Welcome & Introduction
Dana Wollins, DrPH, MGC
Vice President, Clinical Affairs & Guidelines
IDSA

• 74th in a series of weekly calls, initiated by CDC 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.
Today’s Call: COVID-19 Treatment Updates

**Anti-SARS-CoV-2 Monoclonal Antibodies for Treatment and Prevention**

Rajesh Gandhi, MD, FIDSA  
Director, HIV Clinical Services and Education,  
Massachusetts General Hospital  
Co-Director, Harvard Center for AIDS Research and  
Professor of Medicine  
Harvard Medical School  
Chair, HIV Medicine Association

Kathryn M. Edwards, MD  
Sarah H. Sell and Cornelius Vanderbilt Professor  
Division of Infectious Diseases  
Department of Pediatrics  
Vanderbilt University Medical Center

**Ivermectin: What are the Data & What’s Fueling its Use**

Lindsey R. Baden, MD  
Associate Professor of Medicine  
Harvard Medical School  
Director of Clinical Research, Division of Infectious Diseases  
Brigham and Women’s Hospital

Travis Stark, DPM  
Medical Officer, Adverse Event Monitoring Unit  
Clinical Disease and Health Services Team  
Health Systems and Worker Safety Task Force  
CDC COVID-19 Response

**Emerging Therapies under Investigation: Focus on Fluvoxamine**

Shmuel Shoham, MD  
Associate Professor of Medicine  
Transplant and Oncology Infectious Disease Program  
Johns Hopkins University School of Medicine
Question?
Use the “Q&A” Button

Comment?
Use the “Chat” Button
Anti-SARS-CoV-2 Monoclonal Antibodies for Treatment and Prevention

Rajesh Gandhi, MD, FIDSA
Director, HIV Clinical Services and Education, Massachusetts General Hospital
Co-Director, Harvard Center for AIDS Research and Professor of Medicine
Harvard Medical School
Chair, HIV Medicine Association

Disclosures (for past two years): Member, NIH & Infectious Diseases Society of America COVID-19 Treatment Guidelines Panels; Investigator, AIDS Clinical Trials Group and COVID-19 Prevention Network trials on anti-SARS CoV-2 monoclonal antibodies
Anti-SARS CoV-2 Monoclonal Antibodies for Treatment and Prevention

Rajesh T. Gandhi, MD
Massachusetts General Hospital
Harvard University Center for AIDS Research

Disclosures (for past two years):
Member, NIH & Infectious Diseases Society of America COVID-19 Treatment Guidelines Panels;
Acknowledgments: Dr. Arthur Kim. Efe Airewele.
## Outpatient Treatment Across the COVID-19 Spectrum

### Stage/Severity:

<table>
<thead>
<tr>
<th>Asymptomatic/Presymptomatic</th>
<th>Mild Illness</th>
<th>Moderate Illness</th>
<th>Severe Illness</th>
<th>Critical Illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ SARS-CoV-2 test but no symptoms</td>
<td>Mild symptoms (e.g., fever, cough, taste/smell changes); no dyspnea</td>
<td>O₂ saturation ≥ 94%, lower respiratory tract disease</td>
<td>O₂ saturation &lt;94%, respiratory rate &gt;30/min; lung infiltrates &gt;50%</td>
<td>Respiratory failure, shock, multi-organ dysfunction/failure</td>
</tr>
</tbody>
</table>

### Disease Pathogenesis:

- **Viral replication**
- **Inflammation**
- **Hypercoagulability**

### Potential treatment:

- **Antivirals**
- **Antibody therapy**
- **Decrease inflammation**

---

Gandhi RT, CID, 2020
Gandhi RT, Lynch J, del Rio C. NEJM 2020
Anti-SARS CoV-2 Monoclonal Antibodies for Treatment

• Emergency Use Authorizations (EUAs) for treatment of ambulatory patients with mild to moderate COVID-19 at high risk of progression and within 10 days of symptom onset:
  • Casirivimab + Imdevimab (600/600 mg) (IV administration preferred; subcutaneous is alternative)
  • Bamlanivimab + Etesevimab (700/1400 mg) (IV)
  • Sotrovimab (IV)
Anti-SARS CoV-2 Monoclonal Antibodies for Post-Exposure Prophylaxis

• Casirivimab/imdevimab (subcutaneous or intravenous) for post-exposure prophylaxis in individuals who are at high risk for progression to severe COVID-19 and are:

