The Clinical Horizon of Coronavirus Treatment (Oct 12, 2020)

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Catholic Health
Objectives

- Recognize the current magnitude of clinical complications of SARS-CoV 2
- Describe current treatment options for SARS CoV 2 infection

Conflicts of Interest/Research Support

- Research Funding: National Institutes of Health
  - (R01AI148560, UM1AI106701, UM1AI068636)
- Other: None

The sun rises. Early December 2019 the first pneumonia cases of unknown origin were identified in Wuhan

- Symptoms develop **5-6 days** (1-14) after infection
  - Fever = **43.8%** on admission and **88.7%** during hospitalization
  - Cough = **67.8%**
  - Fatigue = **38.1%**
  - SOB = **18.6%**
  - Myalgia/arthralgia = **14.8%**
  - Sore throat = **13.9%**
  - Headache = **13.6%**
  - Chills = **11.4%**
  - GI = **5%**

WHO-China Joint Mission on COVID-19 Report

Initial symptom severity (n = 55,924)

- **Mild to Moderate**: 80%
- **Severe**: 14%
- **Critical**: 6%
- **None (<1)**: 0%

**February 2020**

**CFR was only 3.8%**

**Severe** = dyspnea, respiratory frequency ≥30/minute, blood oxygen saturation ≤93%, PaO2/FiO2 ratio <300, and/or lung infiltrates >50% of the lung field within 24-48 hours

**Critical** = respiratory failure, septic shock, and/or multiple organ dysfunction/failure

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WHO-China Joint Mission on COVID-19 Report
# Update on Newly Discovered Coronavirus

<table>
<thead>
<tr>
<th></th>
<th>SARS CoV</th>
<th>MERS CoV</th>
<th>SARS-CoV 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Virion Structure</strong></td>
<td>Enveloped RNA virus</td>
<td>Enveloped RNA virus</td>
<td>Enveloped RNA virus</td>
</tr>
<tr>
<td><strong>Outbreak period</strong></td>
<td>2003-2004</td>
<td>2012-present</td>
<td>Dec 2019-present</td>
</tr>
<tr>
<td><strong>Initial site of isolation</strong></td>
<td>Guangdong province, China</td>
<td>Saudi Arabia</td>
<td>Wuhan, China</td>
</tr>
<tr>
<td><strong>No. of countries/cases</strong></td>
<td>29</td>
<td>27</td>
<td>&gt;70</td>
</tr>
<tr>
<td><strong>No. of cases (mortality)</strong></td>
<td>8,096 (9.6%)</td>
<td>2,494 (~34%)</td>
<td>~109,936 (N=3,806)(3.4%)* &gt;6,129 critical (~14%)</td>
</tr>
<tr>
<td><strong>No. of cases U.S.</strong></td>
<td>8</td>
<td>2 (2014)</td>
<td>538 (WA, IL, CA, AZ, Mass, Wis )</td>
</tr>
<tr>
<td><strong>Reservoir (intermediate host)</strong></td>
<td>Bats (palm civet)</td>
<td>Bats (dromedary camels)</td>
<td>Bats (likely a zoonosis)</td>
</tr>
<tr>
<td><strong>Incubation period</strong></td>
<td>2-7 days (range, 2-21)</td>
<td>2-7 (range, 2-14 days)</td>
<td>2-14 days (mean 5-6)</td>
</tr>
<tr>
<td><strong>Infectivity, rho</strong></td>
<td>1.8-2.5</td>
<td>0.3-1.3</td>
<td>~3 (2.4-3.8)*</td>
</tr>
<tr>
<td><strong>Super spreaders</strong></td>
<td>Yes</td>
<td>Yes (common)</td>
<td>Yes (many examples)</td>
</tr>
<tr>
<td><strong>Asymptomatic/mild</strong></td>
<td>No</td>
<td>Rare</td>
<td>Yes/Yes</td>
</tr>
<tr>
<td><strong>Spread</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Attack Rate</strong></td>
<td>10.3% to 60%</td>
<td>4 to 20%</td>
<td>20-30%, 80% (early study)?</td>
</tr>
<tr>
<td><strong>Transmission (including to HCP)</strong></td>
<td>Droplet/Direct, Airborne/Indirect?</td>
<td>Droplet/Direct, Airborne/Indirect?</td>
<td>Droplet/Direct, Airborne/Indirect/Fecal</td>
</tr>
<tr>
<td><strong>Treatment (PEP)</strong></td>
<td>Supportive (none)</td>
<td>Supportive (none)</td>
<td>Supportive (drugs CU)</td>
</tr>
<tr>
<td><strong>Infection Prevention</strong></td>
<td>Airborne, contact, face shield</td>
<td>Airborne, contact, face shield</td>
<td>Airborne, contact, face shield</td>
</tr>
</tbody>
</table>

*About 83% of cases are mild or asymptomatic. Mortality Rates are age Stratified: 80+ = 14.8%, 70-79 = 8%; 60-69 = 3.6%, 50-59 = 1.3%, 40-49 = 0.4%, <40 = 0.2%, less than 15% = 0%.
6% of positively tested
ARDS (ICU)


1.4-60% CFR amongst ARDS
Cardiovascular

• Prevalence
  - Hypertension = 17%
  - Cardiac disease = 16.4%
  - Arrhythmia as high as 17%

• Mortality
  - History of CVD = 5x mortality (10.5%)
  - 7% of COVID-19 deaths attributed to MI

Diabetes

- Prevalence
  - 5-11% in 20k cases
  - 14-32% in severe COVID-19

- Case reports of DKA

- Mortality

- 1-2.75x likely lead to ARDS

- 2.3% among 44k cases


Other complications

- **Hepatobiliary** (LFTs, Lactate, etc.) = 51%
- **GI** (appetite, diarrhea, etc.) = up to 50%
  - Abdominal pain associated with severity
- **Renal**
  - AKI up to 15% (60-90% mortality)
  - Elevated SrCr (20%), low GFR (13%)
  - Proteinuria (44-63%), Hematuria (27%)
- **Neurological** = 36.4%
- **Thyrotoxicosis** = 56%
- **Musculocutaneous**
  - Myalgia (36%), Elevated CK (33%)
  - Rash (20%)
- **Hematologic (coagulopathy)**
  - Lymphopenia = 40-70%, Thrombocytopenia = 40-69%
- **Other special population considerations**

