COVID-19 OVERVIEW AND LITERATURE REVIEW
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OUTLINE

- EPIDEMIOLOGY
- PATHOGENESIS
- CLINICAL COURSE
- DIAGNOSIS
- MANAGEMENT
COVID-19. How did we get here?

December 2019: cluster of pneumonia of unknown etiology reported in Wuhan China


Initial association with the Seafood Market of Wuhan

Transmission to humans thought to be from bats with intermediate host (pangolin or turtles?)

As the outbreak progressed person to person transmission seemed to be the main mode of transmission
In the US: 367,507 cases, 10,908 deaths (April 6, 2020)

https://coronavirus.jhu.edu/map.html
PATHOGENESIS
Like SARS-CoV, SARS-CoV-2 uses ACE2 as an entry receptor to enter ACE2 expressing cells.

Genetically Similar to SARS-CoV

4 genera of Coronaviruses: α, β, γ, δ.

α and β able to infect mammals while γ and δ tend to infect birds

Previously 6 Coronaviruses identified as human-susceptible, including SARS-CoV (2002-2003, 8000+ cases, 800 deaths - 10%) and MERS-CoV (2012, 850+ cases, 330+ deaths - 35%)

SARS-CoV-2 is also a β coronavirus. It shares 79.6% genome sequence identity to SARS-CoV and 50% identity to MERS-CoV

Angiotensin Converting Enzyme 2 (ACE2)

Expressed in the lung alveolar epithelial cells, also in heart and kidneys

Binding of the spike-protein to host cells results in the downregulation of ACE2

→ this mechanism may contribute to the severity of lung damage in SARS

Main role = degradation of Ang II → results in formation of Ang 1-7, has role in regulating the balance of circulating AngII/Ang1-7 levels

Ang II induces pulmonary vasoconstriction in response to hypoxia

Ang II also increases vascular permeability facilitating pulmonary edema

Tikellis C., Thomas M. Angiotensin-converting enzyme 2 (ACE2) is a key modulator of the renin angiotensin system in health and disease. Int. J. Pept. 2012;2012:256–294
Invasion of the respiratory mucosa

Triggers a series of immune responses and the production of cytokine storm in the body

Transmission

Droplets
Airborne?
$R_0 = 2.2 - 3.6$

Infected surfaces

Fecal-oral?

Surface Stability of SARS-CoV-2

Pulmonary Function Tests: Advice from ATS

Potential for coughing, droplet formation during maneuvers

Difficult to screen patients because they often have respiratory symptoms from a variety of etiologies

Only do PFTs if essential for immediate treatment decisions

PPE measures: protection against aerosolized droplets for staff, wiping surfaces, discuss with infection control team

https://www.thoracic.org/professionals/clinical-resources/disease-related-resources/pulmonary-function-laboratories.php
Infection Prevention and Control Strategies

Suspected/positive cases should be on contact and droplet isolation in AIIR

Symptomatic patients who are waiting for a room should wear a surgical facemask and stay 6 feet away from others

Caregivers and visitors limited

Caregivers should wear gown, gloves, surgical mask with facemask

Aerosol generating procedures: intubation, CPR, bronchoscopy → need N95 respirator mask
Incubation Period

Median incubation period: 5.1 days

97.5% of those who develop symptoms will do it by Day 12

Clinical Features in Adults

Fever in 98%
Cough in 76%
Dyspnea in 55%
Fatigue or myalgia in 44%
Sputum production in 28%
Diarrhea in 3%

Severity Classification

Based on largest case series to date involving 72,314 cases (from Chinese Center of Disease Control and Prevention)

**Mild** (81%): no pneumonia or mild pneumonia

**Severe** (14%): dyspnea, RR >30/min, SO2 < 93%, PF ratio < 300, and/or lung infiltrates > 50% within 24-48 hours

**Critical** (5%): respiratory failure, septic shock, and/or multiple organ dysfunction

Complications

ARDS
Pneumonia
Acute cardiac injury
Acute kidney injury
Secondary infection
Shock
Disease Severity By Age

