DISCLAIMER

Immune Deficiency Foundation (IDF) education events offer a wide array of educational presentations, including presentations developed by healthcare and life management professionals invited to serve as presenters. The views and opinions expressed by guest speakers do not necessarily reflect the views and opinions of IDF.

The information presented during this event is not medical advice, nor is it intended to be a substitute for medical advice, diagnosis or treatment. Always seek the advice of a physician or other qualified health provider with questions concerning a medical condition. Never disregard professional medical advice, or delay seeking it based on information presented during the event.
MISSION

Improving the diagnosis, treatment, and quality of life of people affected by primary immunodeficiency through fostering a community empowered by advocacy, education, and research.
VISION

IDF seeks to ensure that everyone in the U.S. affected by PI has a fully informed understanding of

1. the PI diagnosis that affects them,
2. all available treatment options,
3. the expected standard of care,
4. all their opportunities for connection and support within the PI community.
Questions?

https://community.primaryimmune.org/s/newask
800-296-4433
Get Connected Groups

https://primaryimmune.org/support-services

Virtual groups exclusively for individuals & families living with PI
IDF Forums

Coming soon to your home!

- September 14: SCID Compass Lunch & Learn: Gene Therapy Updates for ADA SCID
- September 15: Antibody Deficiency: What Does It Mean?
THANK YOU TO OUR SPONSORS

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HORIZON  accredo  octapharma
ADMA BILOGICS  AstraZeneca  Pharming
X4 Pharmaceuticals  KEDRION Biopharma  ENZYVANT  Chiesi
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Please see Important Safety Information on slides 2-5 and refer to GAMUNEX-C full Prescribing Information and XEMBIFY full Prescribing Information.
A WORD FROM OUR SPONSOR

Pharming

Immune Deficiency Foundation
Pharming Healthcare, Inc.

Brian Hartline, MD

Senior Director, Medical Affairs
Introduction to Pharming Healthcare

- A global, commercial stage biopharmaceutical company developing innovative protein replacement therapies and precision medicines for the treatment of rare diseases and unmet medical needs.
- Pharming’s main product candidate portfolio is focused on the rare diseases of hereditary angioedema (HAE), activated PI3Kδ syndrome (APDS) and Pompe disease.

For more information about Pharming, visit: pharming.com/
What is activated PI3Kδ syndrome (APDS)?

**APDS**
Is a Primary Immune Regulatory Disorder (PIRD)

Caused by variants in the genes *(PIK3CD or PIK3R1)* encoding subunits of PI3Kδ enzyme complex and affects both B and T cells

---

**Wide Range of Clinical Manifestations**

- Severe infections, permanent lung damage
- Severe swollen lymph nodes, spleen and liver
- Developmental delay, failure to thrive
- Severe, chronic herpes virus infections
- Enteropathy
- Lymphoma
- Autoimmunity including anemias & bleeding disorders

---

*Also known as PASLI (p110δ-activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency).
APDS, activated phosphatidylinositol 3-kinase δ syndrome; PASLI, p110δ-activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency; PIRD, primary immune regulatory disorder.

For more information on APDS, visit: [AllaboutAPDS.com](http://AllaboutAPDS.com)
Definitive diagnosis through genetic testing may change treatment

Pharming partnership with Invitae & Gene Matters

- **SPONSORED, NO-CHARGE GENETIC TESTING** – no cost to qualified patients in the USA and Canada
- **FAST** – results within 2 weeks on average (10-21 days)
- **DESIGNED TO BE EASY FOR PROVIDERS** – online form
- **DESIGNED TO BE EASY FOR PATIENTS** – blood draw kits (preferred), buccal swab kits, saliva kits, or mobile phlebotomy
- **COMPREHENSIVE** – choice of 429-gene Primary Immunodeficiency Panel, or 574-gene Inborn Errors or Immunity and Cytopenias Panel
- **SUPPORTED** – option for sponsored, no-charge genetic counseling provided by GeneMatters
- **FAMILY TESTING** – sponsored, no-charge genetic testing for blood relatives of patients with pathologic or likely pathologic variants

For more information: [allaboutapds.com/diagnosing-apds/](allaboutapds.com/diagnosing-apds/) or [navigateapds.com](navigateapds.com)
COVID-19 Update

September 1, 2022

Michele Pham, MD
Assistant Professor of Medicine
Associate Chief of Allergy & Immunology for Primary Immunodeficiency
University of California, San Francisco
Focuses