  ➢ Not fully vaccinated or not expected to mount adequate immune response to COVID vaccination (eg immunosuppressed individuals) AND

    □ Have been exposed* to individual with COVID-19

    or

    □ At high risk of exposure because of occurrence of COVID-19 in same institutional setting (eg nursing home, prison)

*Within 6 feet for >=15 min, providing care at home, direct contact, exposed to respiratory droplets of infected person
What are the Data for Use of Anti-SARS CoV-2 Antibodies for Treatment?
Bamlanivimab/Etesevimab: Outpatient Treatment

• Outpatients with mild to moderate COVID within 3 days of first positive test; 1 or more risk factors for developing severe COVID-19 (n=1035)

• IV bamlanivimab 2800 mg/etesevimab 2800 mg or placebo

Results:

• 70% reduction in COVID hospitalization or any cause of death by day 29 (P<0.001)

• Similar results with bamlanivimab/etesevimab 700/1400 mg (authorized dose)
Casirivimab/Imdevimab: Outpatient Treatment

- Outpatients (n=4057) with mild to moderate COVID: placebo or intravenous casirivimab/imdevimab (various doses)
- Modified full analysis set: +PCR; ≥1 risk factor for severe COVID

Results:
- In 600/600 mg group, 70% reduction in COVID hospitalizations or death
- More rapid resolution in symptoms in antibodies group: 10 vs. 14 days
Sotrovimab: Outpatient Treatment

• Outpatients with mild to moderate COVID-19 at high risk of hospitalization (n=583)

• Randomized to receive sotrovimab or placebo

Result:
• 85% reduction in hospitalization or death

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Hospitalized/death</th>
<th>Percent Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sotrovimab</td>
<td>291</td>
<td>3 (1%)</td>
<td>85% (p=0.002)</td>
</tr>
<tr>
<td>Placebo</td>
<td>292</td>
<td>21 (7%)</td>
<td></td>
</tr>
</tbody>
</table>
What about SARS-CoV-2 Variants?
Variants and Anti-SARS-CoV-2 Antibodies: In Vitro Studies

• Alpha (B.1.1.7): susceptible to the authorized antibodies

• Beta (B.1.351), Gamma (P.1)
  • Marked reduction in susceptibility to bam/ete
  • Casirivimab/imdevimab, sotrovimab expected to retain activity

• Delta (B.1.617.2)
  • Bamlanivimab/etesevimab, casirivimab/imdevimab, sotrovimab expected to have activity

### Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Variants with Bamlanivimab/Etesevimab

<table>
<thead>
<tr>
<th>Lineage</th>
<th>Country 1st Identified</th>
<th>WHO Nomenclature</th>
<th>Key Substitutions Tested</th>
<th>Fold Reduction in Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.1.351</td>
<td>South Africa</td>
<td>Beta</td>
<td>K417N + E484K + N501Y</td>
<td>431</td>
</tr>
<tr>
<td>P.1</td>
<td>Brazil</td>
<td>Gamma</td>
<td>K417T + E484K + N501Y</td>
<td>252</td>
</tr>
<tr>
<td>B.1.617.2/AY.3</td>
<td>India</td>
<td>Delta</td>
<td>L452R + T478K</td>
<td>no change</td>
</tr>
<tr>
<td>AY.1/AY.2 (B.1.617.2 sub-lineages)</td>
<td>India</td>
<td>Delta [+K417N]</td>
<td>L452R + T478K + K417N</td>
<td>1,235</td>
</tr>
<tr>
<td>B.1.427/B.1.429</td>
<td>USA (California)</td>
<td>Epsilon</td>
<td>L452R</td>
<td>9</td>
</tr>
</tbody>
</table>

**Source:** [FDA, FACT SHEET FOR HEALTH CARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF BAMLANIVIMAB AND ETESEVIMAB](https://www.fda.gov/media/145802/download)
Resumption in Distribution of Bamlanivimab/Etesevimab

Important Updates

September 3, 2021 - HHS is immediately implementing changes to help promote optimal and equitable use of the available supply of monoclonal antibodies while efforts to procure additional product. Learn More >>

September 2, 2021 - FDA and ASPR announce resumption in use and distribution of bamlanivimab/etesevimab in all U.S. states, territories, and jurisdictions under the conditions of authorization for EUA 94. Learn More >>

August 27, 2021 - FDA and ASPR announce resumption in use and distribution of bamlanivimab/etesevimab in certain states. Learn More >>
What about people who develop COVID-19 after vaccination?

