Webinar Moderator

Emily Blumberg, MD, FAST

- Director of the Transplant Infectious Diseases Program and the Infectious Diseases Fellowship
- University of Pennsylvania
Webinar Moderator

Oren K. Fix, MD, MSc, FAASLD

• Clinical Associate Professor at the Washington State University Elson S. Floyd College of Medicine

• Co-Chair of the AASLD Clinical Oversight and Education Subcommittee
Webinar Agenda

Talks
Webinar and Presenter Introductions
“Outpatient management of COVID19 & monoclonal antibodies”
“Safety & efficacy of mRNA & adenoviral vaccines”
"Implications of SARS-CoV-2 viral variants”
“Therapeutic & vaccine recommendations in liver disease and transplant recipients“
Panel Discussion / Q&A

Speakers
Dr. Blumberg & Dr. Fix
Dr. Daniel Kaul
Dr. Onyema Ogbuagu
Dr. Adam Lauring
Dr. Mark Russo
All
Webinar Q&A

• Submit your questions anytime during the webinar in the Q&A box at the top or bottom of your screen.

• Questions will be answered at the end of the presentations.
Webinar Presenter

Adam S. Lauring, MD, PhD
• Assistant Professor in the Departments of Internal Medicine
• University of Michigan
Onyema Ogbuagu, MBBCh, FACP, FIDSA

• Associate Professor of Medicine
• Director of the HIV Clinical Trials program of the Yale AIDS Program
• Section of Infectious Diseases of the Yale School of Medicine
Webinar Presenter

Mark W. Russo, MD, MPH, FAAASLD

- Medical Director of Liver Transplantation
- Chief, Division of Hepatology
- Clinical Professor of Medicine
- Carolinas Medical Center-Atrium Health
AASLD’s COVID-19 Clinical Oversight & Education Subcommittee

- Co-chair, Oren K. Fix, MD, MSc, FAASLD, Swedish Medical Center (Washington)
- Co-chair, Robert J. Fontana, MD, FAASLD, University of Michigan (Michigan)
- David C. Mulligan, MD, FACS, FAASLD, Yale University, (Connecticut)
- David L. Thomas, MD, Johns Hopkins University (Maryland)
- Mark W. Russo, MD, MPH, FAASLD, Carolinas Medical Center (North Carolina)
- Nancy S. Reau, MD, FAASLD, Rush University (Illinois)
- Laura M. Kulik, MD, Northwestern Medical Faculty Foundation (Illinois)
- Bilal Hameed, MD, University of California (California)
- Ryan M. Kwok, MD, Uniformed Services University (Maryland)
- Elizabeth K. Goacher, PA-C, MHS, AF-AASLD, Duke University (North Carolina)
- Jennifer C. Price, MD, PhD, University of California, San Francisco (California)
- Daniel S. Pratt, MD, FAASLD, Massachusetts General Hospital (Massachusetts)
- Jaime Chu, MD, Icahn School of Medicine at Mount Sinai (New York)
- Brendan M. McGuire, MD, University of Alabama (Alabama)
- Mark W. Russo, MD, MPH, FAASLD, Carolinas Medical Center (North Carolina)
- Michael Schilsky, MD, FAASLD, Yale University (Connecticut)
- Andrew Reynolds, (Patient Advocate)
- Raymond Chung, Massachusetts General Hospital (Massachusetts) (ex-officio)
- K. Rajender Reddy, University of Pennsylvania Medical Center (Pennsylvania) (ex-officio)
- Elizabeth C. Verna, MD, MS, Columbia University (New York) (ex-officio)
MAB Treatment for COVID-19

Daniel Kaul MD
Director Transplant Infectious Disease
Division of Infectious Disease
Disclosures and Acknowledgements

• Research support: Gilead Sciences, Shire, J&J, NIAID, Astra Zeneca, Lilly

• DSMB: Noveome

• Advisory Boards: none

• Some of the data presented is not peer reviewed
Topics

• MAB role in therapy
• Need for early identification
• Administration challenges
• Antibody escape
• Role of MAB in persistent infection
Monoclonal antibodies only recommended treatment for ambulatory patients