• SARS-CoV-2 Infections and Variants
• SARS-CoV-2 Vaccinations
• Preventative therapies
• Treatments for COVID-19
Daily Trends in COVID-19 Cases in the United States Reported to CDC

Likely underreporting in US because not all home tests are being reported. One study estimated that only 3% of results of all tests produced by 4 testing brands were voluntarily reported.
Daily Trends in Number of New COVID-19 Hospital Admissions in the United States

**Deaths**
- New Deaths (Daily Avg): 387

**Hospitalizations**
- New Admissions (Daily Avg): 5,255

**Death Trends**
- Jul 2022
- Aug 2022

**Admission Trends**
- Jul 2022
- Aug 2022

**Total Deaths**: 1,039,055
**Current Hospitalizations**: 29,963
U.S. COVID-19 Community Levels by County - CDC

As of August 25, 2022:
- High: 29.5%
- Moderate: 42.9%
- Low: 27.6%

The District of Columbia, Massachusetts, Nevada, and Rhode Island are the only jurisdictions to have all counties at low Community Levels.
Vaccination Rates

- 262,643,277 People who received at least one dose (79.1% of the U.S. population)
- 223,914,723 People who are fully vaccinated* (67.4% of the U.S. population)
- 48.5% Percentage of the Population ≥ 5 Years of Age with a 1st booster dose
- 33.7% Percentage of the Population ≥ 50 Years of Age with a 2nd booster dose
Variants Are Expected

**Current Variant of Concern = Omicron**

**PATHOGEN PROGRESSION**
This diagram shows how the coronavirus SARS-CoV-2 has evolved to spawn several related variants. The latest are BA.4 and BA.5 along the Omicron lineage, which has dominated infections this year.

- Other variants
  - Alpha
  - Gamma
  - Omicron
    - BA.1
    - BA.2
    - BA.4
    - BA.5
    - BA.2.12.1
  - Beta
  - Delta
  - Delta-plus

**OMICRON’S NEW IDENTITIES**
Cases of COVID-19 are rising again in South Africa, after the emergence of Omicron variants called BA.4 and BA.5.

Based on data from NextStrain.

https://www.nature.com/articles/d41586-022-01240-x
These variants have been the most able to escape the antibodies raised through infection or vaccination by previous variants.

Subvariants
BA.5 - 88.7%
BA.4 - 7.5%

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

• BA.4 and BA.5 have mutations in the spike protein (area responsible for infection (helps virus enter) and an important area immune responses are targeted)
  • causes them to elude immune responses
    • Allows them to infect people with prior immunity.
    • increasingly greater replication advantages → higher viral loads

• Small study using sera of people who were infected early on during Omicron, some of whom had been vaccinated:
  • Vaccinated+BA.1 infection had higher neutralization for BA.4 and BA.5 than unvaccinated + BA.1 infection
Omicron Subvariant of COVID-19 - BA.5 Variant

• Associated with less severe disease compared to other major variants
• Some studies have shown a reduced risk of
  • Hospitalization
  • Intensive care unit admission
  • In-hospital mortality
• While illness due to the Omicron may be milder, the high volume of cases continues to lead to high hospitalization rates and may result in excess burden on the health care system
COVID-19 Infection

• Incubation Period
  • Within 14 days following exposure
    • Most cases occurring 3-5 days after exposure
  • Varies by viral variant
    • Incubation period for the Omicron variant appears to be slightly shorter than other variants (3 days for symptom development after exposure)

• Period of infectiousness
  • Most infectious in the earlier stages of infection (starting a few days prior to the development of symptoms)
  • Transmission after 7 to 10 days of illness is unlikely

• Prolonged viral RNA shedding after symptom resolution is not clearly associated with prolonged infectiousness.
  • Prolonged shedding of SARS-CoV-2 has been reported in patients who are immunocompromised.
    • General population 11 days
    • Immunodeficient patients 20 days
Symptoms of BA.4 and BA.5
Similar to prior SARS-CoV-2 variants

- Cough
- Fatigue
- Runny nose
- Sore throat
- Headache

- Shortness of breath
- Gut symptoms
- Fever
Poor awareness of Omicron Infection in Adults

- Adult employees and patients enrolled in a COVID-19 blood study in Los Angeles – of those who had serological evidence of a recent Omicron infection, 56% reported being unaware of their infection. 10% had mild symptoms they attributed to a common cold.
  - Testing positive between 9/15/21 and 5/4/22

• Suggests that low rates of Omicron variant infection awareness may be a key contributor to rapid transmission of the virus within communities

• Potentially good news that more people have had it then they realize – closer to herd immunity?