- For people who develop COVID-19 after receiving SARS-CoV-2 vaccination, prior vaccination should not affect treatment decisions, including use of and timing of treatment with monoclonal antibodies.
What are the Data for Use of anti-SARS CoV-2 Antibodies for Post-exposure Prophylaxis?
Casirivimab/Imdevimab: Post-exposure prophylaxis

- Phase 3 placebo-controlled trial among household contacts of person with positive SARS CoV-2 test within past 96 hours
- Casi/imdev (600/600 mg) or placebo given subcutaneously

Results:
- Among participants who were PCR-negative and seronegative at baseline (n=1505), 81% reduction in symptomatic SARS CoV-2 infection in casirivimab/imdevimab group (P<0.0001)
- Among infected participants, antibody group had shorter duration of symptoms (1.2 vs. 3.2 weeks) and shorter duration of high viral loads (0.4 vs 1.3 weeks)

<table>
<thead>
<tr>
<th>Symbolic representation of the table content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic SARS CoV-2 Infection in Participants who were PCR and antibody negative at baseline</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Antibodies</td>
</tr>
</tbody>
</table>

O’Brien M et al, NEJM 2021
IDSA Guidelines on the Treatment and Management of Patients with COVID-19

Published by IDSA on 4/11/2020. Last updated, 9/3/2021


Casirivimab/imdevimab recommended for post-exposure prophylaxis in people who are at high risk for progression if infected (see guidelines for details)

Anti-SARS CoV-2 monoclonal antibody products are recommended for outpatients with mild-to-moderate COVID-19 who are at high risk of disease progression (see EUA criteria)

See guidelines for details

What about patients hospitalized due to COVID-19?
Casirivimab/Imdevimab in Hospitalized Patients: RECOVERY

- Hospitalized patients (n=9785) randomized to usual care with casirivimab 4,000 mg + imdevimab 4,000 mg IV or usual care alone.

Results
- 28-day all-cause mortality: 20% vs. 21% (no difference)
- In those seronegative for anti-spike protein antibody, reduction in mortality with casi/imdev: 24% vs. 30% (rate ratio 0.80; 95% CI, 0.70–0.91; P = 0.001)

https://www.medrxiv.org/content/10.1101/2021.06.15.21258542v1.full.pdf
Casirivimab/Imdevimab in Hospitalized Patients

- Casirivimab/imdevimab not yet authorized for treatment of hospitalized patients
- We need rapid and reliable serology test to identify seronegative individuals
- Casirivimab/imdevimab only available through expanded access program for hospitalized patients who are not on high flow oxygen or mechanically ventilated

Rapidly evolving information with more to come ....
Anti-SARS CoV-2 Monoclonal Antibodies: Summary

Treatment:
• mAbs authorized to treat high-risk outpatients with mild-moderate COVID-19
  • Not authorized for use in people hospitalized due to COVID-19; may be used in people hospitalized for reasons other than COVID-19 (see FDA FAQ)
  • In the future, mAbs may have role in seronegative hospitalized patients but need rapid and reliable serologic test

Post-exposure prophylaxis:
• Casirivimab/imdevimab authorized for post-exposure prophylaxis for people who are at higher risk for severe COVID-19 who are not fully vaccinated or who are not expected to mount an immune response (eg immunocompromised hosts)
Post-Exposure Prophylaxis and Treatment Across the COVID-19 Spectrum

**Exposure**
- Asymptomatic/Presymptomatic: + SARS-CoV-2 test but no symptoms
- Mild Illness: Mild symptoms (e.g., fever, cough, taste/smell changes); no dyspnea
- Moderate Illness: O₂ saturation ≥ 94%, lower respiratory tract disease
- Severe Illness: O₂ saturation <94%, respiratory rate >30/min; lung infiltrates >50%
- Critical Illness: Respiratory failure, shock, multi-organ dysfunction/failure

**Viral replication**

**Antivirals**
- Remdesivir
- Dexamethasone
  - In some patients: IL-6 inhibitor or Jak inhibitor
- IL-6 inhibitor or Jak inhibitor

**Casi/imdev**
- (high risk, not fully vaccinated or immunosuppressed)

Gandhi RT, CID, 2020
Gandhi RT, Lynch J, del Rio C. NEJM 2020
Anti-SARS-CoV-2 Monoclonal Antibodies for Treatment and Prevention: Pediatric Considerations