<table>
<thead>
<tr>
<th>Setting and severity of illness</th>
<th>Ambulatory care: mild-to-moderate disease</th>
<th>Hospitalized: mild-to-moderate disease without need for suppl. oxygen</th>
<th>Hospitalized: severe but non-critical disease (sPO2 &lt;94% on room air)</th>
<th>Hospitalized: critical disease (e.g., in ICU needing MV, or septic shock, ECMO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>• Monoclonal antibodies</td>
<td>• Supportive care</td>
<td>• Corticosteroids</td>
<td>• Corticosteroids</td>
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<tr>
<td></td>
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<td></td>
<td>• Tocilizumab</td>
<td>• Tocilizumab</td>
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<td></td>
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<td></td>
<td>• Remdesivir</td>
<td>• +/− remdesivir</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Bari + remdesivir</td>
<td></td>
</tr>
</tbody>
</table>

Mechanism of action

• Binds receptor binding domain of spike protein

• Dual antibody preparations to reduce potential for variant escape
Monoclonal Antibodies for COVID-19 (EUA granted)

• Anti-spike neutralizing monoclonal antibody that binds to the receptor-binding domain of SARS-CoV-2

• Regeneron:
  • REGN10933 + REGN10987

• Eli Lilly:
  • LY-CoV555 (bamlanivimab) B-mab
  • LY-CoV555 + LY-CoV116 (etesevimab)
Regeneron Halts Trial for Antibody Cocktail in Sickest COVID-19 Patients

by Global Biodefense Staff  October 30, 2020, 1:05 pm
OUTPATIENTS TREATED WITHIN 7 DAYS OF ONSET OF SYMPTOMS (3.0 DAYS MEDIAN)

- 2.4gm versus 8.0gm of REGN-COV2 versus placebo
- 41% negative baseline antibody (much higher viral loads, greater chance of medical event)
- Greater effect in those with higher viral titers

MEDICALLY ATTENDED EVENT

- 6/93 (6%) placebo
- 6/182 (3%) active
# Bamlanivimab +/- Etesevimab

## Events of COVID-19 Related Hospitalization or Emergency Room Visit Within 28 Days After Treatment

### All Subjects

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Events</th>
<th>Rate</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>156</td>
<td>9</td>
<td>5.8%</td>
<td>-</td>
</tr>
<tr>
<td>LY Mono (All Doses)</td>
<td>309</td>
<td>5</td>
<td>1.6%</td>
<td>0.020</td>
</tr>
<tr>
<td>LY Combo</td>
<td>112</td>
<td>1</td>
<td>0.9%</td>
<td>0.049</td>
</tr>
<tr>
<td>LY Mono + Combo</td>
<td>421</td>
<td>6</td>
<td>1.4%</td>
<td>0.0067</td>
</tr>
</tbody>
</table>

### Age ≥ 65 or BMI ≥ 35

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Events</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>52</td>
<td>7</td>
<td>13.5%</td>
</tr>
<tr>
<td>LY Mono (All Doses)</td>
<td>101</td>
<td>4</td>
<td>4.0%</td>
</tr>
<tr>
<td>LY Combo</td>
<td>31</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>LY Mono + Combo</td>
<td>132</td>
<td>4</td>
<td>3.0%</td>
</tr>
</tbody>
</table>

BMI = Body Mass Index; ER = Emergency Room
P-values are from the Fisher’s exact test
LY-CoV555 Mono is pooled data from 700 mg, 2800 mg, and 7000 mg

https://investor.lilly.com/static-files/081a5ef7-f5d6-4acc-b0d2-7ae4daf9e953
MAB as prevention in high-risk exposed persons

Regeneron (press release)
- 400 patients in same household as COVID-19 patient
  - Placebo
    - 23/223 (10%) asymptomatic infection
    - 8/223 (4%) symptomatic infection
    - 100x higher peak viral load
  - MAB:
    - 10/186 (5%) asymptomatic infection
    - 0/186 symptomatic COVID-19

NH residents

https://investor.lilly.com/static-files/081a5ef7-f5d6-4acc-b0d2-7ae4daf9e953
Plan of action to administer monoclonal antibodies under outpatient EUA

Confirm your site wants to participate
- Review needs for treatment in outpatient settings
- Ensure site prepared to meet needs for treatment or willing to make required investments
- Confirm site leadership supportive of participation
  - Including senior clinical leadership (e.g., Chief Medical Officer)
- Approval of product for use by the hospital’s Pharmacy and Therapeutics Committee (or equivalent committee)

Prepare your site and staff for outpatient mAbs administration
- Ensure sufficient supply of needed materials for treatment
  - Infusion supplies, resuscitation equipment, etc.
- Develop staffing and personnel plan to support treatment
- Allocate needed facilities and equipment to support administration
- Ensure existing infection prevention plan sufficient
  - Adjust existing plan if needed to safely manage patient flow
  - Consider potential security requirements if needed
- Review drug administration needs with staff
- Inquire with hospital leadership about reimbursement process
- Prepare for adverse events data tracking process