Joung JAMA 2022
Re-infection with COVID

- The highest reinfection rate was observed in the Omicron variant:
  - 30x more frequent in Omicron variant than the Alpha variant
  - 10x more frequent in the Delta Variant

- Study in Turkey found that reinfection was 0.46% in Alpha, 1.16% in Delta and 13% in Omicron variants.
  - 16.5% of reinfection cases caught COVID-19 for the second time 3–6 months after the first COVID-19 infection, 36.7% after 6–12 months, and 46.8% after >12 months

- Risks of re-infection
  - Emergence of new coronavirus variants
  - Natural waning immunity gained from vaccination or previous infections
  - Decrease in COVID-related precautions like mask wearing and physical distancing

- Reinfection with BA.5
  - Limited data to support whether a person can get BA.5 twice but it is unlikely that it would occur within 1 month of infection
  - In theory as your immunity wanes, you could be more susceptible again to the same virus (ex BA.5) but likely after months a new variant would emerge.

Ozudogru Ir J Med Sci. 2022
COVID-19 and immunodeficiencies

• Approximately 3% of Americans have immunocompromising conditions

• People who are immunocompromised are diverse and the severity of COVID-19 can vary significantly in this group
  • Those with additional issues, ex older, with lung disease, heart disease, renal disease may have a higher risk of severe COVID
  • Patients with innate immune system issues (IFN) and T cell issues may be at higher risk for severe COVID-19

• Lacking data on clinical outcomes in PID patients with omicron BA.5 infection
Prevention of Infection
Prevention of COVID-19

• COVID-19 vaccination
• Continuing to maintain precautions when possible
• Tixagevimab plus cilgavimab (Evusheld) as SARS-CoV-2 pre-exposure prophylaxis if eligible
Precautions

• Avoid those that are sick
• Physical distancing
• Wear a well-fitting, high quality mask or respirator (N95s and KN95s). Properly fitting respirators provide the highest level of protection.
• Avoid poorly ventilated or crowded indoor settings. Being outside is safer than being indoors
• When indoors with others, try to improve ventilation as much as possible – fans, open windows/doors, HEPA filters/HVAC systems
• Wash your hands often with soap and water or use a hand sanitizer that contains at least 60% alcohol.
COVID-19 Vaccines in the US

**mRNA vaccines:** gives your cells instructions (mRNA) to make a piece of S protein
- **BNT162b2** (Pfizer-BioNTech) - 95%/100%
- **mRNA-1273** (Moderna) – 94%/100%

**Adjuvanted recombinant protein vaccine:** contains proteins from virus. When your body sees the proteins it stimulates an immune response
- **NVX-CoV2373** (Novavax) – 89%

**Adenoviral vector vaccine:** Uses a different weakened virus to enter your cells, it delivers genetic material from the COVID-19 virus that gives your cells instructions to make copies of the S protein
- **Ad26.COV2.S** (Janssen/Johnson & Johnson) – 66%/85%

X/X = Efficacy in trials of vaccines in preventing symptomatic/severe COVID19
CDC vaccination recommendations for those with immunodeficiencies

- **Pfizer** (12 years+) and **Moderna** (18 years+) mRNA
  - 3 initial doses, 1st booster 3 months after 3rd dose and 2nd booster 4 months after 4th dose
    - Pfizer
      - 6mo – 4 years: 3 doses
      - 5-11 years: 3 doses + 1 booster
    - Moderna
      - 6mo-11 years: 3 doses

- **J&J** (18 years+) – 1 dose, mRNA 4 weeks after, 1st booster dose 2 months after, 2nd booster dose 4 months after

- **Novavax** (12 years +) – 2 initial doses, 1st booster
Immunogenicity and Tolerability of COVID-19 mRNA Vaccines in PID Patients with Functional B Cell Defects

SARS-CoV-2 specific T-cell response assessed by interferon gamma release assay

- 80.0% positive
- 66.7% positive

33 patients with humoral defect
- 15 patients with CVID
- 18 patients with other antibody deficiencies
- 63.6% received BNT162b2
- 30.3% received mRNA-1273