ClinicalTrials.gov = >3185 studies for COVID-19

- ACTT 2: remdesivir + baricitinib
- Vitamin C, D and Zinc
- Auxora
- Baricitinib + HQ
- Interferon Beta, Alpha
- Lopinavir/ritonavir + HQ
- Umifenovir
- Ribavirin
- Triiodothyronine

- Adjunctive IV IG
- Checkpoint inhibition and other immunomodulators: i.e. CD47, EDP1815
- Methylprednisolone
- Oseltamivir + Azithro
- acalabrutinib, a BTK inhibitor
- Melatonin
- Stromal Cell
- Triiodothyronine
- Various respiratory adjuvants
- And many more…
NIH guidelines: Remdesivir

- Because remdesivir supplies are limited, prioritize remdesivir for recommended use in
  - hospitalized patients who require supplemental O2 but who do not require high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO (BI).
  - **Require** Supplemental O2, duration = 5 days or until hospital discharge, whichever comes first (AI).
  - Lack of improvement after 5 days, optimal duration is unknown though some experts extend up to 10 days (CIII).
- **Require** *High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO,* = uncertainty

ACTT-1

- 1059 prelim analysis
- 8 point ordinal scale
- ACTT-2 and -3 (combination with immunomodulators) are underway
- Moderate disease trial underway
NIH guidelines: CQ/HCQ +/- Azithro

- **Against** the use of chloroquine (including high dose) or hydroxychloroquine for the treatment of COVID-19 in hospitalized patients (AI).

- In nonhospitalized patients, the Panel **recommends against** the use of chloroquine or hydroxychloroquine for the treatment of COVID-19, except in a clinical trial (AI).

- The Panel **recommends against** using hydroxychloroquine plus azithromycin to treat COVID-19, except in a clinical trial (AIII).

- **QTc** prolongation, Torsade de Pointes, ventricular arrhythmia, and cardiac deaths. If chloroquine or hydroxychloroquine is used, clinicians should monitor the patient for adverse events, especially prolonged QTc interval (AIII).
RECOVERY

- Ongoing, open-label national UK study across 176 hospitals
- 1561 randomized to HQ
- 17% high-flow, 60% O2
- Azithro and steroid use similar in both arms

**Table 2: Effect of allocation to hydroxychloroquine on main study outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hydroxychloroquine (n = 1561)</th>
<th>Usual care (n = 3155)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28-day all-cause mortality</td>
<td>418 (26.8%)</td>
<td>788 (25.0%)</td>
<td>1.09 (0.96 to 1.23)</td>
</tr>
<tr>
<td><strong>Secondary outcomes:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharged from hospital within 28 days</td>
<td>941 (60.3%)</td>
<td>1982 (62.8%)</td>
<td>0.92 (0.85 to 0.99)</td>
</tr>
<tr>
<td>Receipt of mechanical ventilation or death*</td>
<td>388/1300 (29.8%)</td>
<td>696/2623 (26.5%)</td>
<td>1.12 (1.01 to 1.25)</td>
</tr>
<tr>
<td>Death</td>
<td>308/1300 (23.7%)</td>
<td>572/2623 (21.8%)</td>
<td>1.09 (0.96 to 1.23)</td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>118/1300 (9.1%)</td>
<td>215/2623 (8.2%)</td>
<td>1.11 (0.89 to 1.37)</td>
</tr>
</tbody>
</table>

HCQ, or Azithro, or HCQ+Azithro

- New York
- Observational
- Large sample (1438)
- No differences in ECG

NIH guidelines: Lpv/Rit and other PIs

- The Panel recommends against using lopinavir/ritonavir (AI) or other HIV protease inhibitors (AIII) to treat COVID-19, except in a clinical trial.
Lpv/Rit

- Randomized, open-labeled
- N = 199
- Not statistically different - underpowered
- No difference in LOS or viral clearance

PK/PD Lpv/Rit in COVID-19

- Brief report, case series
- Only trough
- 60-120 fold below potential threshold for SARS-CoV-2 EC50 (16.4)

**Table. Lopinavir and Ritonavir Trough Concentrations in Patients Hospitalized With COVID-19**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Lopinavir, μg/mL*</th>
<th>Ritonavir, μg/mL*</th>
<th>Age, y</th>
<th>Sex</th>
<th>Body Mass Index, kg/m²</th>
<th>C-reactive Protein Level, mg/L</th>
<th>Albumin Level, g/L</th>
<th>Treatment Day</th>
<th>Concomitant Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.2</td>
<td>&lt;0.19</td>
<td>72</td>
<td>Female</td>
<td>29</td>
<td>1.6</td>
<td>39.9</td>
<td>10</td>
<td>Oxazepam</td>
</tr>
<tr>
<td>2</td>
<td>19.9</td>
<td>0.56</td>
<td>21</td>
<td>Female</td>
<td>-</td>
<td>7.8</td>
<td>37.3</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>14.6</td>
<td>0.22</td>
<td>65</td>
<td>Female</td>
<td>24.5</td>
<td>19.3</td>
<td>37.4</td>
<td>10</td>
<td>Candesartan</td>
</tr>
<tr>
<td>4</td>
<td>24.3</td>
<td>0.67</td>
<td>26</td>
<td>Male</td>
<td>26.5</td>
<td>40.0</td>
<td>36.1</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>10.3</td>
<td>&lt;0.19</td>
<td>52</td>
<td>Female</td>
<td>30</td>
<td>7.9</td>
<td>37.1</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>10.0</td>
<td>&lt;0.19</td>
<td>79</td>
<td>Male</td>
<td>22</td>
<td>4.0</td>
<td>34.7</td>
<td>7</td>
<td>Atenovastin, bisoprolol, edoxaban, and pantoprazole</td>
</tr>
<tr>
<td>7</td>
<td>12.6</td>
<td>0.20</td>
<td>67</td>
<td>Female</td>
<td>36</td>
<td>39.1</td>
<td>39.5</td>
<td>6</td>
<td>Mefinavir, ezetimibe, bisoprolol, valsartan, amlopiine, pantoprazole, and metamizole</td>
</tr>
<tr>
<td>8</td>
<td>23.0</td>
<td>&lt;0.19</td>
<td>53</td>
<td>Male</td>
<td>29</td>
<td>184.7</td>
<td>32.6</td>
<td>4</td>
<td>Bisoprolol, triazolam, and budesonide/formoterol</td>
</tr>
</tbody>
</table>

* Drug levels were quantified by liquid chromatography-tandem mass spectrometry.