Develop procedures to identify and treat patients in timely manner
- Prepare for scheduling and routing of referrals from testing center or other HCPs to treatment
- Ensure hospital staff and doctors aware of outpatient treatment availability
- Ensure patient privacy (HIPAA compliant) maintained during process
- Communicate to patient that EUA issued for investigational treatment but does not constitute research on behalf of the hospital
Outpatient or admitted for non-Covid-19 reason

No supplemental oxygen (or stable)

Mild to moderate disease

Symptoms < 10 days

High risk of progression
Viral variants and MAB escape

- Combinations help but some variants have potential to escape
- Probably more vulnerable than polyclonal + T-cell response generated by vaccines and natural infection


MAB severely immunocompromised

• Patients with severe T-cell and B-cell deficiencies may have difficulty clearing SARS-CoV-2

• Intermittent recurrent viral shedding and response to therapy with relapse common
Summary

- Monoclonal antibody only directed therapy with reasonable evidence base available to outpatients
- Early is better so system to identify and administer for vulnerable patients is critical
- Efficacy in immunized unknown
- Some variants might be a major issue even for combination products
- Role of monoclonal antibody in highly immunocompromised with persistent infection unknown
COVID-19
Safety and efficacy of mRNA and Viral Vector Vaccines

Onyema Ogbuagu, MD, FACP, FIDSA
Associate Professor of Medicine
Director, HIV Clinical trials program
Section of Infectious Diseases
Yale School of Medicine
Disclosures

- Research program support from Pfizer and Sanofi (COVID vaccine studies)
Viral vector vaccines – how they work

• New“ish” vaccine approach – First FDA approved vaccine was VSV for Ebola in 2019
• Simulates natural infection
• Viral vectors may be replicating or non-replicating
• Doesn’t alter host DNA
mRNA vaccines—how they work

• Modified RNA overcomes limitations with stability and immunogenicity (decades of work)
• Fragile, requires formulation with LNPs to protect RNA form degradation (eliminated ~ hours)
• Many applications including cancer Rx and other infectious diseases

Source: NIH.gov
## Lead Vaccine platforms- some pros and cons

<table>
<thead>
<tr>
<th>PROS</th>
<th>CONS</th>
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<tbody>
<tr>
<td>mRNA</td>
<td></td>
</tr>
<tr>
<td>Pfizer; Moderna</td>
<td>Potent, Easy to produce</td>
</tr>
<tr>
<td>Astra Zeneca, J and J</td>
<td>Induce robust T cell responses</td>
</tr>
<tr>
<td>Sinovac</td>
<td>Safer than live attenuated</td>
</tr>
<tr>
<td>Novavax</td>
<td>Relatively safe</td>
</tr>
<tr>
<td></td>
<td>Cheap to produce</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>PROS</td>
<td>Cold-chain</td>
</tr>
<tr>
<td></td>
<td>2 dose requirement</td>
</tr>
<tr>
<td></td>
<td>Lipid nanoparticles associated with allergies</td>
</tr>
<tr>
<td>CONS</td>
<td>Anti vector immunity</td>
</tr>
<tr>
<td></td>
<td>Cell based manufacturing</td>
</tr>
<tr>
<td>CONS</td>
<td>Requires large quantities of virus/ production</td>
</tr>
<tr>
<td></td>
<td>Safety testing</td>
</tr>
<tr>
<td></td>
<td>Require adjuvant</td>
</tr>
<tr>
<td>CONS</td>
<td>Tend to trigger less T cell responses, require adjuvants</td>
</tr>
<tr>
<td></td>
<td>Laborious protein purification process</td>
</tr>
</tbody>
</table>

References: Flanagan KL, Front Immunol, 2020

Image credit- mRNA (NIH), Viral vector, Protein subunit (Times of India), Inactivated virus (Fraunhofer IZI)
Evading antivector immunity

- Single dose vaccine (high viral “payload”)
- ½ dose followed by full dose
- Increasing duration between doses
- Rare human or primate adenoviral vector
- 2 sequential & different Ad Vector platforms
- Vaccine combos (mRNA and viral vector)

