Division of Pulmonary, Allergy, and Critical Care

Treatment of COVID-19: Antivirals

Laura Ferguson, MD, MS

April 02, 2020
Outline

- Brief virology background, *in vitro* data

- **Specific anti-viral agents**
  - Hydroxychloroquine
  - Remdesivir
  - Favipiravir
  - Lopinavir/Ritonavir

- Additional therapies

- Current Penn guidance (4-2-2020)
SARS and MERS: recent insights into emerging coronaviruses

Emmie de Wit, Neeltje van Doremalen, Darryl Falzarano & Vincent J. Munster

*Nature Reviews Microbiology* 14, 523–534 (2016) | Cite this article

- Replication schematic from 2016 based on Sars-CoV-1 and MERS
- Sars-CoV-2 receptor: ACE2
- Note potential therapeutic targets
  - Entry
  - Endosomal acidification/release
  - Replication
  - Assembly
  - Release
- Investigational drugs:
  - Chloroquine/Hydroxychloroquine
  - Lopinavir/Ritonavir
  - Favipiravir
  - Remdesivir
  - Interferon

Wit et al., Nature Reviews Microbiology, 2016
Many other drug targets mentioned in this paper- great additional reading for those interested

Targeted viral components:
- Envelope, spike glycoprotein, enzymes, nucleic acids

Targeted host factors:
- Innate immune response (interferon), signaling pathways in viral replication, receptors for viral entry, proteases, and endocytosis pathways
In vitro data using Vero E6 cell line
Cytotoxicity to cells,
Viral copy number (RT-PCR), immunofluorescence of viral protein
- Remdesivir, Chloroquine, Ribavirin, Nitaxanide, Penciclovir, Favipivir, Nafamostat
- Two had high selectivity index and low cytotoxicity
Hydroxychloroquine (Chloroquine)

- Raises pH of endosome, preventing viral membrane from merging with endosome
- In vitro data (Wang, et al and Liu, et al)
- Small RCT from China (Chen et al., MedRxiv preprint)
  - N=62, all mild
  - Standard: O2, “antivirals”, “antibacterials”, IVIG +/- steroids
  - Intervention: standard + HCQ 200mg BID from days 1-5
  - CT day 1 to 5, fever, cough, progression, “adverse effects” →
  - HCQ patients sicker?, small numbers, unclear timing
- Non-randomized study from France (Gautret et al)
  - N=14 for HCQ, 6 for HCQ+Azithro
  - N=16 controls from outside institution
  - Looked at % pts with (+) PCR →
- Expert concensus in China:
  - HCQ for all patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All</th>
<th>Control</th>
<th>HCQ</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases, n</td>
<td>62</td>
<td>31</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>44.7 (15.3)</td>
<td>45.2 (14.7)</td>
<td>44.1 (16.1)</td>
<td>0.8809</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29 (46.8%)</td>
<td>15 (48.3%)</td>
<td>14 (45.2%)</td>
<td>0.7991</td>
</tr>
<tr>
<td>Female</td>
<td>33 (53.2%)</td>
<td>16 (51.7%)</td>
<td>17 (54.9%)</td>
<td></td>
</tr>
<tr>
<td>Fever, day (SD)</td>
<td>2.6 (1.0)</td>
<td>3.2 (1.3)</td>
<td>2.2 (0.4)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Cough, day (SD)</td>
<td>2.4 (1.1)</td>
<td>3.1 (1.5)</td>
<td>2.0 (0.2)</td>
<td>0.0016</td>
</tr>
</tbody>
</table>

Progressed to severe illness
- 4 (6.5%) vs 4 (12.9%) vs 0
- 2 (3.2%) vs 0 vs 2 (6.4%)
Remdesivir

