COVID-19 Hot Topics

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Disclosures

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Disclosures

I have no disclosures.
Learning Objectives

By the end of the presentation, listeners will be able to:

- Describe SARS-CoV-2 and its role in causing COVID-19, including pathogenesis, therapeutic targets, current circulating variants.
- Discuss the management and prevention of COVID-19, including vaccines, monoclonal antibodies, and antiviral medications, and an approach to selecting therapies.
- Discuss the new and evolving landscape of COVID-19 treatments.
67% FN 33% FN 20% FN at +3 days

Presymptomatic stage

Onset of symptoms

Days since Onset of Symptoms

Viral antigen

IgG

IgM

Viral RNA

Culturable Virus (correlate of infectiousness)
Positive RT-PCR Test
Positive Antigen Test
High IgG and Total Antibody Titers
Outpatients (typically)

Hypoxia requiring Hospitalization (typically)

About 7-12 days
Anti-spike: MABs Vaccines Convalescent Plasma*
Vaccine: 66% prevention of symptomatic disease in Omicron

99% reduction in serious illness or death
<table>
<thead>
<tr>
<th>Pre-Exposure Prophylaxis</th>
<th>Treatment, currently used</th>
<th>Treatment, not currently used</th>
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<tbody>
<tr>
<td>Tixagevimab + Cligavimab</td>
<td>Sotrovimab</td>
<td>Bamlanivimab + Etesevimab</td>
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<td>Bebtelovimab*</td>
<td></td>
<td>Casirivimab + Imdevimab</td>
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<td>Sotrovimab</td>
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</table>
Indications for Pre-Exposure Prophylaxis with tixagevimab + cligavimab (EvuSheld, Astra Zeneca)

- Age > 12 and more than 40kg, **AND**
- **Not** currently infected with COVID-19, **AND** EITHER
  - Moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments and may not mount an adequate immune response to COVID-19 vaccination, **or**
  - Vaccines are not recommended due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID19 vaccine component(s).
Tixagevimab + cligavimab is not a substitute for vaccination!
Indications for Treatment with bebtelovimab (Eli Lilly)

- Age > 12 and more than 40kg, **AND**
- Is currently infected with COVID-19 within 7 days of onset, **AND**:
- Has at least 1 high risk factor for severe disease, which can include:
  - Age > 65
  - Obesity
  - Hypertension
  - Diabetes
  - Chronic kidney disease
  - Cardiovascular disease, including congenital
  - Pregnant
  - Sickle cell disease
  - Immunocompromised/immunosuppressed
  - Chronic lung disease such as COPD or moderate to severe asthma
  - Dependence on a medical device
  - Congenital metabolic or genetic syndromes
  - Race
Monoclonal antibodies of unclear benefit

- Bamlanivimab + etesevimab (no brand name, Eli Lily)
- Casirivimab + imdevimab (Ronaprev, Regeneron)
- Sotrovimab (Xevudy, GSK)
Pros and Cons of MABs

**Pro:**
- Very effective at reducing hospitalization or death
- Slightly reduces symptom duration
- Duration of protection is about 90 days (180 days with tix/clig)

**Con:**
- Very expensive (>\$2000/dose + infusion costs)
- Requires infusion infrastructure
- Very limited supplies
- May interfere with long-term immunity after infection
- No data to support benefit in BA.2
Anti-spike: MABs
Vaccines
Convalescent Plasma*

1. Entry
   - ACE2 receptor
   - TMPRSS2

2. Uncoating
   - Drop of pH
   - Genomic RNA(+)

3. Translation
   - Ribosome
   - AAA

4. Proteolysis
   - Polypeptides

5. Transcription
   - Replicase-transcriptase complex
   - Pre-genomic RNA( )
   - AAA
   - UUU

6. Translation
   - Subgenomic RNA( )
   - AAA

7. Assembly
   - Genomic RNA( )
   - AAA

8. Release

9. Maturation

Protease Inhibitor: Nirmatrelvir
Nirmatrelvir/ritonavir (Paxlovid, Pfizer)
Nirmatrelvir 150mg BID
Ritonavir 100mg BID
Indications for Treatment with nirmatrelvir + ritonavir (Paxlovid, Pfizer)

- Age > 12 and more than 40kg, **AND**
- Is currently infected with COVID-19 within 5 days of onset, **AND:**
- Has at least 1 high risk factor for severe disease (not specified in the EUA)
Pros and Cons of nirmatrelvir + ritonavir

- **Pro:**
  - Very effective at reducing hospitalization or death
  - More accessible than MABs as an oral drug
  - Relatively cheap ($500 for 5 days)

- **Con:**
  - Must be started within 5 days of symptom onset
  - Ritonavir has substantial and sometimes serious drug-drug interactions
  - MABs + nirmatrelvir do not seem to work
  - Can be hard to find at times
  - Needs renal adjustment:
    - GFR 30-59: 150mg nirmatrelvir BID + 100mg ritonavir BID
    - GFR <30: not recommended
Early Remdesivir to Prevent Progression to Severe Covid-19

**DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIAL**

562 Outpatients with Covid-19, <7 days from symptom onset and with ≥1 risk factor for disease progression

**Covid-related hospitalization or death from any cause by day 28**

<table>
<thead>
<tr>
<th>Intravenous Remdesivir, 3 days</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>N=279</td>
<td>N=283</td>
</tr>
<tr>
<td>0.7% (2 patients)</td>
<td>5.3% (15 patients)</td>
</tr>
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HR, 0.13; 95% CI, 0.03–0.59 (P=0.008)

Remdesivir resulted in an 87% lower risk of Covid-related hospitalizations or death than placebo and had an acceptable safety profile.