SARS-CoV-2 spike protein RBD IgG

- 80.0% positive
- 22.2% positive

Neutralizing activity
- ACE2 receptor blocking activity ≥50%

- 8.3% positive
- 25.0% positive

ACE2 – angiotensin-converting enzyme 2; CVID – common variable immunodeficiency; RBD – receptor binding domain; SAD – specific antibody deficiency; XLA – X-linked agammaglobulinemia
SARS-CoV-2 ACE2 blocking activity level in primary immunodeficiency disorder patients with functional B-cell defects

- CVID (n = 10)
- Specific antibody deficiency (SAD)/hypogammaglobulinemia (n = 4)
Breakthrough infections after vaccination can occur and are higher with Omicron

- substantially less likely to cause severe disease than infection in unvaccinated individuals
- lower number of symptoms
- shorter duration of symptoms
- lower likelihood of persistent symptoms for >28 days
- higher likelihood of asymptomatic infection compared with infection in unvaccinated individuals

Studies suggest that vaccine protection against INFECTION wanes over time but protection against HOSPITALIZATION and SEVERE COVID-19 remains high, especially in those who have received boosters

Uptodate Accessed 8/30/22, Nanduri MMWR 2021, Tenforde MMWR 2021

For Immediate Release: August 31, 2022
Bivalent SARS-CoV2 Vaccine Boosters

• Both Pfizer and Moderna’s bivalent boosters include
  1. an mRNA component of the original strain to provide an immune response that is broadly protective against COVID-19
  2. an mRNA component in common between the omicron variant BA.4 and BA.5 lineages to provide better protection against COVID-19 caused by the omicron variant.

• Bivalent vaccine doses
  • Pfizer – 30-μg dose – 12+years
  • Moderna – 50-μg dose – 18+years

Bivalent SARS-CoV2 Vaccine Boosters

• FDA’s decision is based on:
  • Extensive safety and effectiveness data for each of the monovalent mRNA COVID-19 vaccines
  • Safety and immunogenicity data obtained from a clinical study of a bivalent COVID-19 vaccine that contained mRNA from omicron variant BA.1 lineage
    • “non-inferior neutralizing antibody response” against the original SARS-CoV-2 virus
    • good immune response against the latest omicron subvariants BA.4 and BA.5
  • Pre-clinical data obtained using a bivalent COVID-19 vaccine that contained mRNA of the original strain and mRNA in common between the BA.4 and BA.5 lineages of the omicron variant
    • strong neutralizing antibody response against the Omicron BA.1, BA.2, BA.4 and BA.5 subvariants, as well as the original virus

Bivalent SARS-CoV2 Vaccine Boosters

• Can receive if at least 2 months out from last COVID primary dose or booster dose
• Mixing is OK
• US government has already ordered 170 million doses
• Anticipated roll out next week/mid September
• Monovalent mRNA COVID-19 vaccines are not authorized as booster doses for individuals 12+ years
• Stay tuned!
Timing

• Timing with relation to non-COVID-19 vaccines - any time and if needed can be given at the same time with other vaccines
  • In a randomized trial, frequency of adverse effects and immunogenicity were largely similar when a COVID-19 vaccine (BNT162b2 or ChAdOx1) was given with either a flu vaccine or placebo
• Timing with relation to IVIG/ScIg Therapy – anytime
• Timing with relation to Evusheld – 2 weeks before or anytime after Evusheld
Evusheld – tixagevimab + cilgavimab

- PREVENTS Infection
- Engineered to be long-lasting – half life 90 days
- Tixagevimab 300 mg + cilgavimab 300 mg administered as 2 consecutive 3-mL intramuscular (IM) injections
- Repeat dose every 6 months
- Not a substitute for COVID-19 vaccination
- Most of the prior monoclonal antibodies that were used are no longer used for post-exposure prophylaxis since Omicron variants are not susceptible to these agents
Evusheld Authorized for:

• Individuals aged ≥12 years and weighing ≥40 kg
• Cannot have COVID-19 or recent exposure
• Moderately to severely immunocompromised
• May have an inadequate immune response to COVID-19 vaccination
Moderately or severely immunocompromised

Examples include:

