WELCOME

Sheila R. Garrity, JD, MPH, MBA
Associate Vice President for Research Integrity

Robert H. Miller, PhD
Vice President for Research

2020 Spring Regulatory Update and Hot Topics in Clinical Research

COVID-19: The Virus, Preparedness in the time of Crisis, and Clinical Research
2020 Spring Regulatory Update and Hot Topics in Clinical Research

COVID-19: The Virus, Preparedness in the time of Crisis, and Clinical Research

KEYNOTE
9:15am – 10:15am

Daniel S. Chertow, MD, MPH
Clinical Center and Laboratory of Immunoregulation
National Institute of Allergy and Infectious Diseases
National Institutes of Health (NIH)
Disclosures

• None
While this pandemic is global, it is also very personal.
Learning objectives

• Overview biology of coronaviruses (CoVs)
• Discuss coronavirus disease 2019 (COVID-19)
  – Biology, epidemiology, and pathogenesis
  – Clinical manifestations and management
• Planning for the future
  – Public health measures to limit spread
  – Preparing for the next wave of illnesses
Coronavirus biology
Viral structure and diversity

- Spherical enveloped, positive-strand RNA viruses
- 4 genera: alpha, beta, delta, and gamma
- Wide host range in animals
- Commonly cause respiratory illnesses in humans

Structural proteins: Spike, Envelope, Membrane, Nuclear
Human coronaviruses

- **Endemic human CoVs**
  - 229E, NL63, OC43, HKU1
  - 15-30% of common colds

- **SARS-CoV**
  - Global epidemic, 2002-2003
  - 8096 cases, 774 deaths (9.6%)

- **MERS-CoV**
  - Recognized in 2012 and ongoing
  - 2494 cases, 858 deaths (34.4%)

COVID-19 epidemiology
Pneumonia in Wuhan City, China

- Cluster reported to WHO on December 3rd, 2019
- Common exposure to local seafood/animal market
- Novel virus isolated termed SARS-CoV-2
- Genetic sequence is most similar to bat CoVs

Global distribution of cases

2,241,778 cases
152,551 deaths

https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports
Rapidly rising cases in the United States

720,630 cases
37,202 deaths

Estimated distribution of case severity

- Total cases: 100%
- Severe illness: 14%
- Critical illness: 5%
- Death: 2%

## Age-specific case fatality ratios

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Confirmed cases, N (%)</th>
<th>Deaths, N (%)</th>
<th>Case fatality ratio, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9</td>
<td>416 (0.9)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10-39</td>
<td>11,768 (26.3)</td>
<td>26 (2.5)</td>
<td>0.2</td>
</tr>
<tr>
<td>40-49</td>
<td>8,571 (19.2)</td>
<td>38 (3.7)</td>
<td>0.4</td>
</tr>
<tr>
<td>50-59</td>
<td>10,008 (22.4)</td>
<td>130 (12.7)</td>
<td>1.3</td>
</tr>
<tr>
<td>60-69</td>
<td>8,583 (19.2)</td>
<td>309 (30.2)</td>
<td>3.6</td>
</tr>
<tr>
<td>70-79</td>
<td>3,918 (8.8)</td>
<td>312 (30.5)</td>
<td>8.0</td>
</tr>
<tr>
<td>≥ 80</td>
<td>1408 (3.2)</td>
<td>208 (20.3)</td>
<td>14.8</td>
</tr>
</tbody>
</table>

China CDC Weekly. 2020, Vol 2; No. 8.
COVID-19 clinical manifestations
Clinical findings, 1099 hospitalized patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients</th>
<th>ICU care</th>
<th>No ICU care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, year</td>
<td>47</td>
<td>52</td>
<td>45</td>
</tr>
<tr>
<td>Female</td>
<td>42%</td>
<td>42%</td>
<td>42%</td>
</tr>
<tr>
<td>Any comorbidity</td>
<td>24%</td>
<td>39%</td>
<td>21%</td>
</tr>
<tr>
<td>Fever</td>
<td>89%</td>
<td>92%</td>
<td>88%</td>
</tr>
<tr>
<td>Cough</td>
<td>68%</td>
<td>71%</td>
<td>67%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>38%</td>
<td>40%</td>
<td>38%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>18.7%</td>
<td>38%</td>
<td>15%</td>
</tr>
</tbody>
</table>

Common laboratory findings

- Leukopenia, lymphopenia, leukocytosis
- Among severe illness
  - Elevated serum creatinine
  - Elevated transaminases and direct bilirubin
  - Elevated cardiac enzymes
  - Disordered coagulation

Rapidly progressive respiratory failure

Illness Day 8

Illness Day 15

Illness timeline, 41 hospitalized patients

5 day incubation (range 2-10 days)

6 deaths (15%)

Clinical complications

- ARDS/bacterial co-infection
- Renal insufficiency/failure
- Hepatic injury
- DIC and venous thromboembolism
- Distributive or cardiogenic shock
Acute myo-pericarditis by cardiac MRI

- 53 year-old woman with 1 week fever and cough
- SARS-CoV-2 positive
- HR 100, BP 90/50
- EKG: diffuse ST-segment elevations
- 2D Echo: EF 40%, effusion without tamponade

Inciardi, RM et al. JAMA Cardiology. 2020 Mar 27.
COVID-19 clinical management
CDC guidance on PPE for healthcare workers caring for COVID-19 patients

• Minimum requirements
  – Gloves, gown, eye protection
  – Medical/surgical face-mask

