Participating in the Webinar

All attendees will be muted and will remain in Listen Only Mode.

Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.

How to Receive CME and MOC Points

LIVE VIRTUAL GRAND ROUNDS WEBINAR

ACG will send a link to a CME & MOC evaluation to all attendees on the live webinar.

ABIM Board Certified physicians need to complete their MOC activities by December 31, 2022 in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after March 1, 2023 for this activity.
MOC QUESTION
If you plan to claim MOC Points for this activity, you will be asked to: Please list specific changes you will make in your practice as a result of the information you received from this activity.

Include specific strategies or changes that you plan to implement. THESE ANSWERS WILL BE REVIEWED.

ACG Virtual Grand Rounds
Join us for upcoming Virtual Grand Rounds!

Week 4, 2022
Feeding Tubes: What GI’s Need to Know in 2022
John Fang, MD
January 27, 2022 at Noon Eastern

Week 5, 2022
Weight Loss Interventions for Patients with Non-alcoholic Fatty Liver Disease
Violeta Popov, MD, PhD, FACG
February 3, 2022 at Noon Eastern
Disclosures:

*All of the relevant financial relationships listed for these individuals have been mitigated.

Moderator:
Samir Shah, MD, FACG
Dr. Shah, faculty for this educational event, has no relevant financial relationship(s) with ineligible companies to disclose.

Speaker:
Erin K. Spengler, MD
Dr. Spengler, faculty for this educational event, has no relevant financial relationship(s) with ineligible companies to disclose.

Speaker:
Francis A. Farraye, MD, MSc, MACG
Advisory Boards: Arena, IMS, Braintree, GSK, IBD Educational Group, Iterative Scopes, Janssen, Pfizer, Sebela; Stockholder: Innovation Pharmaceuticals; DSMB: Baccain Therapeutics, Lilly, Theravance

Speaker:
Freddy Caldera, DO, MS
Dr. Caldera, faculty for this educational event, has no relevant financial relationship(s) with ineligible companies to disclose.

Speaker:
Gil Y. Melmed, MD
Consultant: AbbVie, Arena, Bristol-Myers-Squibb, Boehringer-Ingelheim, Janssen, Medtronic, Pfizer, Samsung Bioepis, Takeda; Research Grant: Pfizer for unrelated investigator-initiated study.

COVID-19 Vaccine Boosters and Other Updates from the Advisory Committee on Immunization Practice (ACIP)

Freddy Caldera, DO, MS
Associate Professor of Medicine
University of Wisconsin Department of Medicine
Division of Gastroenterology & Hepatology
fcaldera@medicine.wisc.edu
@dr_fcalderaibd
Objectives

- Provide updates of Interim Clinical Consideration for COVID-19 Vaccines by the Advisory Committee of Immunization Practice (ACIP)
- Define whom the ACIP considers moderate to severely immunosuppressed
- Define the terms fully vaccinated, up to date with vaccines, additional doses, and booster doses.

Changes in the Interim Clinical Considerations for COVID-19 Vaccines

- August 2021: Additional doses of mRNA COVID-19 vaccine doses after primary vaccine series for immunocompromised people
- September 2021: Booster Doses of Pfizer-BioNTech of COVID-19 Vaccine: underlying medical conditions, occupational exposure, etc.
- October 2021: Booster doses of Moderna and Janssen COVID-19 Vaccines
- November 3, 2021: Recommendations and clinical guidance for use of Pfizer-BioNTech COVID-19 vaccine in children aged 5-11 years
Changes in the Interim Clinical Considerations for COVID-19 Vaccines

- November 2021: Broadening recommendations for COVID-19 Vaccine booster doses to all persons ≥18 years of age
- December 10th: Booster doses of Pfizer-BioNTech COVID-19 vaccine for those 16-17 years of age
- December 17th: Updated guidance on use of Janssen (J&J) with preferential recommendations for mRNA vaccines
- January 2022: Shorten interval between primary series and booster from 6 to 5 months.

Goals of COVID-19 Vaccination

- Goals of COVID-19 vaccination: prevention of severe disease (hospitalization, ICU, mechanical ventilation)
- Boosters protect against symptomatic disease
Goals of COVID-19 Vaccination

- Goals of COVID-19 vaccination: prevention of severe disease (hospitalization, ICU, mechanical ventilation)


ACIP Recommendations for COVID-19 Vaccination

- Fully vaccinated
  - Means a person that has received their primary series of COVID-19 vaccines.
- Up to date
  - Means a person who has received all recommended COVID-19 vaccines, including any booster dose(s) when eligible
  - This includes an additional doses for individuals who are immunocompromised or booster doses at regular time points.
When are Patients Fully Vaccinated?

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Ages Recommended</th>
<th>Primary Series</th>
<th>Fully Vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer-BioNTech</td>
<td>5+ years old</td>
<td>2 doses Given 3 weeks (21 days) apart</td>
<td>2 weeks after final dose in primary series</td>
</tr>
<tr>
<td>Moderna</td>
<td>18+ years old</td>
<td>2 doses Given 4 weeks (28 days) apart</td>
<td>2 weeks after final dose in primary series</td>
</tr>
<tr>
<td>Johnson &amp; Johnson’s Janssen</td>
<td>18+ years old</td>
<td>1 dose</td>
<td>2 weeks after 1st dose</td>
</tr>
</tbody>
</table>

A Booster Dose Five months after completion of a primary series of COVID-19 vaccination

- People who have completed a primary series and a booster may be better protected against symptomatic infection with Omicron than those without booster
- Two studies from Israel document the effectiveness of Pfizer-BioNTech booster dose 5 months after primary series and against severe illness and death secondary to COVID-19
- The ACIP updated their recommendation

Bar-on et al NEJM 23 December 2021, Arbel et al NJEM 23 Dec 2021
Who should get a booster dose and when?