NIH guidelines: Immunomodulators

• There are insufficient data for the Panel to recommend either for or against the use of
  - Interleukin (IL)-1 inhibitors (e.g., anakinra)
  - Interferon beta for the treatment of early (i.e., <7 days from symptom onset) mild and moderate COVID-19.

• The Panel recommends against the use of the following, except in a clinical trial:
  - Anti-IL-6 receptor monoclonal antibodies (e.g., sarilumab, tocilizumab) or anti-IL-6 monoclonal antibody (siltuximab) (BI).
  - Interferons (alfa or beta) for the treatment of severely or critically ill patients with COVID-19 (AIII).
  - Bruton’s tyrosine kinase inhibitors (e.g., acalabrutinib, ibrutinib, zanubrutinib) and Janus kinase inhibitors (e.g., baricitinib, ruxolitinib, tofacitinib) (AIII).
Early experience with TOC

- Italian tertiary centers
- N = 1351 (179 with TOC)
- Pneumonia
- Primary outcome = respiratory recovery score (Brescia COVID respiratory severity score)
- >50% not in ICU
- 77% improved

Press releases, Sep.

• COVACTA
  - Phase 3, Randomized placebo controlled, in 450 adults
  - Primary outcome = improved clinical status over 4 weeks
  - Failed to meet primary or several key secondary endpoints (4 week mortality)
  - No statistical difference in primary (OR 1.19; 95% CI, 0.81–1.76; \( P = 0.36 \)) or in mortality
    (19.7% vs. 19.4%; difference of 0.3%; 95% CI, -7.6% to 8.2%; \( P = 0.94 \))

• CORIMUNO-TOCI
  - Open label, randomized trial with/without SOC in 129 adults across France
  - Mortality and proportion requiring ventilation lower in TOC group, details forthcoming
HQ+/-Azithro+/-Toc

- Retrospective, observational cohort, Hospital network in NJ
- Among 547 ICU patients, 134 receiving TOC
- 30 day unadjusted mortality with and without tocilizumab of 46% versus 56%.

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% conf. interval</th>
<th>P-value</th>
<th>30-day mortality rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
<td></td>
</tr>
<tr>
<td>Any HCQ in hospital</td>
<td>0.99</td>
<td>0.80</td>
<td>1.22</td>
<td>0.92</td>
</tr>
<tr>
<td>HCQ+AZI in hospital</td>
<td>0.98</td>
<td>0.75</td>
<td>1.28</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Factorial main effects and interaction of HCQ and AZI

|                                |        | Lower       | Upper   | P-value   | 30-day mortality rate |
|                                |        | Lower       | Upper   |           |                       |
| HCQ main effect                | 1.02   | 0.83        | 1.27    | 0.83      | 0.25 (HCQ only) 0.20 (Neither) |
| AZI main effect                | 0.89   | 0.72        | 1.10    | 0.28      | 0.20 (AZI only) 0.20 (Neither) |
| Interaction                    |        |             |         | 0.091     | 0.18 (Both) 0.20 (Neither) |

Tocilizumab therapy in the Intensive Care Unit

|                                |        | Lower       | Upper   | P-value   | 30-day mortality rate |
|                                |        | Lower       | Upper   |           |                       |
| Toci in ICU                    | 0.76   | 0.57        | 1.00    | 0.053     | 0.46 | 0.56 |

https://doi.org/10.1371/journal.pone.0237693.t002
Lpv/Rit+Interferon+Ribavirin

- Open label, randomized
- N = 127
- Both arms had Lpv/Rit
- Lopinavir/Ritonavir + Ribavirin + Interferon beta-1b (n=52)
- Significantly shorter time to negative nasopharyngeal swab.
- Mostly mild illness
NIH guidelines: Convalescent Plasma

- There are insufficient data to recommend either for or against the use of convalescent plasma for the treatment of COVID-19.

- Convalescent plasma should not be considered the standard of care for the treatment of patients with COVID-19.

- 08/26/20: FDA assigns EUA status
U.S. Convalescent Plasma Expanded Access Program (EAP)

- Cohort with N = 35k, mostly critically ill
- In 3500, reduced mortality with higher AB and earlier administration

NIH guidelines: Dexamethasone

- The Panel **recommends** using **dexamethasone** 6 mg per day for up to 10 days or until hospital discharge, whichever comes first, for the treatment of COVID-19 in hospitalized patients who are mechanically ventilated (AI) and in hospitalized patients who require supplemental oxygen but who are not mechanically ventilated (BI).

- The Panel **recommends against** using **dexamethasone** for the treatment of COVID-19 in patients who do not require supplemental oxygen (AI).

- If dexamethasone is not available, the Panel recommends using alternative glucocorticoids such as **prednisone**, **methylprednisolone**, or **hydrocortisone** (see Additional Considerations in the **Corticosteroids** section for dosing recommendations) (AIII).
RECOVERY

- **N = 11.5k** across the UK
- **2k on dexamethasone (6mg QD po or iv) vs. 4k SOC**
- Halted due to sufficient data
- Lower 28-day mortality among on mechanical ventilation or oxygen alone at randomization but not among without respiratory support

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**Table:**

<table>
<thead>
<tr>
<th>Respiratory Support at Randomization</th>
<th>Dexamethasone</th>
<th>Usual Care</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive mechanical ventilation</td>
<td>95/324 (29.3)</td>
<td>283/683 (41.4)</td>
<td>0.64 (0.51–0.81)</td>
</tr>
<tr>
<td>Oxygen only</td>
<td>298/1279 (23.3)</td>
<td>682/2604 (26.2)</td>
<td>0.82 (0.72–0.94)</td>
</tr>
<tr>
<td>No oxygen received</td>
<td>89/50 (17.8)</td>
<td>145/1034 (14.0)</td>
<td>1.19 (0.91–1.55)</td>
</tr>
<tr>
<td>All Patients</td>
<td>482/2104 (22.9)</td>
<td>1110/4321 (25.7)</td>
<td>0.83 (0.75–0.93)</td>
</tr>
</tbody>
</table>

Chi-square trend across three categories: 11.5

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**Graphs:**

A. All Participants (N=6425)

B. Invasive Mechanical Ventilation (N=1007)

C. Oxygen Only (N=1383)

D. No Oxygen Received (N=1535)

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Vaccine Development – targeting 50%

- 8/11/20 Russia approves the first SARS CoV2 vaccine w/o PIII trials
- 10/6/20 FDA announces EUA criteria
- WHO reports over 143 vaccines in preclinical and 33 candidates in clinical trials (+60 in the month of August)
- U.S has invested in more than five candidates through “Operation Warp Speed,” a partnership between the government, scientific community, and drug companies
- Several platforms based on major technical advancements: recombinant adenovirus vector, mRNA, whole-inactivated
- Currently 11 candidates in PIII trials, 19 in PII, 35 in PI.
mRNA-1273

Adenovirus-vectored = ChAdOx1 nCov-19

Audience Poll

Do you plan on getting the coronavirus vaccine when one is available?

