AASLD Presents:

COVID-19 & the Liver: SARS-CoV-2 Diagnostic Testing and Vaccine Development

July 9, 2010
5:00pm – 6:00pm EDT

Presenters:
Joel Ernst, MD
Gopi Patel, MD

Moderator:
Mark W. Russo, MD, MPH, FAASLD
COVID-19 and the Liver: SARS-CoV-2 Diagnostic Testing and Vaccine Development

Mark W Russo, MD MPH FAASLD
Carolinas Medical Center-Atrium Health
Webinar Agenda

- Housekeeping Items – Dr. Mark Russo
- Webinar Contributors – Dr. Mark Russo
- Presenter Introductions – Dr. Mark Russo
- SARS-CoV-2 Diagnostic Testing & Vaccine Development – Dr. Mark Russo
  - Diagnostics and COVID-19 – Dr. Gopi Patel
  - COVID-19 Vaccines – Dr. Joel Ernst
  - Panel Discussion / Q&A
Webinar Q&A

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

Questions will be answered at the end of the presentation.
Clinical Oversight Subcommittee

- Co-chair, Oren K. Fix, MD, MSc, FAASLD, Swedish Medical Center (Washington)
- Co-chair, Elizabeth C. Verna, MD, MS, Columbia University (New York)
- Kimberly Brown, MD, Henry Ford Health System (Michigan)
- Jaime Chu, MD, Icahn School of Medicine at Mount Sinai (New York)
- Bilal Hameed, MD, University of California (California)
- Laura M. Kulik, MD, Northwestern Medical Faculty Foundation (Illinois)
- Ryan M. Kwok, MD, Uniformed Services University (Maryland)
- Brendan M. McGuire, MD, University of Alabama (Alabama)
- Jennifer C. Price, MD, PhD, University of California, San Francisco (California)
- Daniel S. Pratt, MD, FAASLD, Massachusetts General Hospital (Massachusetts)
- Nancy S. Reau, MD, Rush University (Illinois)
- Mark W. Russo, MD, MPH, FAASLD, Carolinas Medical Center (North Carolina)
- Michael Schilsky, MD, FAASLD, Yale University (Connecticut)
- Norah Terrault, MD, MPH, FAASLD, Keck Medicine of USC (California)
- Andrew Reynolds, (Patient Advocate)
- Raymond Chung and K. Rajender Reddy (ex-officio)
Webinar Moderator
Mark W. Russo, MD, MPH, FAASLD

Medical Director of Liver Transplantation, Chief, Division of Hepatology, and Clinical Professor of Medicine

Carolinas Medical Center - Atrium Health
Webinar Presenter
Gopi Patel, MD MS

Hospital Epidemiologist – The Mount Sinai Hospital

Associate Professor, Infectious Diseases – Icahn School of Medicine at Mount Sinai
Webinar Presenter
Joel Ernst, MD

Professor of Medicine and Chief of the Division of Experimental Medicine

University of California San Francisco
Webinar Panelist

- Peter Chin-Hong, MD, University of California, San Francisco
- Mercedes Martinez, MD, New York-Presbyterian
- Philippe J. Zamor, MD, FAAASLD, Carolinas Medical Center
COVID-19 Testing

U.S. Cases >3 million
Deaths 131,000
Testing for SARS-CoV-2

Nasal mid-turbinate (NMT) swab, also called Deep Nasal Swab
Insert swab less than one inch (about 2 cm) into nostril (until resistance is met at turbinates). Rotate the swab several times against nasal wall and repeat in other nostril with the same swab.

Anterior nares specimen
Insert the swab at least 1 cm (0.5 inch) inside the nostril (naris) rotating the swab and leaving in place for 10 to 15 seconds. Sample both nostrils with same swab.

Nasopharyngeal wash/aspirate or nasal wash/aspirate
Attach catheter to suction apparatus. Instill 1 mL-1.5 mL of non-bacteriostatic saline (pH 7.0) into one nostril. Begin gentle suction/aspiration and remove catheter while rotating it gently.

Saliva tests
Home Kit tests
Testing for Antibody to SARS-CoV-2

The two major antigenic targets of SARS-CoV-2 virus against which antibodies are detected are:
- Spike glycoprotein (S) and nucleocapsid phosphoprotein (N).
- S protein is essential for virus entry and is present on the viral surface.
- N protein is the most abundantly expressed immunodominant protein that interacts with RNA.
  - Multiple forms of S protein — full-length (S1+S2) or partial (S1 domain or receptor binding domain [RBD])
  - N is more conserved across coronaviruses than S, and within S, RBD is more conserved than S1 or full-length S.
  - Antibodies that bind to the receptor binding domain of the spike protein that allows viral entry into the cell through ACE2 receptor is speculated to be most effective.
A mutation affecting the virus's spike protein changed amino acid 614 from “D” (aspartic acid) to “G” (glycine). D614G mutation

Washington Post June 29, 2020, Aaron Steckelberg
Vaccine development
>100 vaccine projects
At least 8 vaccines in trials
mRNA
DNA vaccine to MERS
ChAdOx1 nCoV-19 vaccine or a licensed vaccine (MenACWY)
molecular clamp technology designed to lock the ‘spike’ protein into a shape

ChAdOx1 nCoV-19 is made from a virus (ChAdOx1), which is a weakened version of a common cold virus (adenovirus) that causes infections in chimpanzees, that has been genetically changed so that it is impossible for it to replicate in humans.