Kathryn M. Edwards, MD
Sarah H. Sell and Cornelius Vanderbilt Professor
Division of Infectious Diseases
Department of Pediatrics
Vanderbilt University Medical Center

Disclosures: Dr. Edwards is a consultant to Bio-Net and IBM and serves as a member of Data Safety and Monitoring Boards for NIAID, Sanofi, X-4 Pharma, Seqirus, Moderna, Roche, and Pfizer.
Anti-SARS-CoV-2 Monoclonal Antibodies for Treatment and Prevention: Pediatric Considerations

Kathryn M. Edwards, MD
Division of Infectious Diseases
Department of Pediatrics
Vanderbilt University Medical Center

William Muller, MD, PhD
Division of Infectious Diseases
Department of Pediatrics
Northwestern University Feinberg School of Medicine
FIGURE 1. Average daily COVID-19 case incidence among persons aged 0–17 years, by age group — United States, August 1, 2020–August 27, 2021

Adolescents and young adults have the highest COVID-19 incidence rates

Since beginning of pandemic at least 7.7 million COVID-19 cases have been reported among persons aged 12–29 years

https://covid.cdc.gov/covid-data-tracker/#demographics
## Table III. Baseline characteristics of patients hospitalized with SARS-CoV-2

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total, N = 281</th>
<th>Respiratory, N = 143</th>
<th>MIS-C, N = 69</th>
<th>Other, N = 69</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coexisting conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>85/250 (34.0%)</td>
<td>62/134 (46.3%)</td>
<td>18/64 (28.1%)</td>
<td>5/52 (9.6%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Respiratory</td>
<td>49/281 (17.4%)</td>
<td>39/143 (27.3%)</td>
<td>6/69 (8.7%)</td>
<td>4/69 (5.8%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Neurologic</td>
<td>23/281 (8.2%)</td>
<td>22/143 (15.4%)</td>
<td>0/69 (0.0%)</td>
<td>1/69 (1.4%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Immunosuppressed</td>
<td>16/281 (5.7%)</td>
<td>13/143 (9.1%)</td>
<td>1/69 (1.4%)</td>
<td>2/69 (2.9%)</td>
<td>.052</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11/281 (3.9%)</td>
<td>8/143 (5.6%)</td>
<td>0/69 (0.0%)</td>
<td>3/69 (4.3%)</td>
<td>.14</td>
</tr>
<tr>
<td>Sickle cell</td>
<td>9/281 (3.2%)</td>
<td>7/143 (4.9%)</td>
<td>2/69 (2.9%)</td>
<td>0/69 (0.0%)</td>
<td>.21</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>18/281 (6.4%)</td>
<td>12/143 (8.4%)</td>
<td>2/69 (2.9%)</td>
<td>4/69 (5.8%)</td>
<td>.30</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>10/281 (3.6%)</td>
<td>10/143 (7.0%)</td>
<td>0/69 (0.0%)</td>
<td>0/69 (0.0%)</td>
<td>.005</td>
</tr>
<tr>
<td>History of smoking</td>
<td>13/228 (5.7%)</td>
<td>10/116 (8.6%)</td>
<td>0/52 (0.0%)</td>
<td>3/60 (5.0%)</td>
<td>.069</td>
</tr>
<tr>
<td>Medical complexity</td>
<td>59/281 (21.0%)</td>
<td>45/143 (31.5%)</td>
<td>5/69 (7.2%)</td>
<td>9/69 (13.0%)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Primary reason for admission</th>
<th>Primary reason for admission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>COVID-19–related</td>
<td>not clearly COVID-19–related</td>
</tr>
<tr>
<td>Total no. of hospitalized adolescents</td>
<td>376 (100.0)†</td>
<td>204 (100.0)†</td>
<td>172 (100.0)†</td>
</tr>
<tr>
<td>Underlying medical condition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 underlying medical condition††</td>
<td>207 (55.1)</td>
<td>144 (70.6)</td>
<td>63 (36.6)</td>
</tr>
<tr>
<td>Obesity***</td>
<td>101 (27.9)</td>
<td>73 (35.8)</td>
<td>28 (17.7)</td>
</tr>
<tr>
<td>Chronic lung disease, including asthma</td>
<td>87 (24.0)</td>
<td>63 (30.9)</td>
<td>24 (15.2)</td>
</tr>
<tr>
<td>Neurologic disorders</td>
<td>43 (11.9)</td>
<td>29 (14.2)</td>
<td>14 (8.9)</td>
</tr>
<tr>
<td>Chronic metabolic disease, including diabetes</td>
<td>32 (8.8)</td>
<td>24 (11.8)</td>
<td>8 (5.1)</td>
</tr>
<tr>
<td>Immunocompromised condition</td>
<td>20 (5.5)</td>
<td>14 (6.9)</td>
<td>6 (3.8)</td>
</tr>
<tr>
<td>Blood disorder, including sickle cell anemia</td>
<td>21 (5.8)</td>
<td>19 (9.4)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>15 (4.1)</td>
<td>9 (4.4)</td>
<td>6 (3.8)</td>
</tr>
</tbody>
</table>
# Deaths in Children and Adolescents Associated With COVID-19 and MIS-C in the United States