R.L. Gottlieb et al. 10.1056/NEJMo2116846
Indications for Treatment with outpatient remdesivir (Veklury, Gilead)

- Age > 12 and more than 40kg*, **AND**
- Is currently infected with COVID-19 within 7 days of onset, **AND:**
- Has at least 1 high risk factor for severe disease

* Patients under 12 were not studied, however observational data exists for pediatric inpatients at 5mg/kg load and 2.5mg/kg daily maintenance
Pros and Cons of Outpatient remdesivir

**Pro:**
- Very effective at reducing hospitalization or death
- Better supply than EUA drugs
- Good safety profile
- Only treatment available for patients under 12 years old or <40kg
- Appears safe with MABs

**Con:**
- Must be started within 7 days of symptom onset
- Repeated IV only formulation is logistically difficult
- Relatively expensive (about $2000 for four 100mg vials)
- Unclear if effective with MABs
Molnupiravir (Legavio, Merck) 800mg BID
Indications for Treatment with molnupiravir (Legavio, Merck)

- Age > 18 and more than 40kg*, **AND**
- Is currently infected with COVID-19 within 5 days of onset, **AND:**
- Has at least 1 high risk factor for severe disease
Pros and Cons of molnupiravir

**Pro:**
- Moderately effective at reducing hospitalization or death
- Relatively good supply
- Good safety profile
- Relatively cheap ( $500 for 5 days)

**Con:**
- Must be started within 5 days of symptom onset
- May be terratogenic
- May be unsafe in pediatrics
- Unclear if effective with MABs
How Do I Decide What to Give?

- Not high risk
  - Vaccinate!
How Do I Decide What to Give?

- Not high risk
  - Vaccinate!

- **High risk, Pre-exposure, not symptomatic**
  - Vaccinate!
  - Tixagevimab/cligavimab (Evusheld) injections every 6 months
How Do I Decide What to Give?

- Not high risk
  - Vaccinate!
- High risk, Pre-exposure, not symptomatic
  - Vaccinate!
  - Tixagevimab/cligavimab (Evusheld) injections every 6 months
- High risk, COVID-19 +, Symptoms ≤ 5 days, adults
  - No CI to ritonavir: Nirmatrelvir/ritonavir
  - CI to ritonavir: MAB referral
  - Consider molnupiravir if other drugs are not available
How Do I Decide What to Give?

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  - Vaccinate!
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  - Consider molnupiravir is other drugs are not available
- High risk, COVID-19 +, Symptoms ≤ 7 days, pediatrics
  - Consider remdesivir
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- High risk, COVID-19 +, Symptoms ≤ 5 days, pediatrics
  - Consider remdesivir
- High risk, COVID-19 +, Symptoms 5-7 days, adults
  - Consider MAB
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- Not high risk
  - Vaccinate!
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- High risk, COVID-19 +, Symptoms ≤ 5 days, pediatrics
  - Consider remdesivir
- High risk, COVID-19 +, Symptoms 5-10 days, adults
  - Consider MAB
- More than 10 days of symptoms
  - Supportive care only
Drug Availability

Evolving Landscape of Therapies

- Outpatient steroids?
- What is the role of antibiotics?
Should I give outpatients systemic steroids?

PMID: 32678530
Should I give outpatients inhaled steroids?
Should I give outpatients steroids?

- Probably no role for oral steroids
- Maybe for inhaled steroids… but better treatments exist
What is the role of antibiotics?

- ...put another way, “what is the incidence of bacterial pneumonia in COVID-19?”
What is the role of antibiotics?

4% Bacterial co-infection at time of admission
What is the role of antibiotics?

- Probably none, unless there is a change in sputum production, or the patient has had prolonged hospitalization.
Take Home Points

- Nirmatrelvir and molnupiravir are beneficial at preventing serious disease in high risk patients
- Consider bebtelovimab when other drugs are not available
- There is little role for antibiotics in outpatient COVID-19 management
Questions?

OUR NEW GUIDANCE: FULLY VACCINATED PEOPLE CAN GATHER PRIVATELY WITH NO MASKS OR DISTANCING, AND CAN VISIT WITH UNVACCINATED LOW-RISK PEOPLE IN ONE HOUSEHOLD. ANY QUESTIONS?

IF MY NEIGHBORS AND I ARE ALL VACCINATED, CAN I VISIT THEM UNMASKED AND DRINK MILK DIRECTLY FROM THE JUG IN THEIR FRIDGE? I...YOU CAN VISIT, YES. AND THE JUG THING? NEXT QUESTION?

I'M FULLY VACCINATED. CAN I RIDE MY BIKE IN MY SISTER-IN-LAW'S HOUSE? IN HER HOUSE? LIKE, DOWN THE STAIRS. I GUESS? YOU SHOULD AT LEAST WEAR A HELMET. EVEN IF SHE'S NOT HIGH-RISK? ANY QUESTIONS?

I'M TWO WEEKS PAST MY SECOND DOSE. CAN I GET A HORSE? THANK YOU ALL FOR COMING. WHAT IF I WEAR A MASK? WHAT IF THE HORSE DOES?

MEETING ENDED BY HOST