<table>
<thead>
<tr>
<th>Race/ Ethnicity</th>
<th>Human Adenovirus seropositivity (Ad 26 vs Ad5 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blacks, Asians (SE Asia)</td>
<td>40-70% vs 90%</td>
</tr>
<tr>
<td>Caucasian (Europe / N. America)</td>
<td>10-20% vs 30%</td>
</tr>
</tbody>
</table>

? Impact on booster doses or for annual vaccines if needed

? Impact of vectors used for COVID affecting their utilization for vaccines for other diseases

Reference: Mast TC et al, Vaccine, 28 (4) (2010), pp. 950-957
Vaccine efficacy
52 Rhesus Macaques challenged intratracheally and intranasally with SARS CoV-2, 6 weeks after Ad26 vaccination (7 variants) or sham vaccine [single shot IM]

BAL and nasal swabs performed after challenge

Results:
- RBD IgG and neutralizing Ab responses detected in 2-4 weeks
- 30/32 vaxed animals had T cell responses
- BAL protection > nasal swabs

Implications: single shot may work AND vaccine may not entirely prevent clinical disease, could be muted when contracted
## Phase 3 vaccine efficacy reports *

<table>
<thead>
<tr>
<th>Sponsor/ Developer</th>
<th>Platform</th>
<th>Phase 3 studies</th>
<th>Efficacy#</th>
<th>Trial expansion</th>
<th>Coming soon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer/ BioNTech</td>
<td>mRNA</td>
<td>Ongoing</td>
<td>95%</td>
<td>Age 12-15 HIV, HBV, HCV Pregnant women</td>
<td>Age 5-11</td>
</tr>
<tr>
<td>Moderna/ NIH</td>
<td>mRNA</td>
<td>Ongoing</td>
<td>94%</td>
<td>Age 12-18</td>
<td></td>
</tr>
<tr>
<td>Johnson and Johnson / BID Boston</td>
<td>Ad 26 vector</td>
<td>Ongoing</td>
<td>66% overall (72% United States) (57% South Africa)</td>
<td>2 dose phase 3 trial ongoing</td>
<td>Peds</td>
</tr>
<tr>
<td>Astra Zeneca/ Uni of Oxford</td>
<td>ChAd Ox1 vector</td>
<td>Ongoing</td>
<td>62% (Full/Full) 90% (Half/Full) 70% (average) (10% South Africa$)</td>
<td>Collaborating with Sputnik V group</td>
<td></td>
</tr>
<tr>
<td>Gamaleya / Sputnik V</td>
<td>Ad Vectors – 5 &amp; 26</td>
<td>Ongoing</td>
<td>92%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Sourced from Press releases and published papers. # primary endpoints variable including differences in endpoint-symptomatic versus moderate to severe disease & timing from single or second vaccination to efficacy endpoint $ efficacy against mild to moderate COVID-19

Vaccine efficacy increases for preventing more severe forms of COVID-19 and death

<table>
<thead>
<tr>
<th>Vaccine Efficacy / COVID severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine type</td>
</tr>
<tr>
<td>NIH / Moderna</td>
</tr>
<tr>
<td>BioNTech/ Pfizer</td>
</tr>
<tr>
<td>Johnson and Johnson</td>
</tr>
<tr>
<td>Astra Zeneca/ Oxford</td>
</tr>
<tr>
<td>Gam-Sputnik V</td>
</tr>
</tbody>
</table>

* Presence or absence of circulating variants, host characteristics, endpoint definitions impact efficacy

# In some studies, no deaths related to COVID-19 occurred in the placebo arm as well

J and J vaccine efficacy (starts 2 weeks post dose)
Vaccine trial participants (subgroups)
### Characteristics of Phase 3 clinical trial populations*

*% in Vaccine arms per FDA briefing documents

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Pfizer (mRNA)</th>
<th>Moderna (mRNA)</th>
<th>Janssen (Viral vector)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese</td>
<td>35%</td>
<td>6.8% (severe)</td>
<td>28.7%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>24.4%</td>
<td></td>
<td>10.2%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7.7%</td>
<td>9.5%</td>
<td>7.8%</td>
</tr>
<tr>
<td>HIV disease</td>
<td>0%</td>
<td>0.6%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Liver disease</td>
<td>0.6%</td>
<td>0.7%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Underlying etiologies of and severity of liver disease not always captured. COVID events in liver disease patients too small to assess efficacy.
How are older folk doing in early phase trials?

Caveat: Different neutralization assays used

Levels of neutralization titers do not always correlate to degree of immunity against disease

GSK / Sanofi protein vaccine “underperformed” in individuals older than 60 years (did not approach levels of neutralizing antibodies in convalescent patients)

Good News is that phase 3 trials showed vaccine efficacy in older = younger
How are transplant folk doing?