## Table 4. Underlying medical conditions for all decedents, decedents who met MIS-C criteria, and decedents who did not meet MIS-C criteria (n = 112)

<table>
<thead>
<tr>
<th>Number of Underlying Medical Conditions</th>
<th>All Decedents (n = 112)</th>
<th>Met MIS-C Criteria (n = 16)</th>
<th>Did not Meet MIS-C Criteria (n = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>None</td>
<td>16</td>
<td>14%</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>24</td>
<td>21%</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>20%</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>13%</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>9%</td>
<td>1</td>
</tr>
<tr>
<td>≥5</td>
<td>25</td>
<td>22%</td>
<td>3</td>
</tr>
<tr>
<td><strong>Metabolic and Endocrine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>47</td>
<td>42%</td>
<td>5</td>
</tr>
<tr>
<td>Diabetes Mellitus&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11</td>
<td>10%</td>
<td>1</td>
</tr>
<tr>
<td>Other&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12</td>
<td>11%</td>
<td>2</td>
</tr>
<tr>
<td><strong>Neurologic and Developmental</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Developmental Disorder</td>
<td>25</td>
<td>22%</td>
<td>3</td>
</tr>
<tr>
<td>Seizure disorder</td>
<td>17</td>
<td>15%</td>
<td>3</td>
</tr>
<tr>
<td>Other&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20</td>
<td>18%</td>
<td>2</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma or Reactive Airway Disease</td>
<td>33</td>
<td>29%</td>
<td>5</td>
</tr>
<tr>
<td>Other&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6</td>
<td>5%</td>
<td>1</td>
</tr>
</tbody>
</table>

Initial Guidance on Use of Monoclonal Antibody Therapy for Treatment of Coronavirus Disease 2019 in Children and Adolescents


Background. In November 2020, the US Food and Drug Administration (FDA) provided Emergency Use Authorizations (EUA) for 2 novel virus-neutralizing monoclonal antibody therapies, bamlanivimab and REGN-COV2 (casirivimab plus imdevimab), for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adolescents and adults in specified high-risk groups. This has challenged clinicians to determine the best approach to use of these products.

Methods. A panel of experts in pediatric infectious diseases, pediatric infectious diseases pharmacy, pediatric intensive care medicine, and pediatric hematology from 29 geographically diverse North American institutions was convened. Through a series of teleconferences and web-based surveys, a guidance statement was developed and refined based on review of the best available evidence and expert opinion.
<table>
<thead>
<tr>
<th>Risk for severe COVID-19</th>
<th>Condition</th>
<th>Recommendation Treatment</th>
<th>Recommendation Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>• Obesity</td>
<td>Suggest administration</td>
<td>Consider if high risk exposure and unvaccinated or unlikely to respond to vaccine</td>
</tr>
<tr>
<td></td>
<td>• Severe Immunocompromise</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Medical complexity with respiratory technology dependence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>• Mild to moderate immunocompromise</td>
<td>Consider administration</td>
<td>Insufficient evidence</td>
</tr>
<tr>
<td></td>
<td>• Chronic respiratory conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Congenital heart disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Sickle Cell Disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>• Diabetes</td>
<td>Suggest no routine use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Chronic kidney disease</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Ivermectin: What are the Data and What’s Fueling its Use

Lindsey R. Baden, MD
Associate Professor of Medicine
Harvard Medical School
Director of Clinical Research, Division of Infectious Diseases
Brigham and Women’s Hospital

Disclosures: Receive research support from NIH, Gates, Wellcome Trust for vaccine and therapeutics development including for SARS-CoV-2. Serve on multiple NIH SMC/DSMBs and the IDSA Covid-19 Treatment Guidelines Committee.
Why is ivermectin considered for treatment?

