COVID-19 Clinical Update
I-TECH Videoconference  September 14, 2020

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Overview

- Epidemiology & virology
- Laboratory testing
- Natural history - reinfection
- Treatment & vaccines
  - 3313 clinical trials as of September 14!
Impact of Social Distancing

- Population: 1030 Maryland residents enrolled in a data platform (Dynata)
- Survey about adoption of non-pharmaceutical protective interventions (NPIs)
- 55 (5.35) self reported having been diagnosed with SARS-CoV-2

<table>
<thead>
<tr>
<th>Variable</th>
<th>aOR SARS-CoV-2</th>
</tr>
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<tbody>
<tr>
<td>Social distancing indoors</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>Ref 0.26 (0.08-0.9)</td>
</tr>
<tr>
<td>Sometimes</td>
<td>0.32 (0.10-0.99)</td>
</tr>
<tr>
<td>Always</td>
<td></td>
</tr>
<tr>
<td>Social distancing outdoors</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>Ref 0.34 (0.10-1.19)</td>
</tr>
<tr>
<td>Sometimes</td>
<td>0.10 (0.03-0.33)</td>
</tr>
<tr>
<td>Always</td>
<td></td>
</tr>
<tr>
<td>Use of public transport</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>Ref 6 (2.1-16.9)</td>
</tr>
<tr>
<td>1-2</td>
<td>3.8 (1.118-12.3)</td>
</tr>
<tr>
<td>3-7</td>
<td>4.29 (1.12-16.5)</td>
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<tr>
<td>&gt;7 times</td>
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<tr>
<td>Visited place of worship</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>Ref 1.41 (0.38-5.31)</td>
</tr>
<tr>
<td>1-2</td>
<td>16 (5.97042.7)</td>
</tr>
<tr>
<td>&gt;=3 times</td>
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Risks for COVID-19 Death in South Africa

- Population: 3,460,932 patients attending public clinics in Western Cape, SA (16%HIV+), 22,308 with COVID-19
- Design: Population-based cohort study to assess factors associated with mortality in people with COVID-19, focusing on association with HIV

- HIV & TB are risks for COVID-19 associated mortality
- Conventional risk factors are still dominant
  - Uncontrolled diabetes more common among those who died than HIV

Boule A. CID 2020
SARS-CoV-2 Virology: G614 vs. D614 Variants Role in Transmissibility

• Background:
  – SARS-CoV-2 sequence diversity is low due to virally encoded proof reading. Change occurs from homologous recombination & cross species transmission
  – Viral changes could affect vaccine response, diagnostics or treatment. Evolution might change viral transmission dynamics or pathogenicity
  – Vaccines & diagnostics focus on viral spoke protein (bind ACE-2)

• Pop. & design: Analysis of globally reported sequences in 599 patients hospitalized with COVID-19
  • Spike G614 replaced D614 as dominant form worldwide
  • G614 had lower RT PCR Cts – ↑ viral load

Korber B. Cell 2020
SARS-CoV-2 Virology: Delta 382 Variant Role in Severity

- Population: 131 hospitalized patients in Singapore 1/20-3/20 enrolled in a prospective study
- Design: retrospective analysis comparing association of viral variants in ORF8 with hypoxemia
- Results:
  - 70% wild type, 22% 382-nucleotide deletion, 8% Mixed infection
  - Δ382 less severe
  - Similar quantities of virus - No difference in replication capacity

<table>
<thead>
<tr>
<th></th>
<th>Hypoxemia</th>
<th>aOR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Wild type (n=92)</td>
<td>26 (28%)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Mixed (n=10)</td>
<td>3 (30%)</td>
<td>1.78 (0.22-11.02)</td>
</tr>
<tr>
<td>Δ382 (n=29)</td>
<td>0 (0%)</td>
<td>.07 (0.00-0.48)</td>
</tr>
</tbody>
</table>

ORF8 could be a target for drug development
Uncertain if ORF8 mutants are more or less transmissible and impact on longer-term viral evolution

Young BE Lancet 2020
SARS-CoV-2 in Salvia vs. Nasopharyngeal Swabs

- Population: 70 in-patients with COVID-19 at Yale hospital
- Design: Comparison of saliva and nasopharyngeal swab specimens
- Results:
  - Larger proportion of saliva specimens positive up to 10 days
  - Quantity of SARS-CoV-2 higher in saliva than NP specimens
  - 495 healthcare workers tested – 13 SARS-CoV-2 + in saliva
  - 9 tested by NP and 7 were negative
    - All had subsequent positive NP tests
SARS-CoV-2 in Salvia vs. Nasopharyngeal Swabs

- Population: 224 patients with symptoms consistent with COVID-19
- Design: Comparison RT PCR results in "enhanced" saliva (sniff & elicited cough) & NP swab specimens
- Results:
  - High agreement in specimen types
  - 1 positive saliva missed by NP swab
  - Mean cycle threshold of RT PCR was lower in NP swabs, suggestive of more RNA