- **Adenosine analogue:** incorporated into viral RNA
  - prevents synthesis, halts viral replication
  - Intravenous
- **Activity *in vitro* against Ebola, SARS, MERS**
  - *In vitro* activity against Sars-cov-2 (Wang et al)
  - Failed *in vivo* studies for Ebola
- **First US case in Washington – compassionate use, recovered**
- **Now compassionate use is limited due to demand**
- **RCT’s underway and actively recruiting:**
  - ACTT trial (NIAID): Remdesivir (5 days) v placebo, n=440, outcome: reported severity on 8-point scale
  - Severe COVID-19 (Gilead): inpatients with sat <94% but not vented
    - standard care v 5 D v 10 D, composite outcome fever + O2 sat
  - Severe COVID-19 (Beijing, recruiting)
  - Mild/Mod COVID-19 (WuHan, recruiting)
Favipiravir

- RNA polymerase inhibitor; activity in vitro against myriad RNA viruses:
  - In vitro activity against Sars-cov-2 (Wang et al)
  - Open label non-randomized in China, n=35 versus 45 historical controls
  - Intervention: Favipiravir + inh IFNa; Control: Lopinavir/Ritonavir + inh IFNa
  - Primary outcome – median time to viral clearance was 5 days faster
- Favipiravir v Arbidol (Chen et al, medRx preprint)
  - Randomized, open label, superiority trial (?details)
  - N=240 (120 per group), unclear patient severity
  - Outcome: clinical recovery at day 7 (cough, fever, O2 needs): 71% v 56% recovered (cough, fever)
- RCTs underway
  - Favipiravir + Tocilizumab (China) and Favipiravir + HCQ (China)
  - Protease inhibitors/ Ostamivir/ Favipiravir/ HCQ (Thailand)
Lopinavir/Ritonavir (Kaletra)

- Lopinavir: HIV protease inhibitor, boosted by Ritonavir cyp450 interaction
- Cao et al, NEJM, 2020
  - RCT, open label
  - PNA on imaging, sat<94% or p:f<300, enrolled ~ day 13 after sympt onset
  - Given 14 days of treatment (400/100 BID) vs no treatment (no placebo pill)
- Primary outcome: clinical improvement
  - discharge or 2 point improvement in 7-point scale
- Randomization stratified by O2 need and by NEWS2 score
  - Cutoff of 5
- Randomization stratified by time from onset of symptoms
  - 12 Days

1. Outpatient, normal activities
2. Outpatient, some impairment
3. Inpatient, RA
4. Inpatient, on O2
5. Inpatient, NIV or HFNC
6. Inpatient, mech vent or ECMO
7. Death
Modified intention to treat analysis excluded the 3 patients in treatment group who died before treatment.

Original sample size calculated to be 160.
A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19