• Yes
• Not sure
• No
Do you plan to get a coronavirus vaccine when one is available?
For some in the United States, the answer is no, according to a survey of 1056 people in mid-May.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Dose Group</th>
<th>Vaccination 1</th>
<th>Vaccination 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any systemic symptom</td>
<td>25 µg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>100 µg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>250 µg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>25 µg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>100 µg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>250 µg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>25 µg</td>
<td></td>
<td></td>
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<td></td>
<td>100 µg</td>
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<tr>
<td></td>
<td>250 µg</td>
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<tr>
<td>Fever</td>
<td>25 µg</td>
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<tr>
<td></td>
<td>100 µg</td>
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<td></td>
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<tr>
<td></td>
<td>250 µg</td>
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<tr>
<td>Chills</td>
<td>25 µg</td>
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<td></td>
<td>100 µg</td>
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<tr>
<td></td>
<td>250 µg</td>
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<tr>
<td>Headache</td>
<td>25 µg</td>
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<td></td>
<td>100 µg</td>
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<td></td>
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<td></td>
<td>250 µg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>25 µg</td>
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<tr>
<td></td>
<td>100 µg</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>250 µg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>25 µg</td>
<td></td>
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<td></td>
<td>100 µg</td>
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<tr>
<td></td>
<td>250 µg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any local symptom</td>
<td>25 µg</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>100 µg</td>
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<td></td>
<td>250 µg</td>
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ASSOCIATED PRESS–NORC CENTER FOR PUBLIC AFFAIRS RESEARCH AT THE UNIVERSITY OF CHICAGO, Accessed 8/31/2020
Genomic evidence for a case of reinfection with SARS-CoV-2

• Posted: 27 Aug 2020
  - 33yo man was diagnosed with COVID-19 on March 26, hospitalized, then recovered. He tested positive for SARS-CoV-2 again on August 15, and whole genome sequencing indicated they were from different clades

• Posted: 2 Oct 2020
  - 60 yo care-home resident re-infected with different strains and with different immunologic responses

• Additional considerations for CoV evolution:
  - 120Kb, $10^{-6}$ mutation rate, 25% recombination (modular), plastic glycoproteins

Preprints with THE LANCET

Into the unknown…

• Complications
  - Metrics for clinical outcome, treatment
  - Re-infection
  - Chronic conditions
  - Steroids in early disease
  - Alkalosis, Hyperkalemia, AKI, Hepatic encephalopathy
  - Biomarkers

• Treatment
  - Confounding variables induce headaches
  - Pharmacogenomics (D614G)
  - Special populations: racial, pregnancy, cancer, etc.
  - Timing (initiation, duration)
  - Combinations – PK/PD conundrum
  - Supportive: ACE-2/ARB inhibitors, Vitamins, Herbals, NO2, etc.


Thank You!

08/29/20 @ 4:30pm
EXTRA SLIDES FOR QUESTIONS
Disease Course

Stage I (Early Infection)
- Viral response phase
- Clinical Symptoms: Mild constitutional symptoms, Fever >99.6°F, Dry Cough, diarrhea, headache
- Clinical Signs: Lymphopenia, increased prothrombin time, increased D-Dimer and LDH (mild)

Stage II (Pulmonary Phase)
- Host inflammatory response phase
- Clinical Symptoms: Shortness of Breath, Hypoxia (PaO2/FiO2<300mmHg)
- Clinical Signs: Abnormal chest imaging, Transaminits, Low-normal procalcitonin
- Potential Therapies: Remdesivir, chloroquine, hydroxychloroquine, convalescent plasma transfusions, Reduce Immunosuppression

Stage III (Hyperinflammation Phase)
- Clinical Symptoms: ARDS, SIRS/Seck, Cardiac Failure
- Clinical Signs: Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin, Troponin, NT-proBNP elevation)
- Potential Therapies: Corticosteroids, human immunoglobulin, IL-6 inhibitors, IL-2 inhibitors, JAK inhibitors

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<thead>
<tr>
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</thead>
<tbody>
<tr>
<td></td>
<td>Prospective open-label, Nonrandomized (n=42)</td>
<td>Prospective observational study (n=80)</td>
<td>RCT (n=30)</td>
<td>RCT (n=62)</td>
<td>Prospective observational study (n=11)</td>
</tr>
<tr>
<td>Treatment</td>
<td>HCQ 200mg TID x 10 days +/- Z-pak vs no treatment</td>
<td>HCQ 200mg PO TID + Z-pak (No control patients)</td>
<td>HCQ 400mg per day x 5 days vs conventional treatment</td>
<td>HCQ 200mg BID vs control</td>
<td>HCQ 200mg TID + Z-pak (No control patients)</td>
</tr>
<tr>
<td>Primary Outcome</td>
<td>Virological clearance at day-6 post-inclusion</td>
<td>Disease progression: Need for oxygen or ICU Admission, viral load</td>
<td>Negative conversion rate of nucleic acid in pharyngeal swab on day 7</td>
<td>Time to clinical recovery</td>
<td>Viral load (nasopharyngeal swab): On days 5–6</td>
</tr>
<tr>
<td>Results</td>
<td>HCQ: 70% HCQ + Z-pak: 100% Control: 12.5%</td>
<td>Day 7: 83% negative VL Day 8: 93% negative VL 3 transferred to ICU ICU mean LOS 5 days</td>
<td>HCQ: 86.7% Control: 93.3% (P &gt; 0.05)</td>
<td>Fever resolution: 2.2 days HCQ vs 3.2 days Improved pneumonia day 6: HCQ 80.6% control group 54.8%</td>
<td>80% positive on days 5-6 of treatment</td>
</tr>
<tr>
<td>Safety</td>
<td>Not documented</td>
<td>N/V: 2.5% Diarrhea: 5% Blurred Vision: 1.2% Death: 1 patient</td>
<td>26.7% of the HCQ group and 20% of the control group had diarrhea and abnormal LFTs</td>
<td>HCQ group: 1 rash and 1 headache occurred</td>
<td>In 1 patient, treatment was stopped after 4 days due to QTc prolongation Death: 1 patient</td>
</tr>
</tbody>
</table>
Chief Complaint and HPI