• Been receiving active cancer treatment for tumors or cancers of the blood
• Received an organ transplant and are taking medicine to suppress the immune system
• Received chimeric antigen receptor (CAR)-T-cell therapy or received a stem cell transplant (within the last 2 years)
• Moderate or severe primary immunodeficiency (such as DiGeorge syndrome, Wiskott-Aldrich syndrome)
• Advanced or untreated HIV infection
• Active treatment with high-dose corticosteroids or other drugs that may suppress their immune response
Tixagevimab-Cilgavimab Evusheld for prevention of Covid-19

Risk factors for an inadequate response to Covid-19 vaccination

- Age ≥60 years
- Obesity
- Immunocompromised status
- Inability to receive vaccines without adverse effects
- Congestive heart failure
- Chronic obstructive pulmonary disease
- Chronic kidney disease
- Chronic liver disease

Persons at increased risk for SARS-CoV-2 exposure

- Health care workers (including staff working in long-term care facilities)
- Workers in industrial settings shown to increase risk of SARS-CoV-2 transmission
- Military personnel
- Students living in dormitories
- Others living together in close or high-density proximity

Levin NEJM 2021
All five cases of severe COVID-19 and both COVID-19 deaths occurred in the placebo group.
Side effects similar to those who received placebo

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Adverse Events (All Grades) Regardless of Causality Occurring in at Least 3% of Subjects Receiving EVUSHELD or Placebo in Primary Safety Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EVUSHELD N= 3,461</td>
</tr>
<tr>
<td>Headache</td>
<td>6%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4%</td>
</tr>
<tr>
<td>Cough</td>
<td>3%</td>
</tr>
</tbody>
</table>

Table 3  Cardiac SAEs Regardless of Causality in PROVENT with Onset Prior to Day 183 Using the Median 6-Month Data Cut-off Date

<table>
<thead>
<tr>
<th></th>
<th>EVUSHELD N= 3,461</th>
<th>Placebo N= 1,736</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with any cardiac SAE*</td>
<td>22 (0.6%)</td>
<td>3 (0.2%)</td>
</tr>
<tr>
<td>SAEs related to coronary artery disease or myocardial ischemia</td>
<td>10 (0.3%)</td>
<td>2 (0.1%)</td>
</tr>
<tr>
<td>Myocardial infarctions†</td>
<td>8 (0.2%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>SAEs related to cardiac failure†</td>
<td>6 (0.2%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>SAEs related to an arrhythmia†</td>
<td>4 (0.1%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Other (cardiomegaly, cardiomyopathy, and cardio-respiratory arrest)</td>
<td>3 (0.1%)</td>
<td>0</td>
</tr>
</tbody>
</table>

* One EVUSHELD recipient and one placebo recipient had two cardiac SAEs each.
† Includes the preferred terms angina pectoris, coronary artery disease, arteriosclerosis, troponin increased, acute myocardial infarction, and myocardial infarction.
‡ Includes the preferred terms acute myocardial infarction, myocardial infarction, and troponin increased (with a discharge diagnosis of myocardial infarction).
§ Includes the preferred terms cardiac failure congestive, acute left ventricular failure, cardiac failure, and cardiac failure acute.
¶ Includes the preferred terms atrial fibrillation, arrhythmia, paroxysmal atrioventricular block, and heart rate irregular.
### Table 1. Efficacy of Monoclonal Antibodies and Antiviral Drugs against Omicron Subvariants in Vitro.\(^\text{a}\)