- All people 12 years and older should receive a booster dose of COVID-19 vaccines, an mRNA vaccine is preferred as a booster dose.
- Original booster doses were recommended 6 months after primary series then recently updated to 5 months after primary series.
- **Homologous booster dose:** The same vaccine product used for the booster dose as was administered for the primary series.
- **Heterologous booster dose (mix-and-match booster):** The vaccine product used for the booster dose differs from the product administered for the primary series.

### When are patients Up to date?

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Ages Recommended</th>
<th>Booster Dose</th>
<th>When Boosted</th>
</tr>
</thead>
</table>
| Pfizer-BioNTech             | 5+ years old     | • 12+ should get a booster dose at least 5 months after the last dose of primary series.  
• Teens 12–17 should only get a Pfizer-BioNTech COVID-19 Vaccine booster  
• 18+ should get a booster dose of either mRNA vaccine            | • A person is considered “boosted” and up to date right after getting their booster dose.                                                                                                                      |
| Moderna                     | 18+ years old    | • 18+ should get a booster dose of either mRNA COVID-19 vaccines at least 5 months                                           |                                                                                                                                         |
| Johnson & Johnson’s Janssen | 18+ years old    | • 18+ should get a booster dose of either (mRNA COVID-19 vaccines) at least 2 months after the first dose of J&J/Janssen COVID-19 Vaccine.  
• You may get J&J/Janssen in some situations                       |                                                                                                                                         |
Percent of subject with humoral seroconversion after two mRNA vaccine doses by condition

Healthy Controls: 95%–100%

Darker blue color is hematologic cancers

Cancer Hemodialysis Organ Transplant Immunosuppressive Therapies

Moderate to Severely Immunocompromised People

- Active treatment for solid tumor and hematologic malignancies
- Receipt of solid-organ transplant and taking immunosuppressive therapy
- Receipt of CAR-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy)
- Moderate or severe primary immunodeficiency (e.g., DiGeorge, Wiskott-Aldrich syndromes)
- Advanced or untreated HIV infection
- Active treatment with high-dose corticosteroids (i.e., ≥20mg prednisone or equivalent per day), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, TNF blockers, and other biologic agents that are immunosuppressive or immunomodulatory

*General Best Practice Guidelines for Immunization, CDC Yellow Book, IDSA 2013 guidelines
Subjects who were seropositive after two doses of mRNA vaccine on Immune-modifying therapy

- Prevent IBD
- Corrale IBD
- Hercules IBD
- autoimmune rheumatic
- covaripad
- Solid organ transplant


Additional dose to primary series

• A subsequent dose of vaccine administered to people who likely did not mount a protective immune response after initial vaccination. An additional dose to the primary series.
  • Primary series + 1

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Age indication</th>
<th>Number of doses in primary series</th>
<th>Additional primary doses in immunocompromised people (interval since second dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer-BioNTech</td>
<td>5-11 and &gt;12 years</td>
<td>2</td>
<td>1 (&gt;28 days)</td>
</tr>
<tr>
<td>Moderna</td>
<td>≥18 years</td>
<td>2</td>
<td>1 (&gt;28 days)</td>
</tr>
<tr>
<td>Janssen</td>
<td>≥18 years</td>
<td>1</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
COVID-19 vaccine and SARS-CoV-2 infection

• COVID-19 vaccination recommended for everyone, regardless of history symptomatic or asymptomatic infection.
  • This applies to primary series, additional primary doses, and booster doses
• People with known current SARS-CoV-2 infection
  • defer vaccination at least until recovery from the acute illness (if symptoms were present) has been achieved and criteria to discontinue isolation have been met.
• Current evidence about the optimal timing between SARS-CoV-2 infection and vaccination is insufficient to inform guidance

COVID-19 Vaccine and Passive Antibody Products

• Limited data on safety and effectiveness in people who received passive antibody products (anti-SARS-CoV-2 monoclonal antibodies or convalescent plasma)
• At this time COVID-19 vaccine should be temporarily deferred as a precautionary measure
  • Passive antibody product used for post exposure prophylaxis: defer COVID-19 vaccine for 30 days (monoclonal antibodies)
  • Passive antibody product used for COVID-19 treatment: Defer COVID-19 vaccination for 90 days (convalescent plasma)
My thoughts based on current available evidence of who should consider getting a fourth mRNA dose?

- All liver transplant recipients
- Not needed for most patients with IBD
- Immunosenescence
  - Older patients
- Those on corticosteroids during or after the primary series.
- Those currently on corticosteroids
- Those with other comorbidities that would increase their risk for Severe COVID-19
- Those treated with mycophenolate or B cell depleting therapy.

