td>132.6</td>
<td>&gt;50,000</td>
</tr>
<tr>
<td>BA.5</td>
<td>583.4</td>
<td>&gt;50,000</td>
</tr>
</tbody>
</table>

*The antibodies that were used in this analysis are listed by their commercial names for readability although they were produced in the authors' laboratories in their generic formulations. Omicron subvariants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are listed according to the World Health Organization labels for the Pango lineage.
† Individual monoclonal antibodies were tested at a starting concentration of 50,000 ng per milliliter on 50% focus reduction neutralization testing. The monoclonal antibody combinations were tested at a starting concentration of 10,000 ng per milliliter for each antibody.
‡ The susceptibility to antiviral drugs was measured as the 50% inhibitory concentration of 50,000 ng per milliliter of triplicate reactions. GS-441524 is the main metabolite of remdesivir and EIDD-1931 is the active form of molnupiravir, both of which are RNA-dependent RNA polymerase inhibitors. Nirmatrelvir (PF-07321332) is a protease inhibitor.
¶ The reference strain was SARS-CoV-2/UT-NC002–1T/Human/2020/Tokyo.

- Data against more recent variants (BA.4.6, BA.2.75.2) pending
Preliminary data: Evusheld Loses Neutralization Potency against BA.4.6
Bebtelovimab Maintains Potency

**Pseudovirus Data:**
Preprints: Wang (above);
R346[T/S/I] mutations impact Evusheld activity; BF.7

Preprint: Sheward
BA.4 vs BA.4.6: Example of Impact of R346T to Evusheld

**BA.4**
- 6 BA.4 mutations within binding footprint: 440, 452, 477, 478, 486, 484

***Evusheld neutralizes BA.4***

**BA.4.6**
- 7 BA.4.6 mutations within binding footprint: R346T, 440, 452, 477, 478, 484, 486

***Evusheld potency likely significantly reduced***

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### Key

<table>
<thead>
<tr>
<th>Key</th>
</tr>
</thead>
<tbody>
<tr>
<td>mAb binding site</td>
</tr>
<tr>
<td>mAb Resistance Residues</td>
</tr>
<tr>
<td>BA.4/BA.4.6 RBD Mutations</td>
</tr>
<tr>
<td>mAb Binding/RBD Lineage Mutations</td>
</tr>
</tbody>
</table>

**Other Lineages with R346T: BF.7, BA.2.75.2**

Note: BA.2.75 w/o R346T is likely susceptible to Evusheld
Pseudovirus neutralization of Omicron variants by Vaccine Sera

- Immune evasion: D614G < BA.2 ~ BA.2.75 < BA.4/5 ~ BA.4.6 ~ BA.4.7 ~ BA.5.9

- R346T, R346S, and N658S in the background of BA.4/5 had minimal impact on vaccine sera neutralization

Wang et al, bioRxiv 2022.09.05.506628; https://doi.org/10.1101/2022.09.05.506628
BA.4.6 US Regional Epidemiology Data

BA.4.6
BA.4.6+BF.7

Regional proportions from specimens collected the week ending 9/17/2022.
US Territories not shown are included in HHS regions:
PR, VI - Region 2
AS, FM, GU, MH, MP, PW - Region 9

Highlight Variant
BA.4.6 × Download Data

Lineages called using pangolin v4.1.2, pangolin-data v1.14 and usher v0.5.4.

Unclassified/For Public Distribution

Updated September 16, 2022
Unclassified/For Public Distribution
## Summary of COVID-19 Preventative Agents & Treatments

<table>
<thead>
<tr>
<th>No Illness</th>
<th>Exposed</th>
<th>Mild to Moderate Symptoms</th>
<th>Hospital Admission</th>
<th>ICU Admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline health status, no infection</td>
<td>Per CDC Close Contact Criteria</td>
<td>Not hospitalized</td>
<td>Hospitalized, no act. medical problems</td>
<td>Hospitalized, high flow oxygen/non-invasive ventilation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hospitalized, not on oxygen</td>
<td>Hospitalized, mechanical ventilation/ECMO</td>
</tr>
</tbody>
</table>

### COVID-19 Vaccines
- None currently authorized for use in any US state or territory.

### Monoclonal Antibodies for PrEP
- Evusheld (tixagevimab + cilgavimab, AZ)

### Oral Antivirals
- Paxlovid (nirmatrelvir + ritonavir, Pfizer) – Alternative
- Lagevrio (molnupiravir, Merck) – Alternative

### Monoclonal Antibodies
- Bebtelovimab (Lilly) – Alternative

Please see [NIH Current Inpatient Therapies](https://www.covid19treatmentguidelines.nih.gov/therapies/)

- There is currently **ample supply** of all therapeutics – every eligible patient should have access to these medications.