Bin Cao, M.D., Yeming Wang, M.D., Danning Wen, M.D., Wen Liu, M.S., Jingli Wang, M.D., Guohui Fan, M.S., Lianguo Ruan, M.D., Bin Song, M.D., Yanping Cai, M.D., Ming Wei, M.D., Xingwang Li, M.D., Jiaan Xia, M.D., et al.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.\(^a\)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 199)</th>
<th>Lopinavir–Ritonavir (N = 99)</th>
<th>Standard Care (N = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR) — yr</td>
<td>58.0 (49.0–68.0)</td>
<td>58.0 (50.0–68.0)</td>
<td>58.0 (48.0–68.0)</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>120 (60.3)</td>
<td>61 (61.6)</td>
<td>59 (59.0)</td>
</tr>
<tr>
<td>Coexisting conditions — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>23 (11.6)</td>
<td>10 (10.1)</td>
<td>13 (13.0)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>33 (6.5)</td>
<td>5 (5.1)</td>
<td>8 (8.0)</td>
</tr>
<tr>
<td>Cancer</td>
<td>6 (3.0)</td>
<td>5 (5.1)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Body temperature, median (IQR) — °C</td>
<td>36.5 (36.4–36.8)</td>
<td>36.5 (36.4–37.0)</td>
<td>36.5 (36.5–36.8)</td>
</tr>
<tr>
<td>Fever — no. (%)</td>
<td>182 (91.5)</td>
<td>89 (89.9)</td>
<td>93 (93.0)</td>
</tr>
<tr>
<td>Respiratory rate ≥24/min — no. (%)</td>
<td>37 (18.8)</td>
<td>21 (21.6)</td>
<td>16 (16.0)</td>
</tr>
<tr>
<td>Systolic blood pressure &lt;90 mm Hg — no. (%)</td>
<td>2 (1.0)</td>
<td>2 (2.0)</td>
<td>0</td>
</tr>
<tr>
<td>White-cell count (&lt;10^9/liter) — median (IQR)</td>
<td>7.0 (5.1–9.4)</td>
<td>7.3 (5.3–9.6)</td>
<td>6.9 (4.9–9.1)</td>
</tr>
<tr>
<td>&lt;4 ×10^9/liter (median) — no. (%)</td>
<td>137 (70.3)</td>
<td>64 (67.4)</td>
<td>73 (73.0)</td>
</tr>
<tr>
<td>&gt;4 ×10^9/liter (median) — no. (%)</td>
<td>20 (10.3)</td>
<td>12 (12.6)</td>
<td>8 (8.0)</td>
</tr>
<tr>
<td>&lt;6 ×10^9/liter (median) — no. (%)</td>
<td>38 (19.5)</td>
<td>19 (20.0)</td>
<td>19 (19.0)</td>
</tr>
<tr>
<td>Lymphocyte count (&lt;10^9/liter) — median (IQR)</td>
<td>0.9 (0.6–1.2)</td>
<td>0.8 (0.6–1.4)</td>
<td>0.9 (0.5–1.2)</td>
</tr>
<tr>
<td>≥10 ×10^9/liter (median) — no. (%)</td>
<td>73 (37.4)</td>
<td>37 (38.9)</td>
<td>36 (36.0)</td>
</tr>
<tr>
<td>&lt;1.0 ×10^9/liter (median) — no. (%)</td>
<td>122 (62.6)</td>
<td>58 (61.1)</td>
<td>64 (64.0)</td>
</tr>
<tr>
<td>Platelet count (&lt;10^9/liter) — median (IQR)</td>
<td>207.0 (158.0–284.0)</td>
<td>201.0 (155.0–287.0)</td>
<td>210.0 (163.0–269.5)</td>
</tr>
<tr>
<td>≥100 ×10^9/liter (median) — no. (%)</td>
<td>186 (95.4)</td>
<td>91 (95.8)</td>
<td>95 (95.0)</td>
</tr>
<tr>
<td>&lt;100 ×10^9/liter (median) — no. (%)</td>
<td>9 (4.6)</td>
<td>4 (4.2)</td>
<td>5 (5.0)</td>
</tr>
</tbody>
</table>