Conclusion

- The recommendation of a 4th dose is not new and not because of concerns of Omicron
- Booster doses are now recommended at 5th months after finishing the primary series
- Recommend a booster dose for all your patients and don’t forget about other vaccines.
Monoclonal Antibody and Small Molecule Treatments for COVID-19

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Professor of Medicine
Mayo Clinic, Jacksonville, FL
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January 25, 2022
Objectives

- Review treatment options for patients with mild to moderate COVID-19 infection
- Review pre-exposure treatment options
- I will not address treatments for patients hospitalized with severe COVID-19 infection [dexamethasone, baricitinib (JAK inhibitor), tocilizumab (IL 6 inhibitor)]
- Recommendations are current through 1/24/2022

Key Concepts for Patients with Inflammatory Bowel Disease

- Treatment for Covid-19 is not a substitute for vaccination
- All individuals 12 and older should receive a three dose mRNA vaccine series if eligible
- Switch from cloth masks to N95 (if available)
- Avoid large indoor gatherings
- Continue to social distance
- EUA: During public health emergencies, the FDA may authorize the use of unapproved drugs or unapproved uses of approved drugs under certain conditions
Goals of Therapy for Out-Patients with Covid 19

- Prevent progression to serious disease, thereby reducing:
  - Visits to urgent care setting, hospitalizations and deaths
  - Reduce duration of illness
  - Reduce infectivity and ongoing transmission
  - Minimize potential of overwhelming the healthcare system

- Given limited drug supplies, the highest priority should be given to patients with the highest risk of progression to severe disease

Not Recommended for Treatment of COVID-19: January 2022

- Convalescent serum
- Ivermectin is ineffective and dangerous
- Hydroxychloroquine/chloroquine is ineffective and associated with cardiac arrhythmias
- Azithromycin
- Zinc, vitamin-C and other supplements
### Key Concepts in Management

<table>
<thead>
<tr>
<th>Features</th>
<th>Asymptomatic or Pre-symptomatic</th>
<th>Mild Illness</th>
<th>Moderate Illness</th>
<th>Severe Illness</th>
<th>Critical Illness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive SARS-CoV-2 test: no symptoms</td>
<td>Mild symptoms (e.g., fever, cough, or change in taste or smell); no dyspnea</td>
<td>Clinical or radiographic evidence of lower respiratory tract disease; oxygen saturation ≥94%</td>
<td>Oxygen saturation &lt;94%; respiratory rate ≥30 breaths/min, lung infiltrates &gt;30%</td>
<td>Respiratory failure, shock, and multi-organ dysfunction or failure</td>
</tr>
<tr>
<td>Testing</td>
<td>Screening testing; if patient has known exposure, diagnostic testing</td>
<td>Diagnostic testing</td>
<td>Diagnostic testing</td>
<td>Diagnostic testing</td>
<td>Diagnostic testing</td>
</tr>
<tr>
<td>Isolation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

#### Proposed Disease Pathogenesis
- Viral replication
- Inflammation

#### Potential Treatment
- Antiviral therapy
- Antibody therapy
- Anti-inflammatory therapy

#### Management Considerations
- Monitoring for symptoms
- Clinical monitoring and supportive care
- Clinical monitoring: if patient is hospitalized and at high risk for deterioration, possibly remdesivir
- Hospitalization, oxygen therapy, and specific therapy (remdesivir, dexamethasone)
- Critical care and specific therapy (dexamethasone, possibly remdesivir)


---

### Antiviral Therapy to Treat Covid Infection
Antiviral Therapies

- Three anti-spike antibodies:
  - Bamlanivimab plus etesevimab (BAM+ETE; FDA EUA 9/16/21)
  - Casirivimab plus imdevimab (CAS+IMD or REGEN-COV; FDA EUA 11/21/21)
  - Sotrovimab (FDA EUA 5/26/21)
- Nirmatrelvir/ritonavir (Paxlovid) is a protease inhibitor (FDA EUA 12/21/21)
- Molnupiravir (Lagevrio) induces RNA mutations preventing viral replication (FDA EUA 12/23/21)
- Remdesivir (Veklury) is a nucleotide prodrug that inhibits viral RNA polymerase (FDA approval 10/20/20)
Remdesivir

- FDA EUA 5/1/20 and full approval 10/20/20
- Given IV once daily for 5-10 days to treat COVID-19 in hospitalized adults and children 12 and older
- Median recovery time was 10 days with remdesivir compared to 15 days for the placebo
- Remdesivir also lowered mortality rates for those receiving supplemental oxygen (4% with remdesivir versus 13% with placebo at day 29 of treatment)
- A recent article in outpatients found that a three-day course of remdesivir in non hospitalized unvaccinated patients with at least one risk factor for progression and started within 7 days of symptoms resulted in 87% lower risk of hospitalization or death compared to placebo (NEJM, December 22, 2021)

Gottlieb RL, et al. NEJM, December 22, 2021

Paxlovid

- EUA on 12/21/21 for the treatment of mild-to-moderate COVID-19 in out patient adults and pediatric patients (12 years of age and older and ≥40 kg) who are at high risk for progression to severe COVID-19
- Pill taken twice daily for five days
- Reduced COVID-19 related hospitalization and death by 88% when given within 5 days of symptom onset, without concerning safety findings
- Key Things to Remember When Prescribing:
  - Multiple drug interactions
  - Reduced dose for moderate renal impairment
  - Not recommended with severe renal impairment or severe hepatic impairment