- Two studies both support the use of saliva for PCR diagnostics
  - Saves PPE
  - Simplifies procedures
  - More acceptable to patients
- Contradictory data on quantity of virus – uncertain how much that matters

Procop GW. JCM 2020
Antibody Response

- Population-based study Iceland
- Among 1215 recovered cases, 25 days after diagnoses, 91-95% of people had antibodies based on 2 pan-IgG tests
- Estimated 26.6% of household exposed and 5% of nonexposed with SARS-CoV-2 positive (PCR or Ab positive)
  - 2.3% of quarantined persons with negative PCR developed antibody
- 0.6% of PCR+ cases and 0.3% of infected persons died (based on 10 deaths)
• Population: 37 symptomatic and 37 asymptomatic persons with positive SARS-CoV-2 PCR tests in Wuhan, China.

• Comparable levels of virus based on Ct 8 weeks following discharge from the hospital.

• 40% of asymptomatic patients and 12.9% of symptomatic patients tested IgG negative.

• Controversy about if and how to use antibody tests persists.

• Probably lots of variable of tests.

• IDSA recommends using an IgG or total immunoglobulin tests (not IgM or IgG/IgM).
SARS-CoV-2 Reinfection

- Patient experiences symptomatic COVID-19 in March, then tests positive on a screening test in an airport in Hong Kong 142 after the first positive test.
- CRP elevated at second test, IgG negative at time of second positive test, but positive 5 days later
- Whole genome sequencing demonstrate that the infecting viruses were from different clades/lineages
  - 1st US/UK lineage March/April
  - 2nd Switzerland/UK July/August
SARS-CoV-2 Reinfection #2

Case History

- March 25: Onset of sore throat, cough, headache, nausea, diarrhea.
- April 18: Tested positive for SARS-CoV-2 by PCR.
- April 27: Symptoms resolved.
- May 9 and 26: Tested negative for virus by two methods.
- June 5: Symptoms worsened -> hypoxia, new infiltrates on CXR – admitted - RT-PCR positive for SARS-CoV-2.
- June 6: SARS-CoV-2 IgM and IgG antibody positive.

• 2nd Case in U.S.
• Sequences supposedly different
SARS-CoV-2 Reinfection #3

Case History
- March: 51 y/o woman develops mild COVID-19 – HA, fever, myalgia, coughing, HA – Positive NP swab
- June – HA, cough, fatigue, rhinitis – 2nd positive NP swab

- Case in Belgium
- Sequences different – 11 point mutations

- Reinfections happen
- Sometimes these reinfections can be more clinically severe
- Retesting people make sense in at least some patients – particularly if we can save sequences – hard to interpret
- No immunity passport!
Corticosteroids

- Background: Recovery trial demonstrated the methylprednisolone decreased mortality in patients with COVID-19 on supplemental 02 or mechanical ventilation
- Meta-analysis of 7 trials among critically ill patients
- 30% reduction in mortality

Sources: WHO Rapid Evidence Appraisal for COVID-19 Therapies WG. JAMA 2020
Convalescent Plasma: Observational Data

- **Background** – Small Chinese RCT did not show CP was effective (underenrolled)
- **Design** – Analysis data open label expanded access program
  - 52% in ICU
  - 8.7% 7 day mortality
- **Outcome**: 7 and 30-day mortality, outcomes stratified by timing of administration & quantity of SARS-CoV-2 IgG in plasma (subset receiving 1 unit)

Source: Joyner MJ. MedRxiv 2020

Suggests that Convalescent Plasma is beneficial if given early and has a high titer of IgG – Not an RCT
Convalescent Plasma: PLACID Trial

- Design – Open label RCT
- Population – 464 hypoxemic hospitalized patients in India with confirmed COVID-19
  - 68% of patients received hydroxychloroquine
  - ~50% received methylpred
  - ~65% received AZM
- Intervention – 2 doses of convalescent vs. standard of care – only 24 patients received CP within 3 days of symptom onset
- Outcome: composite of progression or death at 28 days

<table>
<thead>
<tr>
<th></th>
<th>Standard of Care N=229</th>
<th>CP N=235</th>
<th>CP (with detectable neutralizing antibody [NAbs])</th>
<th>CP (NAbs ≥1:80)</th>
<th>CP (NAbs undetectable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause Mortality</td>
<td>13.5%</td>
<td>14.5%</td>
<td>13.8%</td>
<td>14.9%</td>
<td>18.7%</td>
</tr>
<tr>
<td>Profession to severe disease</td>
<td>7.4%</td>
<td>7.2%</td>
<td>6.8%</td>
<td>8.9%</td>
<td>9.4%</td>
</tr>
<tr>
<td>Composite outcome</td>
<td>17.9%</td>
<td>18.7%</td>
<td>16.9%</td>
<td>17.9%</td>
<td>20.3%</td>
</tr>
</tbody>
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- CP arm had significantly greater resolution of SOB and fatigue at day 7, greater improvement in FiO2 and faster conversion to negative SARS-CoV-2 PCR
- Among 24 pts receiving CP within 3 days of symptom onset - aOR: 0.59 (95% CI: 0.28, 1.24)