GUIDANCE DOCUMENT

Development and Licensure of Vaccines to Prevent COVID-19
Guidance for Industry
JUNE 2020

https://www.fda.gov/media/139638/download
Diagnostics and COVID-19

Gopi Patel, MD MS
Hospital Epidemiologist, The Mount Sinai Hospital
Associate Professor, Infectious Diseases
Icahn School of Medicine at Mount Sinai
- No conflicts of interest
Test! Test! Test!

- Early response to the pandemic hampered by inability to rapidly and accurately diagnose SARS-CoV-2 infection
- First CDC issued tests had issues with negative controls
- FDA Emergency Use Authorization (EUA)
Real-time reverse transcriptase polymerase chain reaction (rRT-PCR)

- Genetic sequence published January 10, 2020
- Platforms repeats amplification process (40 cycles) until cDNA can be detected
- “Gold-standard” for diagnosis of acute infection with SARS-CoV-2

EUA process led to rapid approval of multiple testing platforms

- Abbreviated format in the setting of a public health emergency
- Permitted the use of “contrived” specimens
  - Use of either known positive or contrived specimens can lead to overestimation of sensitivity since in practice infectious material can be missed

Supply chain instability with increased demand for viral transport media, swabs, and reagents

- Personal protective equipment (PPE) required for testing
- Protecting healthcare workers from unnecessary exposures

Limited testing and overwhelmed healthcare systems

- Prioritized testing for those requiring hospitalization
- Inability to rapidly and accurately identify pre-symptomatic and asymptomatic cases leading to “silent-transmission”
Community spread recognized Mar 2, 2020
First case diagnosed in NYS Feb 29, 2020
First MSHS hospitalized case Mar 7, 2020
In-house diagnostic testing available Mar 17, 2020
### Before symptom onset

- Detection unlikely\(^a\)

### After symptom onset

- **PCR - Likely positive**
- **PCR - Likely negative\(^b\)**

#### Antibody detection

<table>
<thead>
<tr>
<th>Week</th>
<th>Symptom onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2</td>
<td></td>
</tr>
<tr>
<td>-1</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Nasopharyngeal swab PCR</td>
</tr>
<tr>
<td>1</td>
<td>Bronchoalveolar lavage/sputum PCR</td>
</tr>
<tr>
<td>2</td>
<td>Virus isolation from respiratory tract</td>
</tr>
<tr>
<td>3</td>
<td>Stool PCR</td>
</tr>
<tr>
<td>4</td>
<td>IgM antibody</td>
</tr>
<tr>
<td>5</td>
<td>IgG antibody</td>
</tr>
<tr>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

---

Sethuraman N et al. *JAMA*. 2020. 323(22) 2249-51
- **False-negatives**
  - May not be appropriately isolated
  - Prevents enrollment in clinical trials

- **Role of repeat testing**
  - Early infection can be missed
    - PCR positivity may decline more slowly in sputum and lower respiratory tract specimens
  - Clinical syndrome consistent with COVID-19
    - Alternative site (e.g., lower respiratory tract specimen)

---

Pretest-probability influences how we interpret tests
- Dependent on prevalence, exposure history, and symptoms
- If pre-test probability high the test loses its value

“Real-world” PCR sensitivity is considered to be ~70%
- Even lower with antigen testing

Efforts to decrease pre-test probability matter
- Masking, social distancing, and PPE
○ Antigen testing

- As of July 9, two tests with EUA from the FDA
- Quick and inexpensive (point-of-care)
- Detect protein fragments
- Specific and not sensitive for SARS-CoV-2 (risk of false-negative)
Defining the role of asymptomatic testing

- Consider when there is adequate testing capacity
- High prevalence (10% or greater in the community)
- Major surgery planned or when aerosol-generating procedures anticipated
- Immunocompromised hosts
- Known contacts of a laboratory-confirmed case
- Congregate settings
Persistent or intermittent PCR positivity and discontinuation of transmission-based precautions

- **Symptom-based strategy***
  - Studies demonstrate inability to isolate replicating virus ≥ 9 days from symptom-onset in immune competent hosts