Molnupiravir

- EUA on 12/23/21 for the treatment of mild-to-moderate COVID-19 in outpatient adults who are at high risk for progression to severe COVID-19
- Pill taken twice daily for five days
- In a study of 775 patients, 7.3% of patients treated with molnupiravir within 5 days of symptom onset were hospitalized and none died in contrast to 14% and 8 deaths in the placebo group (50% effective to prevent hospitalization)
- Updated data set demonstrated 30% reduction in hospitalization
- Key Things to Remember When Prescribing:
  - Not authorized in patients < 18 years of age
  - Breastfeeding not recommended
  - No drug interactions identified nor is dosage adjustment needed in patients with any degree of renal or hepatic impairment


Anti Spike Protein Monoclonal Antibodies

- Omicron variant “is not neutralized” by the commonly prescribed monoclonal antibody-based COVID-19 treatments bamlanivimab, etesevimab, casirivimab or imdevimab
- Sotrovimab as a single dose IV infusion has been shown to be effective against all COVID-19 variants including Omicron and is indicated for patients with mild-to-moderate COVID-19 in patients older than 12 and weighing at least 40 kilograms who are at high risk for progression to severe illness
- Not indicated in hospitalized patients and could possibly be associated with worse outcomes in patients requiring supplemental O2
- Limited supplies of this monoclonal antibody at present

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Evolving Recommendations for Non-Hospitalized Patients who are at High Risk of Clinical Progression

Before Feb 2021
• Symptomatic management, no specific therapy

Feb – Dec 23, 2021
Anti-SARS-CoV-2 mAbs -
• Bamlanivimab + etesivimab (BAM + ETE)
• Casirivimab + imdevimab (CAS + IMD or REGEN-COV)
• Sotrovimab (July 2021)

Dec 23, 2021
• Sotrovimab
• Remdesivir (IV x 3 days)

Dec 30, 2021 (list in order of preference)
1. Paxlovid™
2. Sotrovimab
3. Remdesivir
4. Molnupiravir

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Virtual Grand Rounds

Clinical Efficacy Comparison in Non-Hospitalized Patients

<table>
<thead>
<tr>
<th>Drug vs. placebo</th>
<th>0.8% vs. 6.3%</th>
<th>1% vs. 7%</th>
<th>0.7% vs. 5.3%</th>
<th>6.8% vs. 9.7%</th>
</tr>
</thead>
</table>

Events* (%) 88% vs. 95% 80% vs. 87% 30%

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Current and Pending Therapeutics for Covid-19 in the US

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Neutralizing Monoclonal Antibodies</th>
<th>Immune Modulators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad26.COV2.S: adenovirus vectored vaccine (Johnson &amp; Johnson/Janssen)</td>
<td>Bamlanivimab, etrenimab</td>
<td>Baricitinib</td>
</tr>
<tr>
<td>mRNA-1273: messenger RNA vaccine (Moderna)</td>
<td>Casirivimab, peramivir</td>
<td>Desamethasone</td>
</tr>
<tr>
<td>BNT162b2: messenger RNA vaccine (Pfizer-BioNTech)</td>
<td>Sotrovimab</td>
<td>Tocilizumab</td>
</tr>
</tbody>
</table>

Antivirals:
- Molnupiravir
- Remdesivir
- Nirmatrelvir-ritonavir (Paxlovid)
- Remdesivir

Comparison of Recommended Outpatient Therapies

<table>
<thead>
<tr>
<th></th>
<th>Paxlovid™ (1)</th>
<th>Sotrovimab (2)</th>
<th>Remdesivir (3)</th>
<th>Molnupiravir (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age allowed for use</td>
<td>≥ 12 yr</td>
<td>≥ 12 yr</td>
<td>≥ 12 yr</td>
<td>≥ 18 yr</td>
</tr>
<tr>
<td>Initiate within # days of symptom onset</td>
<td>&lt; 5 days</td>
<td>&lt; 10 days</td>
<td>&lt; 7 days</td>
<td>&lt; 5 days</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>PO</td>
<td>IV</td>
<td>IV</td>
<td>PO</td>
</tr>
<tr>
<td>Duration of Therapy</td>
<td>5 days</td>
<td>1 time</td>
<td>3 days</td>
<td>5 days</td>
</tr>
<tr>
<td>Pros</td>
<td>High efficacy</td>
<td>Oral</td>
<td>High efficacy</td>
<td>Greater experience</td>
</tr>
<tr>
<td>Cons</td>
<td>Ritonavir-related drug-drug interactions</td>
<td>Requires IV infusion</td>
<td>Requires 3 days of IV infusion</td>
<td>Not FDA approved for outpatient</td>
</tr>
<tr>
<td>Supply Availability</td>
<td>Limited supply</td>
<td>Limited supply</td>
<td>Commercially available</td>
<td>More supply than Paxlovid™ &amp; Sotrovimab</td>
</tr>
</tbody>
</table>


www.covid19treatmentguidelines.nih.gov
Comparison of Treatment Options for High-Risk Non-Hospitalized Patients with Mild to Moderate COVID-19