• CC: Shortness of breath and cough

• HPI: 48 year old African American Male
  - A “few days ago” he drank some water and felt like it “went down the wrong tube”
  - Almost immediately afterwards shortness of breath and cough developed
  - Spiked fever of 101 F and contacted PCP who instructed him to manage his symptoms at home (Rest + acetaminophen as needed)
  - Cough has been mostly productive consisting of clear-colored sputum
  - Developed body aches effecting his entire body
  - Symptoms continued to worsen and patient decided to go to the emergency department
Patient History

• Past Medical Hx: Diabetes, dyslipidemia, hypertension, GERD, obesity, OSA on CPAP

• Surgical Hx: Cholecystectomy, Tonsillectomy

• Social Hx: Denies drug use, alcohol use, or illicit drug use

• Family Hx: Not available

• Home medications: Atorvastatin 40mg PO QD, Gabapentin 400mg PO TID, Jardiance 10mg PO QD, Metformin 1,000mg PO BID, Omeprazole DR 20mg PO QD, Amlodipine 10mg PO QD

• Allergies: Penicillin's (Hives)
Physical Exam

- **Vitals**: BP 144/76, RR 24, \text{spO2} 73\% on RA, HR 108, Temp 99.4 F
- **General**: Alert and oriented x3
- **HEENT**: Atraumatic, normocephalic. EOMI, moist mucous membranes.
- **CV**: Tachycardic, regular rhythm, normal heart sounds, normal S1 and S2
- **Respiratory**: Tachypnea, essentially clear, but few rare scattered crackles at bases posteriorly
- **Abdomen**: Soft, non-tender, normal bowel sounds
- **Extremities**: Normal, no evidence for cellulitis, full range of motion
- **Psych**: Pleasant and cooperative
Emergency Department Workup

- **Lab work**
  - CBC: WBC: 7.0, Hgb: 15.0, Plts: 166, **Neutrophil: 86%, Lymphocytes: 9%, Bands: 0%**
  - APTT: 31.3, **PT: 18.8(H), INR: 1.6(H), D-dimer: 792 (H)**
  - **Blood gas on 100% NRB:** pH: 7.46, pCO2: 39, pO2: 78, HCO3: 27, oxygen sat: 97%
  - HS troponin: 6, lactic acid: 1.5, influenza A/B negative, **LDH: 411 (H), CRP: 50.9 (H), Ferritin: 688.8(H), Procalcitonin: 0.09**
  - Blood cultures, urine antigens, nasal cultures, tox screen, **COVID-19 testing ordered**
  - BMI: 54.39

- **Imaging/EKG:**
  - **CXR:** Extensive bilateral infiltrates consistent with bilateral pneumonia
  - EKG: Sinus tachycardia, moderate intraventricular conduction delay + nonspecific T-wave abnormality. QTc: 418

- Given NS 500ml IV @ 150ml/hr, Ceftriaxone 1g IV, Azithromycin 500mg IV, Acetaminophen 975mg PO
Diagnostic Lab Findings

- CBC with differential
  - WBC is usually normal (4-11): 7.0
  - Lymphopenia is common (20-40%): 9%
  - Mild thrombocytopenia is common (145-450): 166

- CMP with magnesium and phosphorus
  - LFTs commonly elevated AST/ALT WNL

- Coagulation studies with D-dimer
  - PT/PTT/INR usually normal
  - D-dimer commonly elevated (0-500): 792

- Procalcitonin
  - Usually not elevated* (0-0.10): 0.09

- CRP (0-5): 50.9
  - Usually elevated and increases with progression

- Other Labs:
  - LDH (105-210): 411
  - Ferritin (23.9 – 336.2): 688.8
  - Urine legionella antigens (Negative)
  - Blood cultures (Negative)
  - Troponin (0-20): 6
  - ABG 7.46/39/78/27.7
  - Lactate Not ordered on admission
  - CPK Not ordered on admission
  - G6PD Not ordered on admission

- EKG: Qtc: 418

Diagnostic Imaging: Chest X-Ray

• Patchy ground glass opacities
  - Present bilaterally and predominantly peripherally

• Clear lungs**
  - Seen early in course of disease in many mildly symptomatic patients → Quickly progresses to ground class opacities

• Pleural effusions are uncommon
Patient’s Initial Chest X-Ray

NORMAL CHEST X-RAY

ADMISSION CHEST X-RAY
Imaging Progression

ADMISSION CHEST X-RAY

X-RAY HOSPITAL DAY 4
<table>
<thead>
<tr>
<th></th>
<th>D-Dimer (0-500ng/mL)</th>
<th>Serum Creatinine (0.9-1.3 mg/dL)</th>
<th>CRP (0.0-5.0mg/L)</th>
<th>Ferritin (23.9 – 336.2 ng/mL)</th>
<th>WBC (4.0-11.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCQ+ azithro + cefixone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>792</td>
<td>1.0</td>
<td>50.9</td>
<td>688.8</td>
<td>7.0</td>
</tr>
<tr>
<td>Day 2</td>
<td>-</td>
<td>2.37</td>
<td>-</td>
<td>-</td>
<td>5.2</td>
</tr>
<tr>
<td>Day 3</td>
<td>-</td>
<td>5.73</td>
<td>-</td>
<td>-</td>
<td>5.3</td>
</tr>
<tr>
<td>Day 4</td>
<td>-</td>
<td>7.45</td>
<td>116.4</td>
<td>-</td>
<td>6.1</td>
</tr>
<tr>
<td>Day 5</td>
<td>-</td>
<td>7.74</td>
<td>-</td>
<td>-</td>
<td>8.6</td>
</tr>
<tr>
<td>Day 6</td>
<td>18,129</td>
<td>7.63</td>
<td>176.9</td>
<td>-</td>
<td>9.1</td>
</tr>
<tr>
<td>Day 7</td>
<td>15,919</td>
<td>7.79</td>
<td>152.6</td>
<td>1,814.0</td>
<td>10.2</td>
</tr>
<tr>
<td>Day 8</td>
<td>23,560</td>
<td>7.42</td>
<td>118.6</td>
<td>1,487.3</td>
<td>13.6</td>
</tr>
<tr>
<td>Day 9</td>
<td>-</td>
<td>7.49</td>
<td>-</td>
<td>-</td>
<td>15.6</td>
</tr>
<tr>
<td>Vanco + Cefepime</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Day 10</td>
<td>-</td>
<td>7.49</td>
<td>-</td>
<td>-</td>
<td>19.6</td>
</tr>
<tr>
<td>Day 11</td>
<td>-</td>
<td>7.92</td>
<td>-</td>
<td>-</td>
<td>18.1</td>
</tr>
<tr>
<td>Day 12</td>
<td>-</td>
<td>8.06</td>
<td>-</td>
<td>-</td>
<td>20.7</td>
</tr>
</tbody>
</table>