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**Therapeutic Management of Nonhospitalized Adults With COVID-19**

**Therapeutic Management of Hospitalized Adults With COVID-19**
Bebtelovimab Transition to Commercial Market: bebtelovimab product replacement initiative now available

- **How it works**: A provider who has commercial supply and treats an under or uninsured patient with a purchased dose can request a replacement dose, at no charge, from USG

- **Provider site should**:
  - Have **used all their USG supply** acquired through the HHS distribution program
  - Have **purchased commercial bebtelovimab** and **attest** to using a purchased dose for an under or uninsured patient
  - **Charge a reasonable administration fee** for bebtelovimab for that patient
    - Consideration to waive or reduce fee to be reasonable for the patient being treated

- **Process**: Requests made in the Health Partner Ordering Portal (HPOP)
  - Provider attests to verifying the patient who received treatment was uninsured (has no insurance coverage/can’t afford treatment) or underinsured (can use guidelines for other federal or local programs)

- **How to access**: Providers already registered in HPOP have immediate access; others should contact their state or territorial health department to access HPOP
  - Replacement dose must replace a commercially purchased dose
  - Replacement dose shipped to provider is commercially labelled supply and can be used for any patient; payment is allowable for the replacement dose received
Bebtelovimab Supply Options

Where should I access Bebtelovimab for my administration site?

For my patients with Medicare or Medicaid or who have insurance but are not underinsured or for patients who can afford treatment without insurance:
- Commercially Purchased Product (direct from AmerisourceBergen)

For my patients who are uninsured or underinsured, once my USG supply is depleted and I’ve administered a commercially purchased dose to treat that patient with consideration of administration fees waived or reduced:
- Bebtelovimab Product Replacement Initiative (request to HHS through HPOP)

For my patients who are uninsured or underinsured, where USG supply is available and commercial product has not been purchased:
- State-Allocated USG Supply (request to state/territorial DOH)
Related Resources

- HHS Therapeutics Homepage
- Product Expiration Date Extensions
- Test to Treat Initiative webpage and Fact Sheet
- Test to Treat Site Locator and Digital Tool Kit
- General Therapeutics Locator
- HHS Clinical Implementation Guide
- Outpatient Therapeutics Decision Aid
- Side-by-Side Overview of Outpatient Therapeutics
- ASPR Regional Emergency Coordinators
- CMS reimbursement information for mAbs
- CMS reimbursement information for oral antivirals
Update: Severe manifestations of monkeypox—United States

CDC/IDSA Clinician Call
Saturday, Sept 24th, 2022

Agam Rao, MD
CAPT, U.S. Public Health Service
Monkeypox Subject Matter Expert, CDC
Up to 94% of patients report recent male-to-male sexual contact in the last 3 weeks*

Race/Ethnicity
(9/21/22)

https://www.cdc.gov/poxvirus/monkeypox/response/2022/demographics.html
Signs and symptoms (9/21/22)

Most common:
- Rash (98%)
- Fever (76%)
- Malaise (74%)
- Chills (71%)
- Enlarged lymph nodes (68%)
- Myalgia (65%)

Other:
- Rectal Pain (51%)
- Tenesmus (28%)
- Proctitis (15%)

https://www.cdc.gov/poxvirus/monkeypox/response/2022/demographics.html
Management of most patients

• Most immunocompetent patients recover with pain management* and other supportive care

• Tecoviromat should be considered for some conditions†
  ▪ Severe disease: hemorrhagic disease, large number of lesions, sepsis, encephalitis, ocular or periorbital infections, other conditions requiring hospitalization
  ▪ Lesions involving anatomic areas that could cause severe infection (e.g., pharynx, penile foreskin, vulva, vagina, urethra, anus)
  ▪ Lesions in persons who are at high risk for severe disease
    ✤ Immunocompromise
    ✤ Pediatric populations
    ✤ Pregnant or breastfeeding
    ✤ Condition affecting skin integrity