## Adults: Comorbidities and COVID-19

<table>
<thead>
<tr>
<th>Demographics and clinical characteristics</th>
<th>Total (n=191)</th>
<th>Non-survivor (n=54)</th>
<th>Survivor (n=137)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>56.0 (46.0–67.0)</td>
<td>69.0 (63.0–76.0)</td>
<td>52.0 (45.0–58.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td>0.15</td>
</tr>
<tr>
<td>Female</td>
<td>72 (38%)</td>
<td>16 (30%)</td>
<td>56 (41%)</td>
<td>..</td>
</tr>
<tr>
<td>Male</td>
<td>119 (62%)</td>
<td>38 (70%)</td>
<td>81 (59%)</td>
<td>..</td>
</tr>
<tr>
<td>Exposure history</td>
<td>73 (38%)</td>
<td>14 (26%)</td>
<td>59 (43%)</td>
<td>0.028</td>
</tr>
<tr>
<td>Current smoker</td>
<td>11 (6%)</td>
<td>5 (9%)</td>
<td>6 (4%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>91 (48%)</td>
<td>36 (67%)</td>
<td>55 (40%)</td>
<td>0.0010</td>
</tr>
<tr>
<td>Hypertension</td>
<td>58 (30%)</td>
<td>26 (48%)</td>
<td>32 (23%)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Diabetes</td>
<td>36 (19%)</td>
<td>17 (31%)</td>
<td>19 (14%)</td>
<td>0.0051</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>15 (8%)</td>
<td>13 (24%)</td>
<td>2 (1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic obstructive lung disease</td>
<td>6 (3%)</td>
<td>4 (7%)</td>
<td>2 (1%)</td>
<td>0.047</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>2 (1%)</td>
<td>0</td>
<td>2 (1%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>2 (1%)</td>
<td>2 (4%)</td>
<td>0</td>
<td>0.024</td>
</tr>
<tr>
<td>Other</td>
<td>22 (12%)</td>
<td>11 (20%)</td>
<td>11 (8%)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

Clinical Features in the Neonatal Period

Cohort study in Wuhan China describes clinical features of 33 newborns of mothers with COVID-19 pneumonia

4 of 33 (12%) had shortness of breath

3 of 33 (9%) were SARS-CoV-2 positive on NP and anal swabs

No deaths

All samples (amniotic fluid, cord blood, and breast milk) negative for SARS-COV-2

### Clinical Features of Neonates

<table>
<thead>
<tr>
<th>Variable</th>
<th>Neonates with SARS-CoV-2, No. (%)</th>
<th>Patients with SARS-CoV-2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n = 30)</td>
<td>Patient 1</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Preterm</td>
<td>16 (53)</td>
<td>GA: 40 wk</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>2 (7)</td>
<td>No; 3250 g</td>
</tr>
<tr>
<td>Asphyxia</td>
<td>1 (3)</td>
<td>No</td>
</tr>
<tr>
<td>Symptoms and complications</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Fever</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>3 (10)</td>
<td>No</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>3 (10)</td>
<td>No</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>2 (7)</td>
<td>No</td>
</tr>
<tr>
<td>Feeding intolerance</td>
<td>2 (7)</td>
<td>No</td>
</tr>
</tbody>
</table>

Vertical Transmission

Inconclusive

Possible as suggested by IgM detection in three neonates with severe SARS-COV-2 infection

Need more information

Clinical Features in Children

2143 children in China reported to CDC from Jan 16- Feb 8 2020

65.9% suspected cases

34.1% laboratory confirmed cases

13% of virologically confirmed cases had asymptomatic infection

5% had dyspnea or hypoxemia

0.6% progressed to ARDS

Age Distribution of Severity Amongst Children

<table>
<thead>
<tr>
<th>Age group*</th>
<th>Asymptomatic</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Critical</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>7 (7.4)</td>
<td>205 (18.8)</td>
<td>127 (15.3)</td>
<td>33 (29.5)</td>
<td>7 (53.8)</td>
<td>379 (17.7)</td>
</tr>
<tr>
<td>1-5</td>
<td>15 (16.0)</td>
<td>245 (22.5)</td>
<td>197 (23.7)</td>
<td>34 (30.4)</td>
<td>2 (15.4)</td>
<td>493 (23.0)</td>
</tr>
<tr>
<td>6-10</td>
<td>30 (31.9)</td>
<td>278 (25.5)</td>
<td>191 (23.0)</td>
<td>22 (19.6)</td>
<td>0 (0)</td>
<td>521 (24.3)</td>
</tr>
<tr>
<td>11-15</td>
<td>27 (28.7)</td>
<td>199 (18.2)</td>
<td>170 (20.5)</td>
<td>14 (12.5)</td>
<td>3 (23.1)</td>
<td>413 (19.3)</td>
</tr>
<tr>
<td>&gt;15</td>
<td>15 (16.0)</td>
<td>164 (15.0)</td>
<td>146 (17.5)</td>
<td>9 (8.0)</td>
<td>1 (7.7)</td>
<td>335 (15.7)</td>
</tr>
<tr>
<td>Total</td>
<td>94</td>
<td>1091</td>
<td>831</td>
<td>112</td>
<td>13</td>
<td>2141</td>
</tr>
</tbody>
</table>

Data were presented with number and percent (%); *Two cases had missing values.

Summary of Clinical Features

Fever and respiratory symptoms are the most common symptoms.

Patients with HTN, diabetes mellitus, and CAD are at greatest risk for worse outcomes.