<table>
<thead>
<tr>
<th>Subvariant</th>
<th>Mean Neutralization Activity of Monoclonal Antibody(\dagger)</th>
<th>Imdevimab</th>
<th>Casirivimab</th>
<th>Tixagevimab</th>
<th>Cilgavimab</th>
<th>Sotrovimab Precursor</th>
<th>Bebtelovimab</th>
<th>Imdevimab+ Casirivimab</th>
<th>Tixagevimab+ Cilgavimab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference(\dagger)</td>
<td></td>
<td>7.4</td>
<td>6.1</td>
<td>6.1</td>
<td>7.0</td>
<td>95.1</td>
<td>2.5</td>
<td>3.4</td>
<td>6.3</td>
</tr>
<tr>
<td>BA.1</td>
<td></td>
<td>&gt;50,000</td>
<td>&gt;50,000</td>
<td>1552.7</td>
<td>2916.9</td>
<td>40727.1</td>
<td>5.8</td>
<td>&gt;10,000</td>
<td>351.1</td>
</tr>
<tr>
<td>BA.1.1</td>
<td></td>
<td>&gt;50,000</td>
<td>&gt;50,000</td>
<td>603.5</td>
<td>&gt;50,000</td>
<td>3769.2</td>
<td>3.9</td>
<td>&gt;10,000</td>
<td>1296.8</td>
</tr>
<tr>
<td>BA.2</td>
<td></td>
<td>329.0</td>
<td>&gt;50,000</td>
<td>2756.6</td>
<td>16.9</td>
<td>&gt;50,000</td>
<td>3.3</td>
<td>835.1</td>
<td>34.6</td>
</tr>
<tr>
<td>BA.2.12.1</td>
<td></td>
<td>238.1</td>
<td>&gt;50,000</td>
<td>335.2</td>
<td>21.0</td>
<td>&gt;50,000</td>
<td>4.0</td>
<td>452.7</td>
<td>38.1</td>
</tr>
<tr>
<td>BA.4</td>
<td></td>
<td>132.6</td>
<td>&gt;50,000</td>
<td>&gt;50,000</td>
<td>53.6</td>
<td>&gt;50,000</td>
<td>2.9</td>
<td>459.1</td>
<td>37.8</td>
</tr>
<tr>
<td>BA.5</td>
<td></td>
<td>583.4</td>
<td>&gt;50,000</td>
<td>&gt;50,000</td>
<td>56.8</td>
<td>&gt;50,000</td>
<td>3.3</td>
<td>1093.1</td>
<td>192.5</td>
</tr>
</tbody>
</table>

Some in vitro studies suggest that tixagevimab-cilgavimab retains neutralizing activity against Omicron but at reduced levels.
Antibody Titers in IVIG/Sclg

• Companies making immunoglobulin products have published studies in the past (Summer 2021) noting that their donor pool has protective antibodies (from vaccination and infection)

• Products usually get to the patient 9-12 months from plasma collection to patient for infusion

• Antibodies from immunoglobulin replacement will add another layer of protection
COVID neutralizing antibodies in Hizentra

SARS-CoV2 antibody levels

Convalescent plasma

Miller JACI 2022
Testing
COVID-19 Testing

1. **Nucleic acid amplifications tests** (ex PCR tests)
   - Sensitivity and specificity are generally high, although performance varies based on the specific assay used, specimen quality, and duration of illness

2. **Antigen tests** (ex rapid antigen tests look for viral proteins)
   - less sensitive than NAATs

3. **Blood Tests** (ex antibodies to SARS-CoV-2 spike protein) – primarily used to identify patients who have had COVID-19 in the past
   - can identify patients with current infection who have had symptoms for three to four weeks.
   - Sensitivity and specificity are highly variable, and cross-reactivity with other coronaviruses has been reported.
COVID-19 Testing - Limitations

• A single antigen test may only be able to correctly identify the virus 60% of the time in patients who have the omicron variant and who display symptoms of the disease,

• The FDA is seeing an increase in samples with the omicron variant that have a relatively low viral load (low positive).

• The lower sensitivity means people testing for COVID should use multiple antigen tests to rule out a negative result, with 24-48 hours between tests

• With higher concern and need for timely diagnosis – get a PCR test
Blood Testing

• Insufficient evidence to recommend for or against the use of SARS-CoV-2 serologic testing (ex. SARS-CoV2 spike protein IgG) to assess for immunity or to guide clinical decisions about using COVID-19 vaccines or Evusheld

• Many, many tests have been developed and are not standardized

• No established reference ranges
Treatment for COVID-19
# Eligibility for Outpatient Therapy

## Inclusion criteria: Meets all of these and no Exclusions

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID-19 infection confirmed by PCR, NAAT, or Antigen testing (including home test)</td>
</tr>
<tr>
<td>Symptomatic with symptom onset within time frames outlined below</td>
</tr>
<tr>
<td>Mild-moderate disease (see Definitions)</td>
</tr>
<tr>
<td>Meets at least one of high-risk for progression to severe COVID-19 criteria (see CDC <a href="https://www.cdc.gov">website</a>)</td>
</tr>
</tbody>
</table>

## Exclusion criteria

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalized <em>for COVID-19</em>^</td>
</tr>
<tr>
<td>New O2 requirement</td>
</tr>
<tr>
<td>Worsening O2 requirement in those on supplemental O2</td>
</tr>
</tbody>
</table>
What is mild/moderate COVID-19?