- Ivermectin: An anti-parasitic agent. FDA-approved for onchocerciasis and strongyloidiasis and used off-label for the treatment of many parasitic infections.
- Although it has *in vitro* activity against some viruses, including SARS-CoV-2, it has no proven therapeutic utility.
  - *In vitro* activity against SARS-CoV-2 requires concentrations considerably higher than those achieved in human plasma and lung tissue to reach the *in vitro* IC$_{50}$.
- Has been shown to have anti-inflammatory effects in *in vitro* and *in vivo* studies; hence hypothesized to have a mechanism beyond its anti-viral effects in the treatment of COVID-19
- Since ivermectin is generally well-tolerated, it has been empirically evaluated in uncontrolled studies for COVID-19, alone and in combination with other off-label medications.
Estimated number of outpatient ivermectin prescriptions dispensed from retail pharmacies
United States, March 16, 2019–August 13, 2021

https://emergency.cdc.gov/han/2021/han00449.asp
Evidence Summary

• Systematic literature review identified 15 studies
  • Ages 8-86 years old, reported outcomes of mortality, symptom resolution, viral clearance, and AEs
  • Eligible studies compared ivermectin against a placebo or standard of care
    • 10 RCTs and 2 non-randomized informed inpatient assessment
    • 8 RCTS informed the ambulatory assessment
  • Design considerations
    • Quality of randomization process and blinding uneven
    • Dose used ranged from 100 to 400 mcg/kg/day for 1 to 7 days
  • Overall relatively small numbers and very small number of events
    • For example, assessing mortality:
      • Hospitalized patients 7 RCTs with 602 enrolled and 26 events
      • Ambulatory patients 7 studies with 1,631 enrolled and 15 events
## Observations

### Inpatients
- No evidence from RCTs for benefit on:
  - mortality
  - symptom resolution or
  - viral clearance

### Outpatients
- No evidence for benefit on
  - mortality
  - disease progression or
  - viral clearance
- Unclear if ivermectin may reduce time to recovery among outpatients
AMA, APhA, ASHP statement on ending use of ivermectin to treat COVID-19

SEP 1, 2021

WASHINGTON, DC – The American Medical Association (AMA), American Pharmacists Association (APhA), and American Society of Health-System Pharmacists (ASHP) strongly oppose the ordering, prescribing, or dispensing of ivermectin to prevent or treat COVID-19 outside of a clinical trial.

Ivermectin is approved by the U.S. Food and Drug Administration (FDA) for human use to treat infections caused by internal and external parasites. It is not approved to prevent or treat COVID-19. Ivermectin is also available to treat certain veterinary conditions; medications formulated or intended for use in animals should not be used by humans. We are alarmed by reports that outpatient prescribing for and dispensing of ivermectin have increased 24-fold since before the pandemic and increased exponentially over the past few months. As such, we are calling for an immediate end to the prescribing, dispensing, and use of ivermectin for the prevention and treatment of COVID-19 outside of a clinical trial. In addition, we are urging physicians, pharmacists, and other prescribers—trusted health care professionals in their communities—to warn patients against the use of ivermectin outside of FDA-approved indications and guidance, whether intended for use in humans or animals, as well as purchasing ivermectin from online stores. Veterinary forms of this medication are highly concentrated for large animals and pose a significant toxicity risk for humans.

https://www.fda.gov/consumers/consumer-updates/why-you-should-not-use-ivermectin-treat-or-prevent-covid-19
Rapid Increase in Ivermectin Prescriptions and Reports of Severe Illness Associated with Use of Products Containing Ivermectin to Prevent or Treat COVID-19

Summary
Ivermectin is a U.S. Food and Drug Administration (FDA)-approved prescription medication used to treat certain infections caused by internal and external parasites. When used as prescribed for approved indications, it is generally safe and well tolerated.

During the COVID-19 pandemic, ivermectin dispensing by retail pharmacies has increased, as has use of veterinary formulations available over the counter but not intended for human use. FDA has cautioned about the potential risks of use for prevention or treatment of COVID-19.