**Note:** HCQ indicates Hydroxychloroquine, ABX indicates Antibiotics, WBC indicates White Blood Cells.
Coagulopathy

- Common: fibrin-platelet micro-thrombi in the pulmonary vasculature

- 183 patients admitted to the Tongji Hospital in Wuhan
  - DIC in 71.4% of non-survivors and 0.6% of survivors

- High fibrinogen levels reduce efficacy of prophylactic dose heparin agents
  - Whole-blood samples obtained from healthy volunteers (n = 10)
  - Results: Hyperfibrinogenemia negated the effect of heparin and was noted in all TEG parameters

Therapeutic Targets

Approaches to inhibit viral replication

Direct acting antivirals

ACE2, TMPRSS2
SARS-CoV-2

Virus entry

Virus release

(remdesivir, favipiravir, galidesivir)
RdRp inhibitors

Release of viral genome

Genomic RNA

Replication

Polyprotein

M protease inhibitors

(lopinavir, ritonavir, nelfinavir, ebvifen)

Translation

Golgi apparatus

Replication

Virion assembly

ACE2, TMPRSS2

SARS-CoV-2

Virus entry

Virus release

Serine protease inhibitors

(camostat, nafamostat)

Endosome maturation and function

(chloroquine, hydroxychloroquine, aprotinin)

Membrane trafficking and signaling

(dasatinib, saracatinib, imatinib, nilotinib, trametinib, selumetinib, gilteritinib, ralitretinib)

Unknown or complex functions

(niclosamide, chloroquine, hydroxychloroquine)

Cell cycle regulation

(dinaciclib)

Nucleus

Golgi apparatus

Virion assembly

ER

Nucleus

Therapeutic Targets
Modulators of inflammatory response and tissue injury

**Early stage**
- Boost immune response
- SARS-CoV-2
  - IFN
  - Pro-inflammatory cytokines
  - Angiotensin II
  - Angiotensin 1-7
  - ACE2
- Treatment: IFN-I (e.g. IFN-α/β)
  IFN-III (IFN-α1-4)

**Late stage**
- Excessive inflammation
- Anti-inflammatory drugs
  - Ulinastatin
  - Angiotensin 1-7
- Treatment: dexamethasone, bericitinib, acalabrutinib,
  tofacitinib, tocilizumab, sarilumab,
  ulinastatin, angiotensin 1-7, nintedanib
<table>
<thead>
<tr>
<th>Therapeutic target</th>
<th>Drug and article reference</th>
<th>Drugs related studies</th>
</tr>
</thead>
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<td><strong>Receptor recognition (ACE2, CD147 receptors)</strong></td>
<td>Human recombinant soluble form of ACE2 (Khan et al., 2017; Montiel et al., 2020; Montiel et al., 2020), Meplazumab (mAb anti-CD147 receptor) (Wang K. et al., 2020)</td>
<td>NCT04335136, NCT04375046, NCT04287686 (withdrawn)</td>
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<td><strong>Clathrin-mediated endocytosis</strong></td>
<td>Hydroxychloroquine (Hq) sulphate (Piot et al., 1995; Yang et al., 2020; Bender et al., 2020) and Chloroquine phosphate (Savarno et al., 2020; Vincent et al., 2020). <em>Multiple targets: clathrin-mediated endocytosis, endosomal pH, TLR7/8, IFN responses, and proinflammatory cytokines release.</em></td>
<td>NCT04275245 - ongoing studies NCT04315948, DisCoVeRy trial, NCT04240453, CHCRT2000029603, NCT04343148, CHCRT2000029609 - discontinued study: Hq arm of Solidarity trial - withdrawn: NCT04347512, NCT04371926</td>
</tr>
<tr>
<td><strong>Endosomal fusion</strong></td>
<td>Baricitinib (Richardson et al., 2020; Stobbing et al., 2020)</td>
<td>NCT04322077, NCT04401579, NCT04362137</td>
</tr>
<tr>
<td><strong>Viral synthesis</strong></td>
<td>Urifanovir (Ding et al., 2020; Lian et al., 2020)</td>
<td>IRC2021/0001257052768N15</td>
</tr>
<tr>
<td><strong>Cytokine response, Th1 response</strong></td>
<td>IL-6 production</td>
<td>Recovery trial, NCT04251871, NCT04255517, CHCRT200000296539, NCT04295274, NCT04295551, NCT04252274, NCT04252274, NCT04252274, NCT04289706, si ACTT-II, NCT04229899</td>
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<td><strong>VEGFA</strong></td>
<td>Remdesivir (Sheehan et al., 2017; Agostini et al., 2018; Beigel et al., 2020; Goldman et al., 2020; Grein et al., 2020; Wang M. et al., 2020; Wu et al., 2020; Wang X. et al., 2020) <em>Multiple targets: viral polyadenylation, mTORC1, Nsp12-RepR, replicase transcription complex, -RTC</em></td>
<td>NCT04257658, SIMPLE trial, WHO Solidarity trial, DisCoVeRy trial, NCT04229899</td>
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<td><strong>Inflammatory response</strong></td>
<td>Favipiravir/target: Nsp12-RepR (Coomes and Hightayan, 2020)</td>
<td>CHCRT2000002964, NCT04252274, NCT04252274, NCT04252274, NCT04252274</td>
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<td><strong>Immuno-modulatory activity</strong></td>
<td>Mesenchymal stem cells (SH et al., 2016; Leng et al., 2020) <em>Multiple targets: inflammatory cytokines, Th2 response, regeneration of damaged cell Thalidomide</em></td>
<td>NCT04362137, NCT04317092, NCT04315850, COVACTA, NCT04320615, NCT04320660, NCT04329560, NCT043275414, BREATHE clinical trial, UK RECOVERY trial NCT04381936, NCT044735629, NCT04273561, NCT04248068</td>
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<td><strong>Neutralizing antibodies</strong></td>
<td>Convalescent plasma (Frogers et al., 2020; Zhou and Zhao, 2020)</td>
<td>NCT04361936, NCT04373460, ISRCTN50189173, NCT04249850, NCT04275201, NCT04441918, NCT04248068</td>
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Anti-HCV nucleotide inhibitors

Remdesivir: Cumulative Incidence of Clinical Improvement from Baseline to Day 36.