Individuals > 65 years, preschool children and infants less than 1 year old are at higher risk for worsening outcomes.

Children are mostly asymptomatic.

Perinatal transmission is not well understood.

Hong H et al., Clinical characteristics of novel coronavirus disease 2019 (COVID-19) in newborns, infants and children, Pediatrics and Neonatology, https://doi.org/10.1016/j.pedneo.2020.03.001
Diagnosis

Nasopharyngeal swab (RT PCR) detects viral nucleic acids – turnaround time (TAT) ~ 24 hours

Rapid diagnostic tests – immunoassays to detect viral antigen, TAT~45 minutes
Commercially available, some are FDA approved

Rapid IgM-IgG antibody blood test – immunoassay to detect human antibody – CE Mark (Europe)

- 88.66% sensitivity
- 90.63% specificity


Sensitivity of RT-PCR Testing in Different Specimens

- Bronchoalveolar lavage (14/15) 93%
- Sputum (72 of 104) 72%
- Nasal swabs: 5 of 8 (63%)
- Fiberoptic brush biopsy (6 of 13) 46%
- Pharyngeal swabs (126 of 398) 32%
- Feces (44 of 153) 29%

Specimens

CDC

- Upper respiratory tract specimens (nasopharyngeal swab)
- Recommends testing lower respiratory tract specimens, if available.
- For patients who develop a productive cough, sputum should be collected and tested for COVID-19. The induction of sputum is not recommended.
- For patients for whom it is clinically indicated (e.g., those receiving invasive mechanical ventilation), a lower respiratory tract aspirate or bronchoalveolar lavage sample should be collected and tested as a lower respiratory tract specimen.

WHO

- At minimum, respiratory material should be collected:- upper respiratory specimens: nasopharyngeal and oropharyngeal swab or wash in ambulatory patients
- And/or lower respiratory specimens: sputum (if produced)
- And/or endotracheal aspirate or bronchoalveolar lavage in patients with more severe respiratory disease. (Note high risk of aerosolization; adhere strictly to infection prevention and control procedures).
Testing Results

Accuracy and predictive values have not been studied yet

Best time to test is a few days after symptom onset
   RNA positive rates peaked in upper respiratory tract specimens at 7-10 days after symptom onset, steadily declined after

Positive confirms COVID-19

Negative test does not rule out COVID-19
   If initial test is negative but suspicion is high, WHO recommends resampling and testing from multiple respiratory tract sites
Diagnosis: Who Should Be Tested?

New York State Guidance

- Prioritize testing for hospitalized patients
- Outpatient testing must not be encouraged, promoted or advertised
- Instruct people with COVID-like illness not requiring hospitalization to stay home.

CDC Guidance

- **Hospitalized** patients who have signs and symptoms compatible with COVID-19 in order to inform decisions related to infection control
- Other **symptomatic** individuals such as, older adults and individuals with chronic medical conditions and/or an immunocompromised state that may put them at higher risk for poor outcomes (e.g., diabetes, heart disease, receiving immunosuppressive medications, chronic lung disease, chronic kidney disease)
- Any persons including healthcare personnel, who within 14 days of symptom onset had close contact with a suspect or laboratory-confirmed COVID-19 patient, or who have a history of travel from affected geographic areas within 14 days of their symptom onset.
Testing Summary

Prioritize testing for hospitalized patients and symptomatic healthcare workers

Timing of test and obtaining a good sample is important

Positive and negative predictive values still being studies
IMAGING AND LABORATORY FINDINGS
Chest Radiographic Findings in COVID-19

<table>
<thead>
<tr>
<th>Patchy consolidation</th>
<th>Pleural effusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perihilar distribution</td>
<td>Peripheral distribution</td>
</tr>
</tbody>
</table>

CT Chest in findings COVID-19

Typical findings:

Prospective study from Rome compared accuracy of CT with RT-PCR for diagnosis
  158 patients, mean age 57 years
  Sensitivity: 97% (95% CI 88-99%)
  Specificity: 56% (95% CI 45-66%)

In those with COVID-19 based on RT PCR, most common findings:
- Peripheral, bilateral multilobe GGO
- Subsegmental vessel enlargement
- Bronchiectasis was seen in 41% of their sample

Rounded GGO

Apical GGO, enlarged blood vessels

Laboratory Findings

WBC can vary

Leukopenia, leukocytosis, and lymphopenia have been reported, although lymphopenia appears most common

Elevated lactate dehydrogenase and ferritin levels

Elevated aminotransferase

Lymphopenia and d-dimer levels associated with mortality

Management

Mainly supportive

Antivirals

Repurposed Drugs

Convalescent Sera
Supportive Care: Home

If stable not requiring hospitalization, isolate at home

Discontinuing home isolation:

- 3 days without fever and improvement in respiratory symptoms, and 7 days since first symptoms (CDC)

- Resolution of fever, improvement in respiratory symptoms, and two negative specimens 24 hours apart

Supportive Care: Hospitalized

Most common and severe complication: ARDS

Initially, supplemental oxygen via nasal cannula, mask

HFNC and NIPPV have higher risk of aerosolization and pathogen spread compared with invasive ventilation

Recommended earlier intubation
Invasive Ventilation

Follow ARDS treatment guidelines

Lung protective ventilation: low tidal volume (4-8 ml/kg), maintain plateau pressures ≤ 30 mmHg, maintain So2 88-95% by adjusting FiO2 and PEEP

Children: use lower plateau pressure ≤ 28 mmHg, tidal volume adapted to severity and respiratory system compliance

Systemic steroids are not recommended

Prone ventilation 12-16 hrs/day

ECMO - role is unclear, multiorgan failure
Antiviral Drugs: Remdesivir

Broad spectrum antiviral inhibits RNA dependent RNA polymerase

Tested in RCT for Ebola

Improves pulmonary function and reduces viral load in mice with MERS\(^1\)

Inhibits SARS and MERS replication in human AEC cultures\(^2\)

Phase 3 clinical trials sponsored by Gilead Sciences, IV remdesivir vs standard of care, recruiting

\(^1\)Sheahan T, Sims A, Leist S et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun. 2020;11(1). doi:10.1038/s41467-019-13940-6

Antiviral Drugs: Lopinavir-Ritonavir

HIV protease inhibitor, in vitro inhibitory activity against SARS-CoV

Randomized controlled open label trial completed, published by Cao et al

Population: 199 adults hospitalized with COVID 19, SO2 94% or less in RA or P:F ratio < 300

Arms: L-R x 14 days + standard care (99) or standard care alone (100)

Primary end point: time to clinical improvement

Result: time to clinical improvement and 28 day mortality similar

Hydroxychloroquine

Antiviral mechanism is not known

In vitro activity against SARS-CoV-2, HCQ > CQ

RCT in China (Chen et al) with 62 patients:-shortened time to recovery, temperature recovery time and the cough remission time in HCQ group -a larger proportion of patients with improved pneumonia in the HCQ group (80.6%, 25 of 31) compared with the control group (54.8%, 17 of 31)

3/30/20: FDA issued emergency use authorization

Zinc and Potential Anti-viral Mechanism

No clinical data for Zn supplementation and SARS-CoV-2

In-vitro studies with Vero-E6 cells cultured with SARS-CoV (2003 SARS virus) show that increasing Zn concentrations in cell media

High Zn concentrations appear to impair RNA synthesis by the SARS-CoV virus\(^1\)

Separate in-vitro oncology studies using human carcinoma cells investigating chloroquine’s ability to induce apoptosis in malignant cells showed that chloroquine is a Zn ionophore and increases intracellular Zn\(^2\)

Synergistic role for Zn and chloroquine speculated

Need more research to determine efficacy

\(^1\)te Velthuis A, van den Worm S, Sims A, Baric R, Snijder E, van Hemert M. Zn\(^{2+}\) Inhibits Coronavirus and Arterivirus RNA Polymerase Activity In Vitro and Zinc Ionophores Block the Replication of These Viruses in Cell Culture. PLoS Pathog. 2010;6(11):e1001176. doi:10.1371/journal.ppat.1001176

Tocilizumab

IL-6 receptor antagonist

Used in RA, JIA

"cytokine storm" in severe illness with COVID-19, correlates with disease severity

Recent launch of phase III trial in Italy for adults with severe COVID-19

FDA approved US clinical trial to start recruiting patients in April

Convalescent Plasma

Small case series show clinical improvement with plasma from individuals who have recovered from COVID-19

Has been used in other viral epidemics (SARS, MERS, Ebola, Influenza)

4/3/2020: FDA opened expanded access protocol, and allows single patient emergency IND. Encouraging requests for clinical trials

Zhang B et al. Treatment with Convalescent Plasma for Critically Ill Patients with SARS-CoV-2 Infection. Chest pre-print doi.org/10.1016/j.chest.2020.03.039
Coming Up

Solidarity trial (WHO): remdesivir, CQ and HCQ, ritonavir/lopinavir, ritonavir/lopinavir + interferon-beta

Vaccine: phase 1 clinical trial for investigational vaccine (mRNA-1273) at KP Washington Health Research Institute
Summary

COVID-19 is now a global pandemic, and the situation is rapidly evolving.

Like SARS-CoV, SARS-CoV-2 uses ACE2 as a key entry receptor.

Clinical course depends on age with older population, infants, and preschool children more affected.

Testing should be prioritized for hospitalized patients.

Management is largely supportive. We need more data to determine effective treatment options.
Thank You