Serum creatinine (µmol/liter) — median (IQR) 69.5 (57.2–82.5) 70.7 (56.4–82.7) 67.4 (58.4–82.5)
<133 µmol/liter — no. (%) 189 (96.9) 93 (96.9) 96 (97.0)
≥133 µmol/liter — no. (%) 6 (3.1) 3 (3.1) 3 (3.0)
Aspartate aminotransferase (U/liter) — median (IQR) 34.0 (26.0–45.0) 33.0 (25.0–42.0) 34.0 (27.0–45.0)
<40 U/liter — no. (%) 155 (79.5) 78 (81.3) 77 (77.8)
≥40 U/liter — no. (%) 40 (20.5) 18 (18.8) 22 (22.2)
Alanine aminotransferase (U/liter) — median (IQR) 33.0 (22.0–55.0) 33.0 (22.0–53.5) 34.0 (22.0–59.0)
≤50 U/liter — no. (%) 115 (59.0) 61 (63.5) 54 (54.5)
>50 U/liter — no. (%) 80 (41.0) 35 (36.5) 45 (45.5)
Lactate dehydrogenase (U/liter) — median (IQR) 325.0 (245.0–433.0) 322.0 (243.0–409.0) 327.0 (245.0–470.0)
≤245 U/liter — no. (%) 50 (25.8) 24 (25.3) 26 (26.3)
≥245 U/liter — no. (%) 144 (74.2) 71 (74.7) 73 (73.7)
Creatine kinase (U/liter) — median (IQR) 69.0 (44.0–115.0) 57.0 (42.0–126.0) 72.0 (45.0–110.0)
≤185 U/liter — no. (%) 168 (86.6) 81 (85.3) 87 (87.9)
> 185 U/liter — no. (%) 26 (13.4) 14 (14.7) 12 (12.1)
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 199)</th>
<th>Lopinavir-Ritonavir (N = 99)</th>
<th>Standard Care (N = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEWS2 score at day 1 — median (IQR)</td>
<td>5.0 (4.0–6.0)</td>
<td>5.0 (4.0–6.0)</td>
<td>5.0 (4.0–7.0)</td>
</tr>
<tr>
<td>Seven-category scale at day 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3: Hospitalization, not requiring supplemental oxygen — no. (%)</td>
<td>28 (14.1)</td>
<td>11 (11.1)</td>
<td>17 (17.0)</td>
</tr>
<tr>
<td>4: Hospitalization, requiring supplemental oxygen — no. (%)</td>
<td>139 (69.8)</td>
<td>72 (72.7)</td>
<td>67 (67.0)</td>
</tr>
<tr>
<td>5: Hospitalization, requiring HFNC or noninvasive mechanical ventilation — no. (%)</td>
<td>31 (15.6)</td>
<td>15 (15.2)</td>
<td>16 (16.0)</td>
</tr>
<tr>
<td>6: Hospitalization, requiring ECMO, invasive mechanical ventilation, or both — no. (%)</td>
<td>1 (0.5)</td>
<td>1 (1.0)</td>
<td>0</td>
</tr>
<tr>
<td>Days from illness onset to randomization — median (IQR)</td>
<td>13 (11–16)</td>
<td>13 (11–17)</td>
<td>13 (10–16)</td>
</tr>
<tr>
<td>Earlier (&lt;12 days of symptom onset) — no. (%)</td>
<td>90 (45.2)</td>
<td>42 (42.4)</td>
<td>48 (48.0)</td>
</tr>
<tr>
<td>Later (&gt;12 days of symptom onset) — no. (%)</td>
<td>109 (54.8)</td>
<td>57 (57.6)</td>
<td>52 (52.0)</td>
</tr>
<tr>
<td>Mean viral load — log_{10} copies per ml at day 1</td>
<td>4.0±2.1</td>
<td>4.4±2.0</td>
<td>3.7±2.1</td>
</tr>
<tr>
<td>Using interferon at enrollment — no. (%)</td>
<td>22 (11.1)</td>
<td>9 (9.1)</td>
<td>13 (13.0)</td>
</tr>
<tr>
<td>Treatments during study period — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasopressors</td>
<td>44 (22.1)</td>
<td>17 (17.2)</td>
<td>27 (27.0)</td>
</tr>
<tr>
<td>Renal-replacement therapy</td>
<td>9 (4.5)</td>
<td>3 (3.0)</td>
<td>6 (6.0)</td>
</tr>
<tr>
<td>Noninvasive mechanical ventilation</td>
<td>29 (14.6)</td>
<td>10 (10.1)</td>
<td>19 (19.0)</td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>32 (16.1)</td>