*https://www.cdc.gov/poxvirus/monkeypox/clinicians/pain-management.html
†https://www.cdc.gov/poxvirus/monkeypox/clinicians/treatment.html
Cases decreasing—United States, September 21, 2022
Severe infections

- Demographics of affected patients
  - 100% male
  - Ages 21–58 years (median= 32 years)
  - Majority Hispanic or non-Hispanic Black
  - Most immunocompromised due to advanced HIV
  - 2 patients receiving chemotherapy for cancer

- Progressive illness
  - >100 lesions; new lesions despite treatment
  - Coalesced lesions and necrosis
  - Significant lymphadenopathy
  - Hemodynamic instability
  - Sepsis and secondary infections
CDC Clinical Consultations

• Available 24/7 through health departments
• Can facilitate
  ▪ Treatment with stockpiled VIGIV and in the future, brincidofovir
  ▪ Determination of antibody response (i.e., serology)
  ▪ Evaluation of certain biopsy and autopsy specimens for orthopoxviruses
  ▪ Genome sequencing, including to evaluate for tecoviromat resistance
  ▪ Case specific advice based on accumulated clinical knowledge

• Learn together about clinical manifestations so that national guidance about use of stockpiled therapeutics and other countermeasures can be made accordingly

• >175 case specific consultations
Spectrum of questions

- Interpretation of unexpected OPX+ test result
- Use of tecoviromat in patients with renal insufficiency
- Suspicion for recurrent monkeypox
- Myocarditis
- Ocular infections
- Encephalitis
- Severe illness in severely immunocompromised persons
Next steps, CDC

• Continue to answer clinical inquiries and provide clinical consultations, therapeutics, and laboratory testing
• Gather information about patient outcomes, including severely ill patients with monkeypox
• Develop interim guidance about use of stockpiled therapeutics (informed by input from clinical experts)
• Promote assistance provided by CDC for management of severe cases
• Increase clinician awareness of severe cases
Acknowledgments

• Clinicians caring for patients with monkeypox
• Health departments investigating cases
• CDC Multinational Monkeypox Outbreak Response
  ▪ Clinical Consultations Team
  ▪ Clinical Guidance Team
  ▪ Vaccine Implementation Team
  ▪ Worker Safety Team
  ▪ Infection Prevention and Control Team
  ▪ Special Case Investigations Team
Severe Monkeypox in a Patient with Newly Diagnosed HIV

Robert L. Atmar, M.D.
Andrew DiNardo, M.D.
Baylor College of Medicine
Clinical Case - History

- 26 yo man (MSM) presented to outside hospital 12 days PTA with rash on flank and back pain
  - Smoked hookah with female friend diagnosed with monkeypox
  - Flank lesions swabbed
  - Prescribed Medrol dose-pack for back pain
  - Notified a few days later of orthopox PCR (+) test → isolate at home

- Day of admission (evening) complained of progressive symptoms
  - Rash involved all of body with black central eschar in some ulcerated lesion
  - Increased dyspnea on exertion, dry cough, post-tussive emesis
  - Continued back pain; painful neck swelling
  - Last sexual partner – 3 months earlier
Clinical Case – Physical Examination

- VS: T 102.8 F, P 128, BP 134/78, RR 20
- Diffuse rash involving face, trunk, extremities; central ulceration/eschar; some necrotic/gangrenous (dry)
- HEENT – facial lesion; oral ulcerations, no eye involvement
- Neck – large tender mass with overlying induration in left neck
- Lungs – Clear
- Cor – Tachycardic
- Abd – no HSmegaly
- Ext – no edema, clubbing
- Neuro – Alert, fully oriented, no focal sensory/motor findings
Clinical Case – Laboratory (initial)

- **Na**: 126 mM
- **BUN/creat**: 30.9/1.4 mg/dL
- **AST/ALT**: 40/19 U/L
- **Tot. bili**: 1.2 mg/dL
- **H/H**: 12.7/36.2 (MCV 78)
- **WBC**: 30.1 (92% PMNs)
- **Platelets**: 140K
- **PT/INR**: 16.3/1.3