• Mild:
  • signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnea, or abnormal chest imaging and who do not meet criteria for moderate, severe, or critical illness

• Moderate:
  • evidence of lower respiratory disease by clinical assessment or imaging, and a saturation of oxygen (SpO2) $\geq$94% on room air at sea level.
Risk Factors* Associated with Severe COVID-19

- Age ≥50 years
- Asthma
- Cancer
- Cerebrovascular disease
- Children with certain underlying conditions
- Chronic kidney disease
- Chronic lung disease (interstitial lung disease, pulmonary embolism, pulmonary hypertension, bronchiectasis, COPD)
- Chronic liver disease (cirrhosis, non-alcoholic fatty liver disease, alcoholic liver disease, autoimmune hepatitis)
- Cystic fibrosis
- Diabetes mellitus, type 1 and type 2
- Disabilities (eg, ADHD, cerebral palsy, congenital malformations, limitations with self-care or activities of daily living, intellectual and developmental disabilities, learning disabilities, spinal cord injuries)
- Heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies)
- HIV

- Mental health disorders (mood disorders including depression, schizophrenia spectrum disorders)
- Neurologic conditions (dementia)
- Obesity (BMI ≥30 kg/m²) and overweight (BMI 25 to 29 kg/m²), or ≥95th percentile in children
- Physical inactivity
- Pregnancy or recent pregnancy
- **Primary immunodeficiencies**
  - Smoking (current and former)
  - Sickle cell disease or thalassemia
  - Solid organ or blood stem cell transplantation
  - Substance use disorders
  - Tuberculosis
  - Use of corticosteroids or other immunosuppressive medications

*Established, probable, and possible
Considerations for Immunocompromised Individuals

• Importance of timely Initiation of COVID-19 therapies
• Symptom management – eg. acetaminophen, rest, fluids
• Discuss with your doctor whether immunosuppressive medications should be reduced or stopped
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<th>Agent</th>
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| Nirmatrelvir-ritonavir       | Antiviral       | ≥12 years of age and weighing ≥40 kg | ≤5 days                              | • Drug-drug interactions with many medications  
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| Remdesivir                   | Antiviral       | ≥3 kg                         | ≤7 days                              | • Requires IV administration x 3 days.                                                                                                                    |
| Bebtelovimab                 | Monoclonal Antibody | ≥12 years of age and weighing ≥40 kg | ≤7 days                              | • Requires IV administration.                                                                                                                             |
| High-titer convalescent plasma | Antibodies     |                               | ≤8 days                              | • Requires IV administration.  
• Blood typing and antibody screen required prior to administration.                                                                                   |
| Molnupiravir                 | Antiviral       | ≥18 years of age              | ≤5 days                              | • Avoid in pregnancy and in those at risk of pregnancy due to potential adverse effects on developing fetus.                                                |
Paxlovid - Nirmatrelvir-ritonavir

- Oral medication
- 5 day course (twice a day)
- Reduces the risk of dying from COVID-19 by 79% and decrease hospitalizations by 73% in at-risk patients ages 65 and older
- Expected to retain activity against Omicron and subvariants
- Metallic taste and gut symptoms
  - Things that may help with metallic taste
    - Eating and drinking
    - Strongly flavored candies - ex cinnamon candies, mints

Arbel NEJM 2022, Najjar-Debbiny Clin Infect Dis 2022
## Outpatient Therapies for Mild-Moderate COVID-19

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<tr>
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<tr>
<td>Remdesivir</td>
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<td>≥28 days old and weighing ≥3 kg</td>
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<td>Bebtelovimab</td>
<td>Monoclonal</td>
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</tr>
<tr>
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<td></td>
<td>≤8 days</td>
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Remdesivir

• IV medication – daily for 3 days
• Sometimes dose is extended for patients in the hospital
• In trials, reduced the risk of COVID-19 related hospitalization by 87% compared with placebo
• Generally well tolerated. Nausea, lower heart rate or blood pressure, and allergic reactions have been reported.
# Outpatient Therapies for Mild-Moderate COVID-19

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Bebtelovimab

- Single IV dose
- Reduced
  - Time symptom resolution from 8 days to 6 days
  - Hospitalization
  - Death

Not all monoclonal antibody treatments remain effective against Omicron
# Omicron Subvariants and COVID-19 Tx