<td>14 (14.1)</td>
<td>18 (18.0)</td>
</tr>
<tr>
<td>ECMO</td>
<td>4 (2.0)</td>
<td>2 (2.0)</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>Antibiotic agent</td>
<td>189 (95.0)</td>
<td>94 (94.9)</td>
<td>95 (95.0)</td>
</tr>
<tr>
<td>Glucocorticoid therapy</td>
<td>67 (33.7)</td>
<td>32 (32.3)</td>
<td>35 (35.0)</td>
</tr>
<tr>
<td>Days from illness onset to glucocorticoid therapy — median (IQR)</td>
<td>13 (11–17)</td>
<td>13 (12–19)</td>
<td>13 (9–17)</td>
</tr>
<tr>
<td>Days of glucocorticoid therapy — median (IQR)</td>
<td>6 (3–11)</td>
<td>7 (3–11)</td>
<td>6 (2–12)</td>
</tr>
</tbody>
</table>
**Table 3. Outcomes in the Intention-to-Treat Population.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 199)</th>
<th>Lopinavir-Ritonavir (N = 99)</th>
<th>Standard Care (N = 100)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to clinical improvement — median no. of days (IQR)</td>
<td>16.0 (13.0 to 17.0)</td>
<td>16.0 (13.0 to 17.0)</td>
<td>16.0 (13.0 to 18.0)</td>
<td>1.31 (0.95 to 1.80)</td>
</tr>
<tr>
<td>Day 28 mortality — no. (%)</td>
<td>44 (22.1)</td>
<td>19 (19.2)</td>
<td>25 (25.0)</td>
<td>-5.8 (-17.3 to 5.7)</td>
</tr>
<tr>
<td>Earlier (≤32 days after onset of symptoms)</td>
<td>21 (23.3)</td>
<td>8 (16.1)</td>
<td>13 (27.1)</td>
<td>-8.0 (-25.3 to 9.3)</td>
</tr>
<tr>
<td>Later (&gt;12 days after onset of symptoms)</td>
<td>23 (21.1)</td>
<td>11 (19.3)</td>
<td>12 (21.1)</td>
<td>-3.8 (-19.1 to 11.6)</td>
</tr>
<tr>
<td>Clinical improvement — no. (%)</td>
<td>8 (4.0)</td>
<td>6 (6.1)</td>
<td>2 (2.0)</td>
<td>4.1 (-1.4 to 9.5)</td>
</tr>
<tr>
<td>Day 14</td>
<td>75 (37.7)</td>
<td>45 (45.5)</td>
<td>30 (10.9)</td>
<td>15.5 (2.2 to 28.8)</td>
</tr>
<tr>
<td>Day 28</td>
<td>148 (74.4)</td>
<td>78 (78.8)</td>
<td>70 (70.0)</td>
<td>8.8 (-3.3 to 20.9)</td>
</tr>
<tr>
<td>ICU length of stay — median no. of days (IQR)</td>
<td>10 (5 to 14)</td>
<td>6 (2 to 11)</td>
<td>11 (7 to 17)</td>
<td>-5 (-9 to 0)</td>
</tr>
<tr>
<td>Of survivors</td>
<td>10 (8 to 17)</td>
<td>9 (5 to 44)</td>
<td>11 (9 to 14)</td>
<td>-1 (-16 to 18)</td>
</tr>
<tr>
<td>Of nonsurvivors</td>
<td>10 (4 to 14)</td>
<td>6 (2 to 11)</td>
<td>12 (7 to 17)</td>
<td>-6 (-11 to 0)</td>
</tr>
<tr>
<td>Duration of invasive mechanical ventilation — median no. of days (IQR)</td>
<td>5 (3 to 9)</td>
<td>4 (3 to 7)</td>
<td>5 (3 to 9)</td>
<td>-1 (-4 to 2)</td>
</tr>
<tr>
<td>Oxygen support — days (IQR)</td>
<td>13 (8 to 16)</td>
<td>12 (9 to 16)</td>
<td>13 (6 to 16)</td>
<td>0 (-2 to 2)</td>
</tr>
<tr>
<td>Hospital stay — median no. of days (IQR)</td>
<td>15 (12 to 17)</td>
<td>14 (12 to 17)</td>
<td>16 (13 to 18)</td>
<td>1 (0 to 6)</td>
</tr>
<tr>
<td>Time from randomization to discharge — median no. of days (IQR)</td>
<td>13 (10 to 16)</td>
<td>12 (10 to 16)</td>
<td>14 (11 to 16)</td>
<td>1 (0 to 3)</td>
</tr>
<tr>
<td>Time from randomization to death — median no. of days (IQR)</td>
<td>10 (6 to 15)</td>
<td>9 (6 to 13)</td>
<td>12 (6 to 15)</td>
<td>-3 (-6 to 2)</td>
</tr>
</tbody>
</table>