Convalescent Plasma did not improve clinical outcomes in people with moderate COVID-19 – Lots we don’t know

Source: Agarway A. MedRxiv 2020
Remdesivir

- **Background**
  - Small Chinese study – no benefit
  - ACTT-1 - Remdesivir decreased time to recovery by 4 days in hypoxemic patients with COVID-19 with a non-significant trend toward ↓ mortality -> FDA approval for severe disease
- **Design** – Open label RCT
- **Population** – COVID-19 pneumonia with 02 sat >94% (no supplemental 02)
- **Intervention**: SOC, 5-days or 10 days of remdesivir
- **Outcome**: Hospital discharge by day 14, 7-point ordinal scale at day 11 (higher score is better)
Remdesivir

• Trial “… suggests modest clinical benefit for a 5 day course compared to standard of care”
• Major questions
  • Who should get Remdesivir
    • Current practice at UW is to limit use to patients with a O2 sat <94%
  • Still some uncertainty about optimal duration
    • 5 days is best supported
  • Effect on discrete outcomes is not clear – ordinal scale as an outcome is hard to interpret
    • Duration of hospitalization, mechanical ventilation, and death are different
  • Role of drug in persons receiving dexamethasone is not clear
    • Dexamethasone is much less expensive and more widely available
Are Nonsteroidal Anti-Inflammatories Safe in COVID-19?

- Previously studies have raised concern that NSAIDS may be unsafe in COVID-19
- Design – Population-based cohort study using Danish health – NSAID users matched to 4 non-users based on propensity scoring
- Population – 9236 Danes with a positive SARS-CoV-2 test
- Exposure – Filled NSAID in 30 days prior to SARS-CoV-2 test
- Outcome: Mortality, hospitalization, ICU, mechanical ventilation

Source: Lund LC PLOS Medicine 2020

Use of NSAIDs was not associated with 30-day mortality, hospitalization, ICU admission, mechanical ventilation, or renal replacement therapy.
Are ACE Inhibitors (ACEi) & ARBs Safe in COVID-19?

- SARS-CoV-2 enters cells via binding to ACE2. Animal studies suggest that ACE inhibitors & ARBs may increase ACE2 expression, potentially increasing COVID-19 risk.
- Design – Systemic review of studies investigating the association of ACEi and ARB use and COVID-19 disease, severity and mortality
- 27 studies included

Evidence does not suggest an association of ACEi or ARB use with SARS-CoV-2 infection or COVID-19 severity or mortality

Source: Caldeira D. IJC Heart & Vasculature 2020
Operation Warp Speed (OWS)

• US government initiative to develop a COVID-19 vaccine by the end of 2020 and have 300 million doses available and deployed by mid-2021
• 4 vaccine candidate selection criteria
  • Robust pre-clinical or early stage data on safety & potential efficacy
  • Potential to enter phase 3 trials by July-Nov 2020 - efficacy outcomes 1st half 2021
  • Platforms allow fast and effective manufacturing - capacity to produce >100 million doses by mid-2021
  • Use of one of 4 vaccine platforms thought most likely to be safe and effective – 6 of 8 planned partnerships announced
## Operation Warp Speed (OWS)

<table>
<thead>
<tr>
<th>Technology</th>
<th>Vaccine</th>
<th>Status</th>
</tr>
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<tbody>
<tr>
<td>mRNA</td>
<td>Moderna</td>
<td>Immunogenic in phase I – phase 3 ongoing</td>
</tr>
<tr>
<td></td>
<td>Pfizer/BioNTech</td>
<td>Immunogenic in phase I – phase 3 ongoing</td>
</tr>
<tr>
<td>Replication defective live vector</td>
<td>ChAdOx – AstraZeneca &amp; Oxford*</td>
<td>Ongoing phase 3 in UK, Brazil and South Africa Phase 3 US trial started in August</td>
</tr>
<tr>
<td></td>
<td>Janssen Ad26</td>
<td>Effective nonhuman primates, ongoing phase 1 with planned phase 3 in September</td>
</tr>
<tr>
<td>Recombinant subunit adjuvant protein</td>
<td>Novavax</td>
<td>Phase 1 done – phase 3 start in September</td>
</tr>
<tr>
<td></td>
<td>Sanofi/GSK</td>
<td>Preclinical – phase 1 in Sept</td>
</tr>
<tr>
<td>Attenuated replicating live vector</td>
<td>Not yet chosen</td>
<td></td>
</tr>
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- Study on hold due to episode of transverse myelitis in a vaccinated study subject
- Development of manufacturing capacity ongoing in parallel with trials
Questions and Discussion