A. Overall

Days since Initiation of Remdesivir

No. at Risk
53 53 43 33 23 13 7 4 1 0

B. Baseline Oxygen Support

Days since Initiation of Remdesivir

No. at Risk
Noninvasive
19 19 15 10 6 2 1 0
Invasive
34 34 28 23 17 11 6 4 1 0

C. Age

Days since Initiation of Remdesivir

No. at Risk
<50 Yr of age
14 14 10 8 5 1 1 1 1
50 to <70 Yr of age
21 21 18 12 8 5 3 1 0
≥70 Yr of age
18 18 15 13 10 7 3 2 1 0
Modest beginnings

- Randomized, placebo
- N=237
- Concomitant treatments allowed
- Onset of symptoms <12 days
- Participants had SpO2 <94 and pneumonia
- Terminated early

Mechanistic PK/PD model - HCQ

HCQ or HCQ+Azithro

- Brazil
- Unblinded
- N = 504
- 15d follow-up
- Differences in AE

Outcomes of Hydroxychloroquine Usage in United States Veterans Hospitalized with COVID-19

- Retrospective analysis of data from patients hospitalized with confirmed SARS-CoV-2 infection in all United States Veterans Health Administration medical centers

- The two primary outcomes were death and the need for mechanical ventilation

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of Patients</th>
<th>Death Rate (%)</th>
<th>Ventilation Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCQ</td>
<td>97</td>
<td>27.8</td>
<td>13.3</td>
</tr>
<tr>
<td>HCQ + AZ</td>
<td>113</td>
<td>22.1</td>
<td>6.9</td>
</tr>
<tr>
<td>No HCQ</td>
<td>158</td>
<td>11.4</td>
<td>14.1</td>
</tr>
</tbody>
</table>

Figure 1. Daily temperature variations of patients in the two groups during 10-day hospitalization period.

Steroids: Conflicting Recommendations

SURVIVING SEPSIS CAMPAIGN

• Recommendation 22:
  - For adults with COVID-19 and refractory shock, we suggest using low-dose corticosteroid therapy over no corticoid therapy

• Recommendation 41:
  - In mechanically ventilated patients with COVID-19 and respiratory failure (without ARDS), we suggest against the routine use of systemic corticosteroids

• Recommendation 42:
  - In mechanically vented patients with COVID-19 and ARDS we suggest using systemic corticosteroids, over not using corticosteroids

INFECTIONIOUS DISEASE SOCIETY

• Recommendation 4:
  - Among patients who have been admitted to the hospital with COVID-19 pneumonia, the IDSA guideline panel suggests against the use of corticosteroids

• Recommendation 5:
  - Among patients who have been admitted to the hospital with ARDS due to COVID-19, the IDSA guideline panel recommends the use of corticosteroids in the context of a clinical trial (Knowledge gap)

• Ribavirin-treated patients who received early hydrocortisone therapy vs those who received placebo (n = 16 non-ICU)
• Plasma SARS-CoV RNA concentrations in the 2\textsuperscript{nd}/3\textsuperscript{rd} week of illness were significantly higher in patients who received tx
• Pts tx with early steroid were less likely to deteriorate clinically
• Review: 401/1,278 SARS cases treated in Guangzhou China
• Use of corticosteroid in confirmed critical SARS resulted in lowered mortality and shorter hospitalization stay, and was not associated with significant secondary lower respiratory infection and other complications

2006: Treatment of Severe Acute Respiratory Syndrome With Glucocorticoids
(Correlative study)

• Non-severe disease, steroid use was generally non-beneficial. Use of >160 mg/day methylprednisone correlated with increased risk of death
• More severe disease, steroid correlated with improved survival (even at relatively high doses and extended courses)

2016: Clinical recommendations from an observational study on MERS: glucocorticoids was benefit in treating SARS patients

Corticosteroid Therapy for Critically ill Patients with the Middle East Respiratory Syndrome

- Analyzed data from a multicenter, retrospective cohort study from 14 participating Saudi Arabian tertiary care hospitals
- Hydrocortisone was the most frequently administered corticosteroid followed by methylprednisolone
- The use of corticosteroid therapy was not associated 90-day mortality but was associated with delayed MERS-CoV RNA clearance

Low-dose corticosteroid therapy does not delay viral clearance in patients with COVID-19

- 25/78 received corticosteroids, divided into general/severe
  - General (9): Oral methylprednisolone hydrocortisone-equivalent dose, 237.5 mg/day x 9 days
  - Severe (16): IV methylprednisolone hydrocortisone-equivalent dose, 250.0 mg/day x 4.5 days
- RT-PCR to assess viral clearance: No significant difference identified in both general group + severe group vs no steroid


Application of Corticosteroid Treatment in Patients with Severe COVID-19 Pneumonia

- 46 hospitalized patients with severe COVID-19 pneumonia hospitalized at Wuhan Union Hospital from January 20 to February 25, 2020, were retrospectively reviewed.
  - The patients were divided into two groups based on whether they received corticosteroid treatment.

- 26 patients received IV administration of methylprednisolone with a dosage of 1-2mg/kg/d for 5-7 days, while the remaining patients did not.

- The average number of days for body temperature back to the normal range was significantly shorter in patients with administration of methylprednisolone.

- Methylprednisolone group had a faster improvement of SpO2, while patients without administration had a significantly longer interval of using supplemental oxygen therapy.