• N95 respirator mask for aerosol-generating procedures

• Balances risk with potential for scarcity

Management of hypoxia

1. **Do it:** Endotracheal intubation
2. **Do it:** Expert in airway to intubate
3. **Do it:** Use N-95/FFP-2 or equivalent and other PPE/infection control precautions
4. **Do it:** Minimize staff in the room
5. **Consider:** if available, Video-laryngoscope

**COVID-19 with hypoxia**

- **Indication for endotracheal intubation?**
  - Yes
  - **Indication for endotracheal intubation?**
    - Yes: **Do it:** Monitor closely for worsening
    - No: **Consider:** HFNC
      - **Not tolerating HFNC or HFNC is not available**
        - **Indication for endotracheal intubation?**
          - Yes: **Do it:** Monitor closely at short intervals
          - No: **Do not:** Delay intubation if worsening
  - No:
    - **Tolerating supplemental oxygen?**
      - Yes: **Do it:** Target SpO₂ 92 to 96%
      - No: **Do it:** Appropriate infection control precautions

## Management of ARDS

<table>
<thead>
<tr>
<th>COVID-19 with mild ARDS</th>
<th>COVID-19 with Mod to Severe ARDS</th>
<th>Rescue/Adjunctive therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Do:</strong></td>
<td><strong>CONSIDER:</strong></td>
<td><strong>CONSIDER:</strong></td>
</tr>
<tr>
<td>Vt 4-8 ml/kg and $P_{plat} &lt; 30$ cm H$_2$O</td>
<td>Higher PEEP</td>
<td>if proning, high P$_{PEEP}$, asynchrony</td>
</tr>
<tr>
<td><strong>Do:</strong></td>
<td><strong>CONSIDER:</strong></td>
<td><strong>CONSIDER:</strong></td>
</tr>
<tr>
<td>Investigate for bacterial infection</td>
<td>NMBA boluses to facilitate ventilation, targets</td>
<td>NMBA infusion for 24 h</td>
</tr>
<tr>
<td><strong>Do:</strong></td>
<td><strong>CONSIDER:</strong></td>
<td><strong>CONSIDER:</strong></td>
</tr>
<tr>
<td>Target SpO$_2$ 92% - 96%</td>
<td>Traditional Recruitment maneuvers</td>
<td>Prone ventilation 12-16 h</td>
</tr>
<tr>
<td><strong>CONSIDER:</strong></td>
<td><strong>CONSIDER:</strong></td>
<td><strong>CONSIDER:</strong></td>
</tr>
<tr>
<td>Conservative fluid strategy</td>
<td>PEEP responsive</td>
<td>if proning, high P$_{PEEP}$, asynchrony</td>
</tr>
<tr>
<td><strong>CONSIDER:</strong></td>
<td><strong>CONSIDER:</strong></td>
<td><strong>CONSIDER:</strong></td>
</tr>
<tr>
<td>Empiric antibiotics</td>
<td>Prone ventilation 12-16 h</td>
<td>NMBA infusion for 24 h</td>
</tr>
<tr>
<td><strong>CONSIDER:</strong></td>
<td><strong>CONSIDER:</strong></td>
<td><strong>CONSIDER:</strong></td>
</tr>
<tr>
<td>Systematic corticosteroids</td>
<td>NIV: High P$_{PEEP}$, asynchrony</td>
<td>STOP if no quick response</td>
</tr>
<tr>
<td><strong>Don't do:</strong></td>
<td><strong>CONSIDER:</strong></td>
<td><strong>CONSIDER:</strong></td>
</tr>
<tr>
<td>Staircase Recruitment maneuvers</td>
<td>Short course of systemic corticosteroids</td>
<td>follow local criteria for ECMO</td>
</tr>
<tr>
<td><strong>CONSIDER:</strong></td>
<td><strong>CONSIDER:</strong></td>
<td><strong>CONSIDER:</strong></td>
</tr>
<tr>
<td>Short course of systemic corticosteroids</td>
<td>Antivirals, chloroquine, anti-IL6</td>
<td>V-V ECMO or referral to ECMO center</td>
</tr>
</tbody>
</table>

COVID-19 pathogenesis
SARS-CoV-2 transmission

• Initial spillover from animal reservoir or intermediate host (not yet identified)

• Human-to-human spread via
  – Large respiratory droplets (e.g., cough, sneeze)
  – Fomites (e.g., contaminated surfaces)
  – Airborne route possible with aerosol-generating procedures (e.g., intubation)

Infection and dissemination

- Infects airway cells (figure)
- Progresses to pneumonia
- Severe lung injury possible
- Disseminates in blood
- Causes direct or indirect organ injury/dysfunction

COVID-19 histopathology

- Lung (A, B)
  - Diffuse alveolar damage
  - Lymphocytic infiltrate
  - Viral cytopathic changes
- Liver (C)
  - Microvesicular steatosis
- Heart (D)
  - Few mononuclear infiltrates

Diffuse immunostaining of SARS-CoV-2 in pneumocytes

Public health measures
Public health measures to limit spread

• Current measures in the US
  – Restrictions on travel and movement
  – Increased testing, case isolation, contact tracing, and quarantine

• Vaccine and therapeutic development ongoing
Preparing for the next wave
Phases of a pandemic

Seasonality of Endemic Human CoVs in the United States, 2011-2018

Strich et al. 2020, submitted
Summary

• SARS-CoV-2 is a new human coronavirus
  – Spreads efficiently from human-to-human
  – High case-fatality ratio

• This outbreak is evolving
  – Updates on optimal care, therapies, and vaccine can be expected
  – Sustained preparedness and ongoing response from the local to international level is essential