**Table 1. Comparison of Treatment Options for High-Risk Nonhospitalized Patients With Mild to Moderate COVID-19**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Efficacy (prevention of hospitalization or death)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nirmatrelvir-ritonavir</td>
<td>• Absolute risk reduction: 6.3%→0.8% • Relative risk reduction: 88% • NNT: 18</td>
<td>• Highly efficacious • Oral regimen • Ritonavir studied (safe) in pregnancy</td>
<td>• Drug-drug interactions</td>
</tr>
<tr>
<td>Soferivparab, 500 mg, intravenous infusion</td>
<td>• Absolute risk reduction: 5%→0.7% • Relative risk reduction: 85% • NNT: 22</td>
<td>• Highly efficacious • Monoclonal antibodies typically safe in pregnancy • Few/no drug interactions</td>
<td></td>
</tr>
<tr>
<td>Remdesivir, 1000 mg, intravenous infusion, 200 mg (day 1) and 100 mg (days 2 and 3)</td>
<td>• Absolute risk reduction: 5%→0.7% • Relative risk reduction: 85% • NNT: 35</td>
<td>• Highly efficacious • Studied in pregnancy • Few/no drug interactions</td>
<td></td>
</tr>
<tr>
<td>Molnupiravir, 800 mg, orally twice daily for 5 d</td>
<td>• Absolute risk reduction: 5%→0.7% • Relative risk reduction: 85% • NNT: 35</td>
<td>• Oral regimen • Not anticipated to have drug interactions</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: IV, intravenous; NNT, number needed to treat.


Outpatient Therapies and Potential Patient Populations

**Table 2. Outpatient Therapies and Potential Patient Populations**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Examples of patient population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nirmatrelvir, 300 mg, plus ritonavir, 100 mg, orally twice daily for 5 d</td>
<td>• Patient not taking interacting medications • Administer as soon as possible and within 5 d of symptom onset</td>
</tr>
<tr>
<td>Soferivparab, 500 mg, intravenous infusion</td>
<td>• Patient taking medication that interacts with nirmatrelvir-ritonavir • Patient able to come to health care facility • Administer as soon as possible and within 10 d of symptom onset</td>
</tr>
<tr>
<td>Remdesivir, intravenous infusion, 200 mg (day 1) and 100 mg (days 2 and 3)</td>
<td>• Patient in health care facility or through home infusion service • Administer as soon as possible and within 7 d of symptom onset</td>
</tr>
<tr>
<td>Molnupiravir, 800 mg, orally twice daily for 5 d</td>
<td>• Adult patient not able to be treated with one of the options above • Not pregnant (if given during pregnancy, shared decision-making) • Administer as soon as possible and within 5 d of symptom onset</td>
</tr>
</tbody>
</table>

Pre-Exposure Prophylaxis (PrEP)

Evusheld FDA EUA 12/8/21 for adults and adolescents (12 years of age and older who weigh at least 88 pounds) for preexposure prophylaxis for prevention of COVID-19

- Eligible Patients
  - Persons who are not currently infected with SARS-CoV-2 and who have not had recent known close contact with someone who is infected with SARS-CoV-2 and
  - Who have moderate to severe immune compromise due to a medical condition or have received immunosuppressive medicines or treatments and may not mount an adequate immune response to COVID-19 vaccination or
  - For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction (such as severe allergic reaction) to a COVID-19 vaccine(s) or COVID-19 vaccine ingredient(s)

- Expected to be effective against Omicron
- Limited availability as of January 2022
- Maybe redosed in 6 months

EVUSHIELD (tixagevimab co-packaged with cilgavimab)
Eligible Patients (Package Insert)

- Active treatment for solid tumor and hematologic malignancy
- Receipt of solid organ transplant and taking immunosuppressive therapy
- (CAR)-T cell or hematopoietic stem cell transplant
- Moderate or severe primary immuno deficiency
- Advanced or untreated HIV infection
- Active treatment with high-dose corticosteroids (≥ 20 mg per day for ≥ 2 weeks), alkylating agents, anti metabolites, transplant related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor necrosis factor blockers and other biologic agents that are immunosuppressive or immunomodulatory (B-cell depleting agents)

EVUSHELD (tixagevimab co-packaged with cilgavimab)

Eligible Patients (Mayo Clinic; Category 1 of 5)

- Lung transplant recipient (any time frame)
- Small bowel transplant recipient (any time frame)
- Receipt of the following immunosuppressive medication within the past year: anti-thymocyte globulin; alemtuzumab; and anti-B-cell therapy, such as rituximab
- B-cell malignancies on active treatment, such as B-cell lymphomas, chronic lymphocytic leukemia, and acute B-cell lymphoblastic leukemia
- Allogeneic stem cell transplant within 12 months of transplant
- Autologous stem cell transplant within six months of transplant
- Receipt of chimeric antigen receptor-T cell therapy within six months of treatment
- Primary or secondary T cell immunodeficiency, including severe combined immunodeficiency
- Recipient of more than one active transplant, different organs (any time frame)
- Acute myeloid leukemia under active treatment
- Multiple myeloma on two drugs
Supply vs Demand

- U.S. government has committed to buy a total of at least 20 million courses of Paxlovid
- U.S. government to purchase 1.2 million doses of Evusheld
- Given the existing shortage, the CDC advisory recommends the treatment be prioritized for high-risk populations

Goal
- When resources are limited, provide therapy to individuals who may derive the most benefits from the treatment – i.e., individuals who are at the highest risk for progression to severe or critical diseases

Reasons for the statement
- Rapidly rising cases of COVID-19 due to the Omicron variant
- As BAM-ETE and REGEN-COV are not active against Omicron, sotrovimab is the only effective anti-SARS-CoV-2 mAb therapy
- Available therapies in short supply