Early, Low-Dose and Short-Term Application of Corticosteroid Treatment in Patients with Severe COVID-19 Pneumonia

Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China

- Retrospective cohort study of 201 patients with confirmed COVID-19 pneumonia admitted to Wuhan Jinyintan Hospital in China
  - Methylprednisolone was given to 62 (30.8%) patients

- Patients who developed ARDS were more likely to be treated with methylprednisolone

- A higher proportion of patients who received methylprednisolone were classified into a higher grade on the Pneumonia Severity Index

Steroids: Optimal Treatment Window

Early intervention (e.g., triggered by desaturation):
- Awake proning or CPAP (keep lungs open)
- Judicious fluid administration & stop nephrotoxins
- Heparin administration to prevent thrombosis
- Low dose steroid to prevent hyper-inflammation?
- Avoid intubation & multi-organ failure

Delayed salvage therapy:
- Intubation required
- Hemodialysis may be needed
- tPA may be needed to lyse clot
- Low dose steroid less effective at this point (?? need for tocilizumab or higher doses of steroid)
- Worse long-term functional outcomes
Viral Load predicts severity
D-dimer levels on admission to predict in-hospital mortality in patients with COVID-19

- Laboratory confirmed Covid-19 were retrospectively enrolled in Wuhan Asia General Hospital from January 12, 2020 to March 15, 2020
  - A total of 343 eligible patients were enrolled in the study
  - D-dimer levels on admission, and death events were collected

- The optimum cutoff value of D-dimer to predict in-hospital mortality was 2.0 µg/ml with a sensitivity of 92.3% and a specificity of 83.3%

- Patients with D-dimer levels ≥2.0 µg/ml had a higher incidence of mortality when comparing to those who with D-dimer levels < 2.0 µg/ml (P < 0.001)

Virchow’s Triad

Hypercoagulability:
- High fibrinogen
- High D-dimer

Vessel wall injury:
- ARDS

Venous stasis:
- Immobile/paralyzed
Anticoagulation

- D-Dimer < 3,000 and not high ARITA score
  - CrCl ≥ 30 mL/min: Enoxaparin 40mg SQ Q12H
  - CrCl < 30 mL/min: Heparin 7,500 units SQ Q8H

- D-Dimer ≥ 3,000 and not high ARITA score
  - CrCl ≥ 30 mL/min: Enoxaparin 1mg/kg Q12H
  - CrCl < 30 mL/min: High dose IV heparin protocol

- High risk ATRIA score and/or fibrinogen ≤ 100, platelets ≤ 50,000, INR ≥ 1.5 (Regardless of D-Dimer)
  - CrCl ≥ 30 mL/min: Enoxaparin 40mg SQ daily
  - CrCl < 30 mL/min: Heparin 5,000 units SQ Q8H

- De-escalate patients being transferred from ICU to floor
  - CrCl ≥ 30 mL/min: Enoxaparin 40mg SQ daily
  - CrCl < 30 mL/min: Heparin 5,000 units SQ Q8H

<table>
<thead>
<tr>
<th>Day</th>
<th>PLTS</th>
<th>INR</th>
<th>D-Dimer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>166</td>
<td>1.6</td>
<td>792</td>
</tr>
<tr>
<td>2</td>
<td>146</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>139</td>
<td>1.5</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>145</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>149</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>175</td>
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<td>7</td>
<td>202</td>
<td>-</td>
<td>15,919</td>
</tr>
<tr>
<td>8</td>
<td>224</td>
<td>1.4</td>
<td>23,560</td>
</tr>
</tbody>
</table>
Anticoagulation: Guideline Recommendations

- **Journal of Thrombosis and Haemostasis:**
  - Recommend: Measure D-dimers, prothrombin time and platelet count (decreasing order of importance) in all patients
  - If there is worsening, more aggressive support and consideration for more ‘experimental’ therapies

- **American College of Cardiology:**
  - Consider prophylactic anticoagulation, although a minority consider intermediate-dose or therapeutic dose to be reasonable
  - It is reasonable to employ individualized risk stratification for thrombotic and hemorrhagic risk, followed by consideration of extended prophylaxis (for up to 45 days) for patients with elevated risk of VTE

- **American Society of Hematology:**
  - Whether critically ill should receive therapeutic-intensity anticoagulation in the absence of confirmed or suspected VTE is currently unknown
  - It is reasonable to consider extended thromboprophylaxis after discharge using a regulatory-approved regimen


Accompanying Bacterial Infection

**Stats:**
- Co-infection = 3.5%
- Secondary infection = 14.3%
- >70% received antibiotics (empiric, varied)

**Surviving Sepsis Campaign**
- Recommendation: In mechanically ventilated patients with COVID-19 and respiratory failure, we suggest using empiric antimicrobials/antibacterial agents, over no antimicrobials. *(Weak recommendation, low-quality evidence)*

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients % Infected</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arezi M, 2020</td>
<td>21</td>
<td>4.8 [0.1; 23.8]</td>
</tr>
<tr>
<td>Barrasa H, 2020</td>
<td>48</td>
<td>12.5 [4.7; 25.2]</td>
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<tr>
<td>Bhatnaj P, 2020</td>
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<tr>
<td>Chen N, 2020</td>
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<td>1.0 [0.0; 5.5]</td>
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<tr>
<td>Chen T, 2020</td>
<td>203</td>
<td>1.0 [0.1; 3.5]</td>
</tr>
<tr>
<td>Liu W, 2020</td>
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</tr>
<tr>
<td>Liu Y, 2020</td>
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<td>16.7 [2.1; 48.4]</td>
</tr>
<tr>
<td>Mo P, 2020</td>
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<tr>
<td>Pongpirul W, 2020</td>
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<tr>
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<td>0.0 [0.0; 4.9]</td>
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<td>Xia W, 2020</td>
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<td>Young B, 2020</td>
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<tr>
<td>Zheng F, 2020</td>
<td>25</td>
<td>16.0 [4.5; 36.1]</td>
</tr>
</tbody>
</table>

Percent with Bacterial Infection: 3.5 [0.4; 6.7]

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients % Infected</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cai Q, 2020</td>
<td>298</td>
<td>10.1 [6.9; 14.1]</td>
</tr>
<tr>
<td>Feng Y, 2020</td>
<td>410</td>
<td>8.5 [6.0; 11.7]</td>
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<tr>
<td>Lin J, 2020</td>
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<tr>
<td>Ling L, 2020</td>
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<td>25.0 [3.2; 65.1]</td>
</tr>
<tr>
<td>Wang L, 2020</td>
<td>339</td>
<td>42.2 [36.9; 47.6]</td>
</tr>
<tr>
<td>Yang X, 2020</td>
<td>52</td>
<td>13.5 [5.6; 25.8]</td>
</tr>
<tr>
<td>Zhou F, 2020</td>
<td>191</td>
<td>14.7 [10.0; 20.5]</td>
</tr>
</tbody>
</table>

Percent with Bacterial Infection: 14.3 [9.6; 18.9]


Whole inactivated

The impending Flu season…

- To reduce the pressure, drugmakers including AstraZeneca PLC, GlaxoSmithKline PLC and Sanofi SA are making about 200 million flu shots this year for shipment to doctors, hospitals and pharmacies, up 13% from last year and a record, according to the U.S. Centers for Disease Control and Prevention.