**RESEARCH LETTER**

**Immunogenicity of a Single Dose of SARS-CoV-2 Messenger RNA Vaccine in Solid Organ Transplant Recipients**

*JAMA, Boyarsky BJ et al. 2021*

- Renal vs non renal
- =>6 yrs vs < 6 years post transplant
- antimetabolite immunosuppression vs non antimetabolite immunosuppression
- mRNA-1273 versus BNT162b2
- ROCHE Elecsys vs EUROIMMUN

**KEY FINDINGS** - younger (10 yr categories), mRNA 1273, and those not on antimetabolite immunosuppression had better responses
Vaccine safety
## mRNA and viral vector vaccine safety records

<table>
<thead>
<tr>
<th></th>
<th>Pfizer (Dose 2) N=3705</th>
<th>Moderna (Dose 2) N=14677</th>
<th>Johnson and Johnson (N = 3356)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local reaction #</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site pain</td>
<td>18.5 - 28.3%</td>
<td>4.1%</td>
<td>33.3 - 58.6%</td>
</tr>
<tr>
<td>Injection Site redness</td>
<td>2.4 – 3.7%</td>
<td>2.0%</td>
<td>4.6 - 9.0%</td>
</tr>
<tr>
<td><strong>Systemic Side effects #</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>29.4 - 38.3%</td>
<td>9.7%</td>
<td>29.7 – 43.8%</td>
</tr>
<tr>
<td>Headaches</td>
<td>13.5 - 26.1%</td>
<td>4.5%</td>
<td>30.4 – 44.4%</td>
</tr>
<tr>
<td>Myalgias</td>
<td>16.6 - 21.7%</td>
<td>9.0%</td>
<td>24 – 39.1%</td>
</tr>
<tr>
<td>Fever</td>
<td>21.8 - 31.4% (all ranges)</td>
<td>1.5%</td>
<td>3.1 – 5.8%</td>
</tr>
<tr>
<td><strong>Non fatal SAEs (related to vaccine)</strong></td>
<td>3 (shoulder injury, arrhythmia, lymphadenopathy)</td>
<td>0.5%</td>
<td>3 (radiculitis, post vax syndrome, hypersensitivity)</td>
</tr>
<tr>
<td><strong>Death (related to vaccine)</strong></td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Pregnancy data?</td>
<td>+ Animal data</td>
<td>+ Animal data</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**# solicited severe (grade 3 or more) adverse reactions**

Source: FDA.gov
Rare events

• **Events:** Low platelets / hemorrhage and thrombotic events

• Of 17 million people vaccinated in UK and Europe, <40 cases have occurred

• Similar to background rate of events if not lower

'Overly cautious': No evidence AstraZeneca's COVID-19 vaccine linked to blood clots

A handful of European nations pause rollout of the Oxford-AstraZeneca vaccine while authorities investigate possible clotting issues.
Summary

• Current batch of authorized vaccines safe and effective > in preventing severe/critical disease and death

• Decreased immunogenicity in older adults portends similar effect for other immunocompromized groups, but efficacy data encouraging

• Limited efficacy data for liver disease patients (need to catalogue disease severity); low immunogenicity for solid organ transplant recipients is concerning.
Implications of SARS-CoV-2 viral variants

Adam Lauring, MD, PhD
University of Michigan Medical Center
alauring@umich.edu
The ins and outs of SARS-CoV-2 variants

Adam Lauring, MD, PhD, FIDSA
Department of Medicine, Infectious Diseases
Department of Microbiology and Immunology
University of Michigan
Disclosures

• Paid consultant on antiviral drugs for Sanofi

• Paid member of Steering Committee for Roche clinical trial, ongoing CENTERSTONE: a global phase IIIb, randomised, double-blind, placebo-controlled clinical efficacy study of baloxavir marboxil for the reduction of direct transmission of influenza from otherwise healthy patients to household contacts
A variant consumers survival guide

Studies Examine Variant Surging in California, and the News Isn’t Good

Two studies confirm that a new coronavirus mutant in California is more contagious, although the scale of its threat is unclear.

Some critics, including Dr. Eric Topol, the founder and director of the Scripps Research Translational Institute, have said that the attention given to the succession of new variants — “scairants,” he has called them — has done little more than frighten the public.