Factors used to determine who may be at highest risk for progression –
- Age – Older → Younger
- Vaccination status – Unvaccinated or Unable to mount response → Vaccinated
- Immune status – Severely immunocompromised → immunocompetent
- Clinical factors – Obesity, diabetes, CV disease, etc. → no risk factor

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Patient Prioritization Risk Groups

<table>
<thead>
<tr>
<th>Tier</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| 1    | • **Immunocompromised**, not expected to mount an adequate immune response to COVID-19 vaccine or SARS-CoV-2 infection due to their underlying conditions, regardless of vaccine status; or  
      • **Unvaccinated Individuals at the highest risk of severe disease** (anyone aged ≥75 years or anyone aged ≥65 years with additional risk factors). |
| 2    | • **Unvaccinated Individuals at risk of severe disease not included in Tier 1** (anyone aged ≥65 years or anyone aged <65 years with clinical risk factors) |
| 3    | • **Vaccinated Individuals at high risk of severe disease** (anyone aged ≥75 years or anyone aged ≥65 years with clinical risk factors)  
      *Note:* Vaccinated individuals who have not received a COVID-19 vaccine booster dose are likely at higher risk for severe disease; patients in this situation within this tier should be prioritized for treatment. |
| 4    | • **Vaccinated Individuals at risk of severe disease** (anyone aged ≥65 years or anyone aged <65 years with clinical risk factors)  
      *Note:* Vaccinated individuals who have not received a COVID-19 vaccine booster dose are likely at higher risk for severe disease; patients in this situation within this tier should be prioritized for treatment. |

http://www.covid19treatmentguidelines.nih.gov

www.covid19treatmentguidelines.nih.gov

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Virtual Grand Rounds

Thank You!

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@FarrayeIBD

American College of Gastroenterology
COVID-19 Vaccine in Patients with Chronic Liver Disease and in Liver Transplant Recipients

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Objectives

- Discuss how chronic liver disease (CLD) and liver transplant recipients (LTr) are unique and why this affects our vaccination recommendations
- Review available COVID-19 vaccine safety and efficacy data in patients with CLD or LT
- Examine the data on vaccine immunogenicity in LTr
- Summarize COVID-19 vaccination recommendations in patients with CLD or history of liver transplant (LT)
Patients with CLD are more likely to die from COVID-19 infection

CLD appears to be a risk factor for COVID-19 mortality
• 2780 patients (pts), 250 with CLD:
  12 vs 4% rate of death, RR 4.6
• NAFLD, NASH, cirrhosis likely increase mortality
• Independent of age, race, BMI, hypertension, diabetes
• Affected by CLD severity:
  • Cirrhosis vs no cirrhosis
  • CP class A vs B or C


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LT recipients with COVID-19 have similar mortality and hospitalization rate, but may have more severe illness

• International registry of LT recipients with COVID, compared to contemporaneous control of non-SOTr patients with COVID
• LT was not independently associated with death; increased age and presence of comorbidities were associated with death


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Patients with CLD have immune dysregulation

- Affects innate and adaptive immunity → hypo-responsive to vaccines
- More advanced liver disease (MELD-Na, CTP score) = more immune dysregulation
- LT recipients: lower response rate to many vaccines
  - Lowest rate of response within 3-6 mo of LT
  - Live-attenuated vaccines not recommended

SOTr have an altered immune response and lower vaccine immunogenicity

- SOTr have lower antibody responses to many vaccinations
- mRNA COVID vaccines response ranges 30-58%
  - Several different immunoassays to determine IgG Ab response
  - Effect on virus-specific T cell response?
  - Ab response ≠ immunity
- Antimetabolite-containing immuno-suppression (IS) (mycophenolate), age, eGFR, appears to negatively influence immune response

References:
Immunogenicity is decreased in liver transplant recipients (LTr), but less so than other SOTr

- 18,215 vaccinated SOTr
- 151 (0.83%) breakthrough infections
- Compared to general population, SOTr’s have 82-fold higher risk of breakthrough infection
- Mortality rate among breakthrough infections: 9.3% breakthrough mortality vs 20.5% from de novo infection in unvaccinated

Breakthrough COVID-19 infection in SOTr is deadly, but vaccines decrease mortality

- Risk of Breakthrough SARS-CoV-2 Infections in Adult Transplant Recipients

<table>
<thead>
<tr>
<th>Fully vaccinated</th>
<th>Breakthrough infections</th>
<th>Hospitalization</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>18215 Transplant recipients in 17 centers</td>
<td>0.83%</td>
<td>0.48%</td>
<td>0.077%</td>
</tr>
</tbody>
</table>
| 101 million Adults in United States | 0.0102% | 0.0099% | 0.00016%

Transplant recipients have lower protection from SARS-CoV-2 infection after vaccination. Transplant recipients should get vaccinated & continue to practice all COVID safety precautions.

American College of Gastroenterology
Third dose of Moderna vaccine improves immunity in SOTr in a randomized control trial

- 120 SOTr who has received 2 doses of mRNA-1273 randomized
- 3rd dose given 2 mo after 2nd dose
- Anti–receptor-binding domain (RBD) Ab (≥100 U/ml) 1 month post
  - 33 of 60 (55%) pts in vaccine group vs.
  - 10 of 57 pts (18%) in placebo group

Hall et al. (Sept 2021) NEJM. Randomized Trial of a Third Dose of mRNA-1273 Vaccine in Transplant Recipients. DOI: 10.1056/NEJMc2111462

COVID-19 vaccines are safe for patients with CLD or history of LT

- Vaccine trials included stable chronic medical conditions: CLD, HCV, HBV. Pts on IS therapy excluded (small # of SOTr in J&J/Janssen trial)
- Both mRNA and adenoviral vector COVID-19 vaccines are safe in patients with CLD, cirrhosis or liver transplant
- No liver-related absolute contraindications

“So, how safe are COVID-19 vaccines?
The short answer: Very.”