- **U/A**: 1+ protein, 1+ ketones, 1+ bilirubin; 0 WBCs, 2 RBC/HPF
- **HIV Ag/Ab combo – POSITIVE**
  - Viral load – 878K
  - **CD4**: 79
  - **CD4%**: 3%
- **Syphilis screen**: negative
- **Ferritin**: 5417 ng/mL
- **Troponin I**: <0.03
- **Blood cultures**: 1/4 bottles corynebacteria
Clinical Case – Initial Radiology

- Admit CXR – no acute abnormality

- CT neck – 6.9 x 7.7 x 9.8 cm dense heterogeneous mass in left neck; multiple deep cervical nodes
Clinical Case – Hospital Course

• HD#2, next morning – consented to TPOXX
• Flexible nasolaryngoscopy – thrush
• HD#2, afternoon – increasing somnolence; evaluation by MICU; fully oriented and protecting airway
  • Non-contrast CT head: no mass lesion
• HD#2, evening/night: progressive confusion/stupor – transfer to MICU with elective intubation for airway protection
• HD#3, early morning: 1st dose IV TPOXX administered
• HD#3, morning: septic shock requiring pressor support, increasing creatinine (1.7); good ventilation/oxygenation
• HD#3, morning: generalized tonic-clonic seizure
Clinical Case – Hospital Course

• Problems: Septic shock with organ failure; encephalopathy/encephalitis?
• Diff dx: monkeypox vs. AIDS-associated OI vs. both
• Empiric treatment for bacterial and OIs; diagnostic studies unrevealing for OI
• Consult CDC for consideration of VIGIV
• Progressive hypotension increasing pressor requirement
• HD#4 – received VIGIV
• HD#5 – dilated, unresponsive pupils, no gag
• HD#6 – Brain scan without cerebral perfusion
Case Summary

• Rapidly progressive illness when presented in patient with previously undiagnosed HIV infection/AIDS

• Autopsy pending

• Opportunities during management
  • Check for evidence of HIV infection in risk groups
  • Avoid high dose steroids in treatment of symptoms
  • Counsel patient to seek care with progressive symptoms
MPOX associated encephalomyelitis

Matthew J. Copeland, DO
Assistant Professor of Medicine, Georgetown University Medical Center
Attending Physician, Division of Infectious Diseases, Medstar Georgetown University Hospital
34-year-old generally healthy man

**Day of Illness (DoI) 2:** Seen at local emergency room with 2 days of diffuse pustular rash (hands, arms, legs, torso), low grade fever, and myalgias. Discharged home to quarantine while awaiting Orthopox PCR testing. PCR swab for Orthopox returns positive (later confirmed MPOX).

- ~DoI 4: Starts to notice LE weakness, balance trouble, and difficulty with urination
- DoI 5: Presents to local ER, found to have LE flaccid paralysis, decreased rectal tone, and urinary hesitancy
- DoI 6: Develops obtundation requiring intubation and is transferred to our hospital

Denies: Respiratory symptoms, dysuria, rectal pain, ocular complaints, hearing changes, diarrhea, vomiting, dysphagia/odynophagia, facial weakness
Medical History

Past Medical History:
1) Early latent syphilis ~6 months prior to illness (treated with single dose IM Penicillin 2.4mil units)
2) Chlamydial proctitis ~6 months prior to illness (treated with doxycycline x 7 days)

Surgical history: tooth extraction in his 20’s; No prior spinal surgery or injections

Social history:
• Identifies as a gay man, in monogamous relationship with male partner
• Travel to NYC ~1 week prior to onset of rash and Texas ~2 weeks prior to onset of rash; no known MPOX contacts
• No recent vaccinations; previously vaccinated against polio and COVID-19 (3 doses mRNA)
• No prior smallpox vaccination
• No GI illness prior to onset
• No significant animal contact, including bites/scratches

Family history: No known history of neurologic disease or familial disorders
Laboratory studies (serum)