Dr. Musser agreed, referring to such reports as “mutant porn.” Highlighting the existence of variants without indicating whether they make any functional difference to real-world patients was no more enlightening than collecting stamps or identifying the birds flying overhead, he said: “‘There’s a bird. There’s another bird.’”

He added: “I think the crucial thing in all of this is that it is extraordinarily difficult for both the medical and lay public to really sort through all this noise about variants. At the end of the day, does any of this mean a hill of beans to anyone?”

Carl Zimmer, NY Times  Gina Kolata, NY Times
Terminology

- **Mutation** – an actual change in the nucleic acid or amino acid sequence (e.g. N501Y, E484K)
- **Variant** – two sequences that are different
- **Lineage** – a variant and its descendants (as in a phylogenetic tree)
- **Strain** – technically a variant that is phenotypically different, but basically a garbage term these days
Variants...of concern...of interest...under investigation

**B.1.17**
- First identified in United Kingdom
- Aka. Variant of Concern 202012/01, VOC-202012/01, 20B/501Y.V1, 20I/501Y.V1
- Variant of Concern

**B.1.351**
- First identified in South Africa
- Aka. 20H/501Y.V2
- Variant of Concern

**P.1**
- First identified in Brazil
- Variant of Concern

**B.1.427**
- First identified in California
- Aka. CA VUI, CAL.20C
- Variant of Interest

**B.1.429**
- First identified in California (United States)
- Aka. CA VUI, CAL.20C
- Variant of Interest

**B.1.526**
- First identified in New York
- Aka. ID04 LH
- Variant of Interest
Spike is *the* antigen

*Wrapp et al. Science 2020*
Lineage B.1.1.7 (aka “the UK variant”)

- It arose as a long branch (immunocompromised host?)
- It spreads more rapidly, so is more difficult to contain
- Does not appear to vary with age (early speculation)
- Newer data suggest that it may cause more severe disease
  - Hard studies to do, lots of caveats

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<tr>
<th>S</th>
<th>DEL69/70.O</th>
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<tbody>
<tr>
<td>S</td>
<td>DEL144/144.O</td>
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<tr>
<td>S</td>
<td>N501Y</td>
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<tr>
<td>S</td>
<td>A570D</td>
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<td>S</td>
<td>D614G</td>
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Are we all Denmark?

US case counts, NY Times

Percent B.1.1.7, outbreak.info
B.1.351 (aka “the South African Variant”)

- It appears to spread rapidly
- Concerns that it is less neutralizable by sera (vax, convalescent)
- E484K!

<table>
<thead>
<tr>
<th>S</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
<td>K417N</td>
</tr>
<tr>
<td>S</td>
<td>E484K</td>
</tr>
<tr>
<td>S</td>
<td>N501Y</td>
</tr>
<tr>
<td>S</td>
<td>D614G</td>
</tr>
<tr>
<td>S</td>
<td>A701V</td>
</tr>
</tbody>
</table>
P.1 (aka “the Brazilian Variant”)  

- Explosive outbreaks in Manaus (reinfection?)
- Has spread fairly quickly
- Troika of mutations also in B.1351
Will monoclonals still work?

Bamlanivimab, LY-CoV555

Starr et al. Science 2021
Will the vaccines still work?

**Liu et al. NEJM 2021 (Pfizer)**

See also Werner NEJM 2021 (Moderna)

Want Nature 2021 (Moderna)
What do the trials say?

- **J&J (Ad26), FDA filing**
  - VE against moderate to severe COVID-19 infection
  - 72% in US, 66% in Latin America (P1) and 57% in South Africa (B.1.351)

- **Novavax (Spike nanoparticle), press release**
  - Overall VE against symptomatic disease 89.3% (75.2;95.4)
    - Post hoc analysis showed similar efficacy against B.1.1.7
  - South Africa phase 2b trial, VE in HIV (-) 60.1% (19.9; 80.1)
    - 93% of cases due to B.1.1351

- **Pfizer (observational study in SIREN cohort), Lancet preprint**
  - December 7, 2020 through February 5, 2021
  - 85% effectiveness, 7 days after second dose
Therapeutic & vaccine recommendations in liver disease and transplant recipients

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Clinical Best Practice Advice for Hepatology and Liver Transplant Providers During the COVID-19 Pandemic: AASLD Expert Panel Consensus Statement