Ivermectin is not authorized or approved by FDA for prevention or treatment of COVID-19. The National Institutes of Health (NIH) COVID-19 Treatment Guidelines Panel has determined that there are currently insufficient data to recommend ivermectin for treatment of COVID-19.

Background
The Centers for Disease Control and Prevention (CDC) confirmed with the American Association of Poison Control Centers (AAPCC) that human exposures and adverse effects associated with ivermectin reported to poison control centers have increased in 2021 compared to the pre-pandemic baseline. These reports include increased use of veterinary products not meant for human consumption.

Ivermectin is a medication that is approved by FDA in oral formulations to treat onchocerciasis (river blindness) and strongyloidiasis. Topical formulations are used to treat head lice and mites. Ivermectin is also used in veterinary applications to prevent or treat internal and external parasitic infections in animals. When used in appropriate doses for approved indications, ivermectin is generally well tolerated.

Distributed via the CDC Health Alert Network
August 26, 2021, 11:40 AM ET
CDC HAN-00449

https://emergency.cdc.gov/han/2021/han00449.asp
Emerging Therapies under Investigation: Focus on Fluvoxamine

Shmuel Shoham, MD
Associate Professor of Medicine
Transplant and Oncology Infectious Disease Program
Johns Hopkins University School of Medicine

Disclosures: Grants: Ansun, F2G
Personal Fees: Celltrion, Adagio, Immunome
DSMG: Karyoharm, Intermountain Health, Adamis
CDC/IDSA Clinician Call
Emerging Therapies Under Investigation: Focus on Fluvoxamine
September 11, 2021

Shmuel Shoham, MD
Associate Professor of Medicine
Transplant and Oncology Infectious Diseases Program
Johns Hopkins University School of Medicine
Fluvoxamine for COVID-19: Potential Mechanisms

– Immune modulation
  • Sigma-1 receptor activation, leading to inositol-requiring enzyme 1α-driven (IRE1) inflammation ↓
  • platelet aggregation ↓
  • mast cell degranulation ↓
  • melatonin level ↑ (Melatonin may reduce inflammation through inhibition of the NLRP3 pathway)

– Antiviral effect
  • Interference with viral entry and endolysosomal viral trafficking
Safety of Fluvoxamine

- Safety record well-known
  - Used worldwide since 1990s
  - No fatality even in overdose
  - No cardiac QTc prolongation
- Main side effects: nausea (25%), insomnia. Mild, temporary.
- FDA warning about ALL antidepressants and increased “suicidality” in mentally ill persons age <25
- Could destabilize bipolar disorder (1% of population)
- Drug interactions:
  - Blocks metabolism of caffeine and rare drugs (eg theophylline)
  - 15-20% of Americans already taking an antidepressant.
Fluvoxamine vs Placebo for Outpatients With Symptomatic COVID-19

- Lenze et al, JAMA 2020
  - RCT (n=152); outpatient
  - Fluvoxamine 50 mg x 1 dose, then 100 mg BID x 2-3 days then 100 mg TID as feasible (only 50% got up to that dose) x 15 days
  - Clinical deterioration: 0/80 FLX patients vs 6/72 (8.3%) placebo (P = .009)
Primary endpoint: clinical deterioration (dyspnea PLUS hypoxia [O2<92%])

Fluvoxamine group: 0% (0/80) deteriorated

Placebo group: 8.3% (6/72) deteriorated.

Lenze et al., JAMA 2020
Prospective Cohort of Fluvoxamine for Early Treatment of COVID-19

• Seftel et al, OFID 2021
  – Prospective self selected cohort in the setting of a mass outbreak (n=65 FLX, 48 usual care)
  – Fluvoxamine 50 mg twice daily
  – Hospitalization 0/65 FLX vs. 6/48 (12.5%) for observation alone
  – Residual symptoms at 14 days 0/65 FLX vs. 29/48 (60%) with observation.
# Observational Cohort

## Prospective cohort of fluvoxamine for early treatment of COVID-19

<table>
<thead>
<tr>
<th>Mass Occupational Outbreak in California</th>
<th>Hospitalization</th>
<th>Symptoms at 14 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>113 non-hospitalized persons</td>
<td>0% (0/65)</td>
<td>0% (0/65)</td>
</tr>
<tr>
<td>• Detected by rapid Ag tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Confirmed by PCR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All offered Fluvoxamine as an optional therapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N = 65</th>
<th>Fluvaxamine 50mg 2x daily for 14 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observation Alone</td>
</tr>
<tr>
<td></td>
<td>12.5% (6/48)</td>
</tr>
<tr>
<td></td>
<td>60% (29/48)</td>
</tr>
</tbody>
</table>