CMP: Cr 0.94, AST 29, ALT 58, Tbili 0.7, protein 8.1, globulin 3.4
CBC: WBC 11.3 (ANC 8K, ALC 2.5K, Mono 700), H/H 14.7/44.2, PLT 327 K
CRP 6 (normal 0-3)
ESR 26
CPK: 238
HIV 4th generation screen and RNA PCR: negative
RPR negative
GC/CT NAAT from urine, pharynx, rectum negative
WNV IgM negative
Lyme IgG negative
ANA negative
C-ANCA 1:20
Anti SM 1:80 and Anti Actin IgG 34
MOG IgG <1:10
AQP 4 Receptor Ab <1.5
ACE level: 24 (normal)
Vitamin B12: 950 (high)
Laboratory studies (CSF)

RBC: 4
WBC: 30 (89% Lymph, 11 % Mono)
Glucose 65
Protein 60
Meningoencephalitis panel negative
HSV/VZV PCR negative
Bacterial culture negative
Fungal/AFB stains negative
VDRL negative
Cryptococcal antigen negative
WNV IgM negative
Lyme IgG negative
Enterovirus PCR negative
Orthopox PCR negative (University of Washington)

Oligoclonal Bands: 3 (abnormal)
ACE level: normal
Aqp 4 Rec Ab negative
MOG Ab negative
NMDA IgG negative
Autoimmune/paraneoplastic panel negative
CT Abd/Pelvis: Rectal wall thickening c/w proctitis, enlarged pelvic lymph nodes

CT Chest: segmental and subsegmental PE in R lung vasculature
Imaging
Hospital Course

(Dol 7): Noted some loss of tone in UE, Starts PO Tecovirimat 600mg BID through OG tube, Starts IV methylprednisolone 1000mg

(Dol 9): Switched to IV Tecovirimat d/t concerns regarding absorption with tube feeds

(Dol 12): Modest improvement in cognition, MRI after 5 days IVMP with unchanged spinal/brainstem disease, IVIG started

(Dol 15): High, spiking fevers, IVIG stopped, treated for MSSA VAP

(Dol 19): MRI Brain wit progression of diffusion restriction through cerebellum and brainstem

(Dol 20): Starts plasma exchange

(Dol 22): Extubated

(Dol 24): Completes 14-day course of Tecovirimat, lesions crusted

(Dol 25): Normal strength UE and improvement in LE weakness; completes 5-day course PLEX

(Dol 26): Receives rituximab maintenance therapy

(Dol 31): Able to sit-stand twice from bed

(Dol 38): Able to transfer to bedside commode

(Dol 44): Ambulates 15 feet with assistance; lesions healed

(Dol 46): Discharged to acute rehab

(Dol 55): Able to complete most ADLs, ambulates with assistance
Final Presumed Diagnosis

MPOX associated encephalomyelitis
Autoimmune vs. CNS viral invasion

Questions this case presented:
- CNS penetration of Tecovirimat? PO vs. IV?
- Best test to evaluate for CNS involvement of MPOX? (PCR vs. IgM)
- Approach to auto-immune associated encephalomyelitis in the setting of active viral infection?
- Vaccination after immune mediated encephalomyelitis?

THANK YOU!
My ID, Neurology, Radiology, and PCCM colleagues at MGUH
Georgetown University Medical Center
The CDC MPOX Response Task Force
Public Health Perspective: TPOXX Program in Maricopa County, Arizona

Vivian Huang, MD, MPH
Assistant Medical Director, Office of Epidemiology & Data Services
Saturday, 9/24/2022, CDC/IDSA Clinical Call
TPOXX Consultations
7/7/22 – 8/22/22

• 221 total MPXV cases
• Provided 62 clinical consultations
• 41/221 cases treated = 18.6%
  • 18 (44%) HIV+
  • 2 (5%) peri-orbital, 1 (2%) orbital
• 9/221 cases hospitalized = 4.1%
  • (6 treated, 3 not treated)
Key Points:

• Process put in place for providers to obtain TPOXX
  • Providers could call to reach Med Epi to go over cases
• At the same time, staged TPOXX across Maricopa County at hospitals and clinics
• Early eye evaluation is important
29 year old male with HIV/AIDS on cART with recently diagnosed MPX and visual loss

Nelson Nicolasora, MD
Clinical Assistant Professor
Division of Infectious Disease
Banner University Medical Center – Phoenix
University of Arizona
Outpatient Timeline

- Reported encounter with a partner diagnosed with MPXV.
- Rash in face, trunk, extremities. MPX PCR negative.