Released: February 2, 2021

AASLD EXPERT PANEL CONSENSUS STATEMENT: VACCINES TO PREVENT COVID-19 INFECTION IN PATIENTS WITH LIVER DISEASE

https://www.aasld.org/about-aasld/covid-19-and-liver
Transplant candidate

Chronic liver disease

With or without cirrhosis

Compensated or decompensated cirrhosis

More intense immunosuppression

Less intense immunosuppression

Posttransplant
Effect of SARS-CoV-2 on the Liver

- Direct viral effect
- Secondary to inflammatory/immune response
- Complications of COVID-19 (myositis, cardiac ischemia)
- Drug hepatotoxicity

COVID-19 + elevated liver tests

Pattern of liver injury with COVID-19
SARS-CoV-2: Hepatocellular and Cholestatic Injury

AST/ALT ELEVATIONS
6%-36%

TBILI/ALP/GGT ELEVATIONS
4.9%-14.8%

Mortality associated with:
ALP, ALB, AST

Is COVID-19 more common among patients with chronic liver disease? Are CLD patients at increased risk for severe outcomes?

Meta-analysis
73 studies, 24,299 patients

COVID pts
3% CLD
OR=1.78 for mortality

nonCOVID pts
3% CLD

Risk factors for severe disease or mortality
- Alcohol liver disease
- HCC
- NAFLD?
- Cirrhosis

Who’s at greatest risk of death?
Mortality risk in cirrhosis, by Child-Pugh class

COVID-19 Rx
33% no cirrhosis
vs
52% cirrhosis
HCQ
LOP/RIT
IFN-alpha

Reference: No cirrhosis

ALD only etiology associated with mortality

Cause of death
COVID lung disease > Liver related > cardiac

## Guidance
### Treatment of underlying liver disease

<table>
<thead>
<tr>
<th></th>
<th>COVID-19 +</th>
<th>No COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>Initiate therapy</td>
<td>Initiate/continue therapy</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Defer therapy</td>
<td>Initiate/continue therapy</td>
</tr>
<tr>
<td>PBC</td>
<td>Defer therapy</td>
<td>Initiate/continue therapy</td>
</tr>
<tr>
<td>AIH</td>
<td>Reduce/DC immunosuppression, exceptions in severe AIH</td>
<td>Initiate/continue therapy</td>
</tr>
<tr>
<td>HCC</td>
<td>Defer surveillance</td>
<td>Continue surveillance and therapy</td>
</tr>
</tbody>
</table>
Management of hospitalized patients with chronic liver disease and COVID-19

- Treat CLD patients with COVID-19 therapy same as those w/o CLD
- Tocilizumab: discontinue if ALT, AST>5XULN (PI)
- Remdesivir: consider discontinuing ALT>10x ULN (PI)
- Patients who are hep B sAg+ treated with dexamethasone, tocilizumab should be on antiviral therapy for hepatitis B
- Consider reducing or discontinuing drugs associated with leukopenia, lymphopenia, such as azathioprine, MMF
- AST, ALT>5XULN may exclude patients from clinical trials
- Tacrolimus should not be routinely reduced or discontinued
Tacrolimus and COVID-19
36 centers, 9 countries
243 LT recipients with COVID-19,
European Liver Transplant Registry

Tacrolimus use 45% reduction in mortality
HR=0.55 (95% CI 0.31-0.99)

>70 y/o HR=4.16 (95% CI 1.78-9.72)
vs≤60 y/o

Mortality

<table>
<thead>
<tr>
<th>Location</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home</td>
<td>0</td>
</tr>
<tr>
<td>Ward</td>
<td>17%</td>
</tr>
<tr>
<td>ICU</td>
<td>54%</td>
</tr>
</tbody>
</table>

TAC only 22%
TAC+MMF 21%
MMF only 10%

# Therapy for COVID-19 and CLD

<table>
<thead>
<tr>
<th>Therapeutic</th>
<th>Metabolism</th>
<th>Regimen</th>
<th>Dose adjustment</th>
<th>Liver test elevations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>CYP3A4</td>
<td>6 mg daily x 10 days</td>
<td>No</td>
<td>Rare</td>
</tr>
<tr>
<td>Remdesivir</td>
<td>74% renally excreted CYP2C8,CY2D6, CYP3A4, OATP1B1, P-gp</td>
<td>200 mg loading-100 mg/d x 10 days</td>
<td>No</td>
<td>5% grade 3, 2% grade 4 Consider DC ALT&gt;10XULN</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>Catabolic Minimal hepatic</td>
<td>4-8 mg single doses</td>
<td>No</td>
<td>2.9% ALT 5XULN DC ALT/AST&gt;5XULN</td>
</tr>
<tr>
<td>Sarilumab</td>
<td>Unknown</td>
<td>200-400 mg single dose</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Monoclonal antibodies</td>
<td>Proteolytic degradation</td>
<td>IV infusion as single doses</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

SHOULD PATIENTS WITH STABLE CHRONIC LIVER DISEASE RECEIVE THE COVID-19 VACCINE?