---

## 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[^5] ng per milliliter</th>
<th>Bebtelovimab</th>
<th>Imdevimab+ Casirivimab</th>
<th>Tixagevimab+ Cilgavimab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference[^6]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BA.1</td>
<td>&gt;50,000</td>
<td>2.5</td>
<td>3.4</td>
<td>6.3</td>
</tr>
<tr>
<td>BA.1.1</td>
<td>&gt;50,000</td>
<td>5.8</td>
<td>&gt;10,000</td>
<td>351.1</td>
</tr>
<tr>
<td>BA.2</td>
<td>&gt;50,000</td>
<td>3.9</td>
<td>&gt;10,000</td>
<td>1296.8</td>
</tr>
<tr>
<td>BA.2.12.1</td>
<td>&gt;50,000</td>
<td>3.3</td>
<td>835.1</td>
<td>34.6</td>
</tr>
<tr>
<td>BA.4</td>
<td>&gt;50,000</td>
<td>4.0</td>
<td>452.7</td>
<td>38.1</td>
</tr>
<tr>
<td>BA.5</td>
<td>&gt;50,000</td>
<td>2.9</td>
<td>459.1</td>
<td>37.8</td>
</tr>
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[^5]: ng per milliliter
[^6]: Reference
# Outpatient Therapies for Mild-Moderate COVID-19

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| High-titer convalescent plasma | Antibodies | ≥12 years of age and weighing ≥40 kg | ≤8 days                                               | • Requires IV administration.  
  • Blood typing and antibody screen required prior to administration.                                                                                     |
| Molnupiravir            | Antiviral       | ≥18 years of age            | ≤5 days                                               | • Avoid in pregnancy and in those at risk of pregnancy due to potential adverse effects on developing fetus.                                             |
Molnupiravir

• 4 capsules every 12 hours for 5 days
• No dose adjustment needed for kidney or liver issues
• Cannot use in those younger than 18 (bone and cartilage issues)
• Not recommended for use in pregnancy and lactation
  • For those of childbearing age, discuss with your doctor recommendations for contraception during and after therapy
• Reduced the risk of hospitalization or death by approximately 31%
# Outpatient Therapies for Mild-Moderate COVID-19

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Hydroxychloroquine, Azithromycin, Metformin, Ivermectin and Fluvoxamine are not effective for COVID-19.
COVID-19 antivirals retain effectiveness against Omicron

<table>
<thead>
<tr>
<th>Susceptibility to Antiviral Drug</th>
<th>Remdesivir</th>
<th>Molnupiravir</th>
<th>Nirmatrelvir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>1.7 µmol</td>
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<td>2.7 µmol</td>
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<td>BA.2</td>
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Takashita NEJM 2022
Rebound COVID

• Return of symptoms and/or return of positive result on antigen test
• Reported to occur after a course of Paxlovid of Molnupiravir. Can also occur without treatments
• Pfizer's clinical trials found rebound in 1-2% of patients (in placebo and treatment). New studies suggest that rebound COVID occurs more often.
• It is unclear why this occurs
• No reports of progression to severe disease among these patients, and per CDC guidance, we do not offer repeat treatment with nirmatrelvir-ritonavir (or any other COVID-19-specific therapy) in such circumstances
Long COVID

• Coronavirus symptoms that continue or return three months after a person becomes ill from infection with SARS CoV-2

• From a June 2022 survey study, nearly 1 in 5 patients with prior COVID have “long COVID”

• Symptoms can include:
  • Tiredness
  • Shortness of breath
  • Cognitive problems
  • Heart problems

https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2022/20220622.htm#:~:text=New%20data%20from%20the%20Household,symptoms%20of%20%E2%80%9Clong%20COVID.%E2%80%9D
Long COVID: Long-Term Effects of COVID-19

• Risk Factors:
  • Women > men
  • Early lung involvement
  • More severe COVID
  • Obesity
  • Asthma
  • Poor general health
  • Unvaccinated

• The more COVID infections you get the higher risk of getting long-term COVID likely due to the inflammation you get with each infection

• Unknown if PID patients are at higher risk. More information needs to be collected

• Treatment of individual issue, symptomatic therapy
• Infection with SARS-CoV2 continues to be a public health issue and will be in our community likely for a long time
• Variants will continue to emerge
• Vaccination and staying up to date with boosters and preventative therapies can help decrease risk of infection, severe disease or death
• There are therapies available for patients at risk of severe COVID-19
• We are learning more and more each day about SARS-CoV2 but there is much still to learn
THANK YOU!

Michele Pham, MD
University of California, San Francisco
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