Day 0

- Increasing conjunctival redness and constitutional SSx's.
- Rashes - some are scabbed, some fresh.
- Doxy, Pred eye gtts to left eye, Ophtho referral
- MPXV PCR of arm lesion (result: D15)

Day 10

- Initiating Rx's:
  - Tecovirimat

Day 17-19

- Increasing left eye pain, irritation, photosensitivity, and blurriness of vision.
- Admitted.
- Started on Trifluridine, Tecovirimat IV.

Day 21

- Trifluridine
Diagnostics

WBC 5.8  Hgb 13.2  Hct 39.2  platelet 254

Diff. Count.
PMN  74.6%
L  10.7%
M  11.3%

ALC 0.62

CMP normal
Meds:

Azithromycin, 500 mg, Oral, Daily

Biktarvy oral tablet, 1 tab, Oral, Daily

Megestrol 40 mg oral tablet, 200 mg= 5 tab, Oral, Daily

Promethazine 25 mg oral tablet, 25 mg= 1 tab, Oral, PRN

Docusate sodium-S 50 mg-8.6 mg oral tablet, 1 tab, Oral, BID
PMH:

5/2021: Diagnosed and treated for:
- HIV/AIDS - CD4 15 VL 132K, Rx Biktarvy
- PJP – Rx Bactrim, changed to Atovaquone for fever, did not comply with Pentamidine
- Giardiasis – Rx Metronidazole

1/27/2022 CD4 19 VL 4270

History of OA, degenerative disc disease, anxiety disorder, depression, and ADHD
• Felt cold
• No chills or fever
• No nausea or vomiting
• Moderate global headache
• No neck stiffness
• No chest pain or dyspnea
• No GI/GU symptoms

• Excessive tearing
• Visual loss, left eye
• Significant eye pain
• Significant photophobia, limits evaluation
• Bed-ridden
• Mild pre-auricular LAD
DAY 21 – DATE OF ADMISSION
Facial and periorbital lesions of MPXV
Day 21 – D1 in Hospital

Day 23 – D3 in Hospital
<table>
<thead>
<tr>
<th></th>
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<th>OS</th>
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<tbody>
<tr>
<td>Visual Acuity:</td>
<td>20/20</td>
<td>20/40</td>
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<tr>
<td>Pupils:</td>
<td>Eq &amp; Reactive</td>
<td>Eq &amp; Reactive</td>
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<tr>
<td>EOM’s:</td>
<td>Full</td>
<td>Full</td>
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<tr>
<td>Adnexae:</td>
<td>Normal</td>
<td>2 vesicles on forehead</td>
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<tr>
<td>Eyelids:</td>
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<tr>
<td>Conjunctiva:</td>
<td>Normal</td>
<td>3+ injected, mostly inferior</td>
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<tr>
<td>Cornea:</td>
<td>Normal</td>
<td></td>
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<tr>
<td>Ant Chamber:</td>
<td>Deep &amp; Clear</td>
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<tr>
<td>IOP:</td>
<td>NTP</td>
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</tr>
</tbody>
</table>
Ophthalmology Management

Ofloxacin (Ocuflox) ophth drops Q-4-h

Trifluridine ophth drops q-2-h Left Eye. Discussed with Katalina in pharmacy; non-formulary, not available in hospital. I discussed that these drops are generally available in outpatient pharmacies; she will urgently research and get the drops in house to start OS q-2-h

Erythromycin ophth q-6-h
Need to avoid topical steroids
Inpatient Timeline

Day 21

- Increased left eye irritation and pain, photosensitivity, and blurriness of vision.
- Right eye 20/20
- Left eye 20/40

Admitted. Started on Gancyclovir IV

- Decrease Trifluridine to q4H L eye, continue R eye TID x 1 week after discharge.
- CMV IgG negative – GCV Dc'd
- Skin lesions starting to involute.

Day 22

- Ulcer at 6 o'clock limbus has shrunken down to ~ 1 mm X 2 mm and superficial.
- Visual acuity unchanged.

- No involvement of right eye.
- Remainder of ophthalmological exam unremarkable.