Pfizer-BioNTech

- ≥16 y/o
- N=21,720
  - Vaccine group
  - stable CLD: N=124
    - HCV, HBV
- Efficacy and safety not reported in CLD subgroup

Moderna

- ≥18 y/o
- N=15,181
  - Vaccine group
  - stable CLD: N=100
- No patient with CLD in vaccine group developed severe COVID-19

*Excluded patients on immunosuppressive therapy

https://www.fda.gov/media/144434/download
Anaphylaxis to mRNA vaccines

Vaccine Adverse Event Reporting System (VAERS)

1,602,064 vaccine recipients
Dec 14, 2020 - Jan 13, 2021

Pfizer-BioNTech
814,648 (50.8%)

Moderna
787,417 (49.2%)

Anaphylaxis 4.5 cases per million

Rates of anaphylaxis with vaccines
Influenza 1.4 per million
Pneumococcal 2.5 per million
Zoster (live attenuated) 9.6 per million

90-100% anaphylaxis in women
90% within 15 minutes

Johnson & Johnson/Janssen vaccine (Ad26.COV2.S) 
>18 y/o

N=21,895 Vaccine group

N=21,888 Placebo group

103 CLD
7 immunocompromised from SOT

1 CLD developed moderate/severe COVID-19 disease 14 days after vaccination

No anaphylaxis immediately following vaccination
5 cases of nonserious urticaria in vaccine group vs 1 in placebo group

https://www.fda.gov/media/146217/download
Should patients with chronic liver disease receive the COVID-19 Vaccine - **YES**

- Do not withhold medication for HBV, HCV, AIH, PBC, HCC
- Patients with fever, current infection should wait until stable
- Administer at recommended intervals, not more than 6 weeks
- Do not restart series if longer than 6 week delay
- Administer at least 14 days apart from other vaccines
- Wait minimum of 90 days to vaccinate after COVID-19 infection if receive monoclonal antibody
Recommendations and COVID-19 vaccination
Liver transplant candidates and living donors

- Liver transplant candidates should receive COVID-19 vaccine prior to transplant whenever possible.
- Healthy living liver donors should receive COVID-19 vaccine electively and preferably prior to donation.
- Even after vaccination maintain COVID-19 precautions, including masking, hand washing, social distancing in large groups.
COVID-19 Vaccine In Solid Organ Transplant Recipients (SOTR)

Preliminary data

187 SOTR vaccinated (35 liver)

- 87% TAC
- 69% MMF
- 55% steroids

50%/50%

Pfizer-BioNTech/Moderna

No self-reported SARS-CoV-2

No rejection
No neurologic complications
No allergic reactions req epi

Developed antibodies after single dose Pfizer-BioNTech/Moderna

- 31%
- 69%

JAMA. Published online March 15, 2021

1 Flu, 1 pouchitis
4% fever, 9% chills, 15% myalgias
38% fatigue, 32% headache

Boyarsky BJ, et al. Transplantation, in press
COVID-19 vaccine recommended for patients with liver disease and liver transplant recipients

Chronic liver disease
- Alcohol
- Hepatitis B
- Hepatitis C
- NAFLD
- PSC/PBC
- Alpha-1-antitrypsin def
- AIH

Compensated cirrhosis
- Decompensated cirrhosis
- HCC

Post-Liver Transplant

Contraindication to vaccine:
- History of immediate allergic reaction to PEG or polysorbate

History of severe food allergies, Guillain Barre are not contraindications
Transplant candidate

Chronic liver disease

With or without cirrhosis

Compensated or decompensated cirrhosis

Posttransplant

More intense immunosuppression

Less intense immunosuppression

Vaccinate
Vaccinate listed patients
1st or 2nd dose 6-12 weeks post OLT

continue meds
Vaccinate living donors
Documents Available:
Vaccine Document: www.aasld.org/VaccineDocument
Vaccine Supplemental Materials: www.aasld.org/VaccineSupplement
Counseling Patients on Vaccines: www.aasld.org/VaccineCounseling

For resources and updates on COVID-19 and the liver, visit aasld.org/COVID19
Panel Discussion

Please submit your questions to the Q&A Chat now.