Sofial D, Boulware DR. Prospective cohort of fluvoxamine for early treatment of COVID-19. Open Forum Infectious Diseases; 2021
Doi: 10.1093/ofid/ofab050
Together Clinical Trials: Brazil

- Multicenter RCT (n=1472)
- Fluvoxamine n=739, Placebo n=733
- Reduced need for hospitalization or an extended ED visit >6 hr
  - Fluvoxamine 10.4% (77/739) vs. 14.7% (108/733) placebo
  - Relative Risk = 0.71; 95% CI: 0.54 - 0.93
- No differences
  - Viral clearance at day 7 OR= 0.75; 95%CI: 0.53 - 1.07
  - Mortality (Outpatient trial) OR= 0.70; 95% CI: 0.36 - 1.30
  - Length of hospitalization. Mean Δ = 1.22 days; 95% CI: 0.98 - 1.53
  - Ventilator days Mean Δ = 1.10; 95% CI: 0.70 - 1.73
**STOP COVID 2: design summary**

StopCovidTrial.com

---

**Participants:**

n=1100
enriched sample*
SARS-CoV-2+
community-dwelling symptomatic (<7d)

* one or more of: African-Am, Latinx, Native-Am, age ≥40, obesity, diabetes, HTN, heart disease (CAD/MI/CHF), lung disease, or immune condition

**Fluvoxamine 100mg twice daily (x15d)**

**Placebo**

**Outcomes:**

**Primary:**
clinical deterioration over 15 days (definition: SOB and/or hospitalization, plus O2 <92%)

**Secondary:**
-15-day and 3 month function (Global Health Scale)
Ongoing trials

- COVID OUT
  - https://covidout.umn.edu

- ACTIV-6: COVID-19 Outpatient Randomized Trial to Evaluate Efficacy of Repurposed Medications
  - https://clinicaltrials.gov/ct2/show/NCT04885530
Patients Already Taking Antidepressants

If taking Monoamine Oxidase Inhibitor (MAOI):
- Do NOT give fluvoxamine.

If taking an SSRI/SNRI:
- If psychiatrically stable, consider switching to fluvoxamine x 15 days, then switch back to original medication.
- If taking low-dose SSRI/SNRI, could keep current medication and add fluvoxamine.
Thank you to Eric Lenze and Angela Reiersen (WUSTL) and David Boulware (UMN) for their expert review, guidance and for generously sharing slides.

Email: sshoham1@jhmi.edu
Twitter: @ShohamTxID
Q&A and Discussion
Links and References


Slide 15: FDA, FACT SHEET FOR HEALTH CARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF BAMLANIVIMAB AND ETSEVIMAB https://www.fda.gov/media/145802/download

Slide 16: https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Bamlanivimab/Pages/default.aspx

https://www.covid19treatmentguidelines.nih.gov

Slide 22: https://www.medrxiv.org/content/10.1101/2021.06.15.21258542v1.full.pdf


Slide 29: https://covid19treatmentguidelines.nih.gov

Slide 37: https://emergency.cdc.gov/han/2021/han00449.asp

Slide 40: https://www.fda.gov/consumers/consumer-updates/why-you-should-not-use-ivermectin-treat-or-prevent-covid-19

Slide 41: https://emergency.cdc.gov/han/2021/han00449.asp

Slide 52: COVID OUT - https://covidout.umn.edu
ACTIV-6: COVID-19 Outpatient Randomized Trial to Evaluate Efficacy of Repurposed Medications:
https://clinicaltrials.gov/ct2/show/NCT04885530
IDSA Guidelines on the Treatment and Management of Patients with COVID-19

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.

Specialty Society Collaborators

American Academy of Family Physicians
American Academy of Pediatrics
American College of Emergency Physicians
American College of Physicians
American Geriatrics Society
American Thoracic Society
Pediatric Infectious Diseases Society
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
CDC-IDSA Partnership: Clinical Management Call Support

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
We want to hear from you!
Please complete the post-call survey.
Clinician calls are now twice a month:

Next Call
Saturday, Sept. 25
A recording of this call will be posted Monday at
www.idsociety.org/cliniciancalls
-- library of all past calls available --

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