- **Test-based strategy**
  - More conservative but resource intensive
  - Recommended for vulnerable individuals at high risk for morbidity
  - Immunocompromised may have prolonged shedding

*Time-based strategy* can be used for asymptomatic patients based on time of diagnosis


- **Cycle thresholds (Ct)**
  - Lower Ct in hospitalized
  - Evidence that replication-competent virus is not isolated in culture at higher Ct
    - No correlation with illness length and duration of PCR positivity
  - Illness severity may correlate with prolonged viral shedding

Binnicker M. *Clin Infect Dis*. 2020 Jun 6; doi.org/10.1093/cid/ciaa735

van Kampen JJA et al. [https://www.medrxiv.org/content/10.1101/2020.06.08.20125310v1](https://www.medrxiv.org/content/10.1101/2020.06.08.20125310v1) published online 9Jun20
Repeat positives and reinfection?

- On average 45 days [3-82 days] from symptom onset
  - 37.5% had symptoms which prompted testing
- 709 contacts traced with 3 “new” cases
  - Unable to culture virus and with evidence of **neutralizing antibodies**
- Repeat isolation period and extensive contact investigations suspended
Serological tests (antibody testing)

- Identify plasma donors
- Confirm patients had SARS-CoV-2 infection
  - Can be used to support clinical assessment in persons presenting late in illness or with post-infectious syndromes (e.g., MIS-C)
- Serosurveillance
- Tool to determine immunologic response after vaccination
  - Establish correlation with immunity?
Types of commercial assays

• Enzyme-linked immunosorbent assays (EIA/ELISA)
• Lateral Flow Assays

Minimize the false positive rate (high specificity)

• Additional data required prior to altering public health recommendations
• Mask, social distance, wear appropriate PPE
Limitations in current diagnostic testing

- Measuring test sensitivity in asymptomatic individuals is a priority
- **False negative results** not uncommon thus cannot reliably rule out infection if the pretest probability is high

Limitations in current serologic testing

- Risk of **false positive results** in low prevalence settings
  - Primarily qualitative
- Unclear clinical utility and durability unknown
TO THE HEALTH CARE WORKERS FIGHTING FOR OUR LIVES, THANK YOU.
COVID-19 vaccines

Joel Ernst, M.D.
Professor, Department of Medicine
Chief, Division of Experimental Medicine
No conflicts of interest
Why are COVID-19 vaccines needed?

- Highly transmissible by the respiratory route, incapacitating and deadly
- Can be transmitted by asymptomatic/presymptomatic individuals
- Can become endemic; community (‘herd’) immunity is unlikely to be achieved by infection
- The economic and human impact of COVID-19 is large
What do we know about immunity to COVID-19?

- Protective immunity may be transient after infection
- Neutralizing antibodies likely contribute to protection
- Presence of antibodies does not guarantee protection
  - Quantity and quality of antibodies not measured by routine assays
  - Some antibodies can be harmful (‘Antibody-Dependent Enhancement’); the ‘right’ antibodies are needed
Multiple approaches to COVID-19 vaccines

- **Inactivated virus** (grow virus, chemically inactivate)
- **Attenuated virus** (modify virus for limited growth)
- **Nucleic acid-based:**
  - DNA→RNA→protein antigen
  - RNA→protein antigen
- **Purified protein ± adjuvant** (HBV, tetanus) **Virus-like particle** (HPV)
- **Viral ‘vector’ delivery of antigen** (Experimental)
Goals of vaccine development

- Safety
- Generate neutralizing antibodies:
  - T cells may also contribute to protection
- Block infection where virus enters (mucosal immunity)
- Generate long-lived immunological memory
- Recognize viral targets that cannot mutate to escape
COVID-19 vaccine development in progress

- Nucleic acid (DNA or RNA) vaccines: ~20 groups
- Viral vectored vaccines: ~25 groups
  - Multiple different viral vectors in use
- Protein-based vaccines
  - Protein subunits: ~28 groups
  - Virus-like protein particles: 5 groups
What are the stages of vaccine development?

- [Discovery/development]
- Is the vaccine safe?
- Does the vaccine stimulate immune responses in humans?
- Does the vaccine protect humans from disease? (efficacy)
- Does the vaccine protect humans in the real world? (effectiveness)
Other essential vaccine considerations

- Rapid large scale production essential in pandemic
- Must be economical on a global scale
- Must be stable, for populations regardless of location (avoid need for refrigeration)
Why does it take so long to develop a new vaccine?

Safety studies in humans require time, to observe for complications.
Can ‘human challenge’ studies help?

- Vaccine protection can be determined in:
  - Large populations naturally exposed to infection (slow, expensive)
  - Small populations of volunteers experimentally exposed to infection (‘human challenge’) (more rapid, less expensive)

- Ethical concerns for human challenges when reliable curative treatment unavailable
Thank you

Questions?
Panel Discussion

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