Day 23

- Improved eye pain and photophobia
- Improved constitutional symptoms.

Discharged on:
- Trifluridine eye gtts;
- Erythromycin ointment;
- Tecovirimat po x 14 days.

- Biktarvy Atovaquone PCP PPx;
- FF-up.

Day 25-26
Severe conjunctivitis with corneal ulceration (4-6'oclock limbus), Hospital Day 2
Diagnostics

HIV VL  8190 copies per mL CD4 25 (2.7%), outpatient resistance testing sent
CRAG – negative
Syphilis screen - negative
Toxo IgG – negative
Coccidioides screen - negative
CMV PCR undetectable/ CMV IgG negative
Urine GC/chlamydia - negative
Hep B surface Ab - >1000, immune
Hep B surface Ag -NR
Hep C Ab - NR
Lessons Learned

Thornhill, et. Al. (NEJM 2022)
528 cases, 41% with HIV & 95% with HIV VL < 50 copies per mL.
3/217 nasal and eye (1% of all mucosal lesions)

20% incidence of conjunctivitis (Jezek JID 1987; Ogoina CID 2020; Farahat Ann Clin Micro 2022; Hughes IJID 2014).

3.6-7.5% keratitis (Ogoina CID 2020; Jezek WHO Bulletin 1988)

"Conjunctivitis" - tend to have more constitutional SSx (Hughes IJID 2014)

Mazzota et. al. (Journal of Infection 8/2022) - PCR + from conjunctival swab with replication-competent virus (grew in culture)
Lessons Learned

• False negative test, delay in results.

• Should one empirically treat while waiting for the test? Consider the host and the severity of illness? Consider the delay in getting the medication.

• A complete eye exam is necessary. Severe photophobia, eye pain and excessive tearing can potentially give a lower read on VA exam.

• Early ophthalmological evaluation is important.

• Maintain DDx.

• Hand hygiene to prevent autoinoculation.

• Care coordination and is key.
Update on COVID-19 Epidemiology: Pragna Patel
Pre-Delta period, March 1, 2020–June 26, 2021; Delta period, June 27–December 18, 2021; Omicron period December 19, 2021–February 28, 2022. ** p-value <0.05. Singson et al. MMWR 2022 71 (27) https://www.cdc.gov/mmwr/volumes/71/wr/pdfs/mm7127a3-H.pdf
https://www.cdc.gov/covid-data-tracker/#variant-proportions

COVID-19 Therapeutics Update: Meghan Pennini
https://www.biorxiv.org/content/10.1101/2022.09.05.506628; https://doi.org/10.1056/NEJMc2207519
Wang et al, bioRxiv 2022.09.05.506628; https://doi.org/10.1056/NEJMc2207519

Update: Severe Manifestations of Monkeypox: Agam Rao
https://www.cdc.gov/mmwr/volumes/71/wr/mm7132e3.htm?s_cid=mm7132e3_w
https://www.cdc.gov/poxvirus/monkeypox/response/2022/demographics.html
https://www.cdc.gov/poxvirus/monkeypox/clinicians/pain-management.html
https://www.cdc.gov/poxvirus/monkeypox/clinicians/treatment.html
An online community bringing together information and opportunities for discussion on latest research, guidelines, tools and resources from a variety of medical subspecialties around the world.

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Society for Critical Care Medicine
Society for Healthcare Epidemiology of America
Society of Hospital Medicine
Society of Infectious Diseases Pharmacists

www.COVID19LearningNetwork.org
@RealTimeCOVID19
#RealTimeCOVID19
FOR WHOM?
- Clinicians who have questions about the clinical management of COVID-19

WHAT?
- Calls from clinicians will be triaged by CDC to a group of IDSA volunteer clinicians for peer-to-peer support

HOW?
- Clinicians may call the main CDC information line at 800-CDC-INFO (800-232-4636)
- To submit your question in writing, go to www.cdc.gov/cdc-info and click on Contact Form
THANK YOU

We want to hear from you!
Please complete the post-call survey.

A recording of this call, slides and the answered Q&A will be posted at
www.idsociety.org/cliniciancalls
-- library of all past calls available --

Contact Us:
Dana Wollins (dwollins@idsociety.org)
Deirdre Lewis (dlewis@idsociety.org)