VAERS Vaccine Adverse Event Reporting System
www.vaers.hhs.gov


American College of Gastroenterology
AASLD Consensus Statement:
COVID-19 Vaccination in CLD

- Do NOT hold antiviral therapy or IS for vaccination
- Do NOT postpone HCC treatment
- mRNA and adenoviral vector COVID-19 vaccines have favorable efficacy/safety profile
- 3 dose primary series: AIH patients on anti-metabolites, HCC in active treatment, CLD patients on prednisone
- All other CLD patients: 2 dose primary series


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AASLD Consensus Statement:
COVID-19 Vaccination in LT candidates

- Pre-LT patients are vaccinated like CLD patients
- Prioritize COVID vaccination prior to LT (required?)
- Non-COVID vaccines should be given along schedule
- Do not delay LT if recently vaccinated
- Vaccinate even if LT is likely to occur prior to 2nd or 3rd dose
- Living donor/recipient vaccinate at least 2 weeks prior, but do not delay if needed
- Family, care givers should be vaccinated
- Continue to wear high quality masks

AASLD Consensus Statement: COVID-19 Vaccination in LTr

- Do not dose within 4 weeks of LT
- 2nd mRNA dose should otherwise be given at earliest appropriate interval after LT
- If not yet vaccinated, administer 1st dose 3 mo after LT; can consider as early as 4 weeks
- All post-LT patients should receive a 3rd dose 28 days after the 2nd mRNA vaccine (3-dose primary series)
- Avoid vaccination in active ACR, high dose corticosteroids
- If liver enzymes increase and do not improve post vaccination – evaluate for ACR


4th dose (booster) recommended for immunosuppressed patients

Recommended by the CDC:
- Booster 5 months after 3 dose primary series
- SOTr, patients on IS
- CDC immunocompromised pts
- Outcomes data to follow

Content source: National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases.
Conclusions: VACCINATE!

- CLD patients and LT recipients have immune dysfunction and a decreased immune response to SARcoV-2 vaccination
- Vaccination in these patients is **safe and reduces mortality**
- **Vaccinate pts PRIOR to LT**, if possible: vaccine response is better

**COVID-19 mRNA vaccine recommendations (CDC):**
- CLD without IS: 2 dose series, booster 5 mo later
- CLD on IS: 3 dose series, booster 5 mo later
- SOTr: 3 dose series, booster 5 mo later
- *3 dose series: 2nd dose day 28, 3rd dose 28 days after 2nd
COVID Vaccination in IBD: An Update

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Professor of Medicine
Cedars-Sinai Medical Center

gil.melmed@cshs.org

Objectives

• Safety of COVID vaccines in people with IBD
• Efficacy of COVID vaccines in people with IBD
• Take-aways / Recommendations
IBD Vaccine Principles B.C. (before Covid)

1. Vaccine efficacy may be blunted by immunomodulators, biologics, and corticosteroids
2. A blunted response does not translate into vaccine ineffectiveness; partial protection is better than none
3. Vaccination on immunosuppression may be associated with accelerated waning of titers
   - Implications not entirely clear, may need to reassess titers / booster
   - Older age may be independent risk
4. Vaccines do not trigger IBD flares

Melmed GY, Rubin DT, McGovern D. Winter is Coming! Considerations for vaccinating patients with IBD during the COVID pandemic. Gastroenterology 2020 (epub)

5. For those on cyclically-administered / infused therapies, it doesn’t matter when the vaccine is administered within the cycle
6. The best time for patients to receive vaccines is whenever they have an opportunity to so
7. Enrolling patients into observational registries will help address questions
Efficacy

- Seroconversion (+/-)
- Antibody levels
- IBD vs healthy controls
- Influence of Medications
- Immune response vs protection

Influence of Biologics on Vaccination: What does it mean?

- Pfizer Vaccine (BNT162b2)
- AstraZeneca Vaccine (ChAdOx1)

Kennedy NK et al. CLARITY IBD study. medRxiv doi: https://doi.org/10.1101/2021.03.25.21254335

IFX, infliximab; Vedo, vedolizumab
Do medications blunt antibody responses?

**Methods:**
- N=582
- mRNA vaccines only
- Excluded if prior COVID

**Results:**
- 99% with seroconversion
- Peak response at 2 weeks
- Differences by medication class


Serologic responses over time

**Methods:**
- N=582
- mRNA vaccines only
- Excluded if prior COVID

**Results:**
- 99% with seroconversion
- Peak response at 2 weeks
- Differences by medication class

Melmed et al. CORALIE IBD study group, ACG 2021 Abstract.
How does IBD response compare to healthy?

- N=IBD 122, HC 60
- mRNA vaccines only
- Antibodies at 28-35d
- Results:
  - Seroconversion: 97% IBD; 100% HC
  - Quant levels higher in HC
  - mRNA-1273 > BNT162b2

Caldera F..., Farraye FA (HERCULES Cohort). Am J Gastro 2022

Serologic Responses in IBD: The ICARUS experience

Wong SY, Dixon R, Martinez Pazos V, Gnatic S, Colombel JF, Cadwell K. Serologic Responses to COVID19 vaccination in ibd patients receiving biologics. Gastroenterology 2021
Can we predict non-response?

- PREVENT-COVID registry (n=1909); 96% seroconversion
- Predictors of NON-SEROCONVERSION
  - Older age
  - BNT162b2 > mRNA1273 (OR 1.0-3.9)
  - Combination anti-TNF+IM
- Beneficial predictors: 5ASA, UST

Weaver et al. PREVENT-COVID Study Group. Am J Gastroenterology 2021

Does vaccine type matter? Probably!

"Qualitative" response:
Seropositivity by 8 weeks

"Quantitative" response:
Log10 [Anti-Spike IgG] (AU/mL)

"Positive" threshold 50 AU/ml (Abbott Labs)

Pozdnyakova, Botwin, Sobhani, Prostko, Braun, McGovern, Melmed, CORALE-IBD Study Group. Gastroenterology Aug 2021
Antibodies or T-Cells?

CORALE-IBD Study Group, Unpublished Data

Safety

- Dose 1 vs Dose 2 vs Dose 3
- IBD vs controls
- Disease exacerbation?
Reactogenicity of mRNA Vaccines in IBD:
Biologics/JAKi Reduce Frequency / Duration / Severity of AE

Symptoms are all generally worse after Dose 2, consistent with clinical trial data.

Less frequent symptoms if on biologics/JAK (green) than no biologics/JAK (purple):
- Injection site
- Fatigue/malaise
- Fever/chills

Reactogenicity of mRNA Vaccines in IBD: Biologics/JAKi Reduce Frequency / Duration / Severity of AE

**Duration of symptoms is shorter** if on biologics/JAK (green) than no biologics/JAK (purple):
- Injection site
- Fatigue/malaise
- Fever/chills
- Memory/mood

**Overall AE less frequent and severe in IBD**

Frequency and severity are both more common in HCW than in IBD (black dots are to the right of purple dots for every category except dose 1 GI symptoms)

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Mujukian et al. CORALE-IBD Study Group. ACG 2021 abstract
Efficacy and Safety of 3\textsuperscript{rd} dose in IBD

How do antibody responses after D3 compare to D2?

- Antibodies after 2\textsuperscript{nd} dose (n=139) and 3\textsuperscript{rd} dose (n=85)
- Higher levels after 3\textsuperscript{rd} dose
  - Steroids/aTNF lower levels
  - mRNA-1273 > BNT162b2

Schell et al. HERCULES Study Group, MedRxIV 2022
Third dose safety: How do symptoms after D3 compare with D2?

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Dose 3 AE</th>
<th>Dose 2 AE</th>
<th>Dose 2 AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site</td>
<td>None/Mild</td>
<td>Moderate</td>
<td>Severe+</td>
</tr>
<tr>
<td>Fatigue or malaise</td>
<td>None/Mild</td>
<td>261(73.31)</td>
<td>61(51.26)</td>
</tr>
<tr>
<td>Headache, dizziness, or</td>
<td>None/Mild</td>
<td>68(19.1)</td>
<td>41(45.56)</td>
</tr>
<tr>
<td>Muscle, bone, joint, or</td>
<td>None/Mild</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea, vomiting, d Dream</td>
<td>None/Mild</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep</td>
<td>None/Mild</td>
<td>68(19.1)</td>
<td>41(45.56)</td>
</tr>
<tr>
<td>Swollen lymph, neck, head,</td>
<td>None/Mild</td>
<td>68(19.1)</td>
<td>41(45.56)</td>
</tr>
<tr>
<td>Eye, ear, mouth, or nose</td>
<td>None/Mild</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough, chills or breathing</td>
<td>None/Mild</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory or mood</td>
<td>None/Mild</td>
<td>68(19.1)</td>
<td>41(45.56)</td>
</tr>
</tbody>
</table>

Do post-D2 symptoms predict post-D3 symptoms?

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Dose 2 AE N/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose 3 AE</td>
<td></td>
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<tr>
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</tr>
<tr>
<td>None/Mild</td>
<td>68(19.1)</td>
</tr>
<tr>
<td>Moderate</td>
<td>41(34.45)</td>
</tr>
<tr>
<td>Severe+</td>
<td>18(20)</td>
</tr>
<tr>
<td>None/Mild</td>
<td>68(19.1)</td>
</tr>
<tr>
<td>Moderate</td>
<td>41(34.45)</td>
</tr>
<tr>
<td>Severe+</td>
<td>31(34.44)</td>
</tr>
</tbody>
</table>
Vaccines are not associated with IBD Flare

Lev-Tzion et al CGH 2021
Weaver et al. PREVENT-COVID Study Group IBD Journal Dec 2021
Summary and Recommendations

• All those with IBD should receive primary series and a booster 5-6 months later
• Prefer mRNA vaccine
• Safety – overall similar or better than general population
• Reassurance that vaccination is NOT associated with or significant flare risk in vast majority
• COVID Vaccines are highly effective in IBD
Questions?

Moderator: Samir Shah, MD, FACG

Speaker: Francis A. Farraye, MD, MSc, MACG

Speaker: Freddy Caldera, DO, MS

Speaker: Erin K. Spengler, MD

Speaker: Gil Y. Melmed, MD

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