**Score on seven-category scale at day 7 — no. of patients (%)**

<table>
<thead>
<tr>
<th>No.</th>
<th>Score on seven-category scale at day 7 — no. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Not hospitalized, but unable to resume normal activities</td>
</tr>
<tr>
<td>2</td>
<td>Hospitalization, not requiring supplemental oxygen</td>
</tr>
<tr>
<td>3</td>
<td>Hospitalization, requiring supplemental oxygen</td>
</tr>
<tr>
<td>4</td>
<td>Hospitalization, requiring supplemental oxygen</td>
</tr>
<tr>
<td>5</td>
<td>Hospitalization, requiring HIFNC or noninvasive mechanical ventilation</td>
</tr>
<tr>
<td>6</td>
<td>Hospitalization, requiring ECMO, invasive mechanical ventilation, or both</td>
</tr>
<tr>
<td>7</td>
<td>Death</td>
</tr>
</tbody>
</table>

**However:**

- Trend toward lower mortality
- Reduced ICU length of stay
- In the Modified intention to treat group (leaving out 3 initial deaths), there was a significant 1 day reduction in median time to improvement (15D versus 16D)
<table>
<thead>
<tr>
<th>Event</th>
<th>Lopinavir–Ritonavir (N=95)</th>
<th>Standard Care (N=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td></td>
<td>number</td>
<td>percent</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>46 (48.4)</td>
<td>20 (21.1)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>16 (16.8)</td>
<td>12 (12.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (9.5)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6 (6.3)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>7 (7.4)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (6.3)</td>
<td>0</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>2 (2.1)</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>4 (4.2)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (4.2)</td>
<td>0</td>
</tr>
<tr>
<td>Stomach ache</td>
<td>4 (4.2)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4 (4.2)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Increased total bilirubin</td>
<td>3 (3.2)</td>
<td>3 (3.2)</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>2 (2.1)</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (2.1)</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (2.1)</td>
<td>0</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>1 (1.1)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>1 (1.1)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Increased creatinine kinase</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>2 (2.1)</td>
<td>0</td>
</tr>
<tr>
<td>Prolonged QT interval</td>
<td>1 (1.1)</td>
<td>0</td>
</tr>
<tr>
<td>Sleep disorders and disturbances</td>
<td>1 (1.1)</td>
<td>0</td>
</tr>
<tr>
<td>Facial flushing</td>
<td>1 (1.1)</td>
<td>0</td>
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</table>

<table>
<thead>
<tr>
<th>Serious adverse event</th>
<th>Any Grade</th>
<th>Grade 3 or 4</th>
<th>Any Grade</th>
<th>Grade 3 or 4</th>
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<tbody>
<tr>
<td>Respiratory failure or ARDS</td>
<td>12 (12.6)</td>
<td>12 (12.6)</td>
<td>27 (27.3)</td>
<td>27 (27.3)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>3 (3.2)</td>
<td>2 (2.1)</td>
<td>6 (6.1)</td>
<td>5 (5.1)</td>
</tr>
<tr>
<td>Secondary infection</td>
<td>1 (1.1)</td>
<td>1 (1.1)</td>
<td>6 (6.1)</td>
<td>6 (6.1)</td>
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<tr>
<td>Shock</td>
<td>2 (2.1)</td>
<td>2 (2.1)</td>
<td>2 (2.0)</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>Severe anemia</td>
<td>3 (3.2)</td>
<td>3 (3.2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Acute gastritis</td>
<td>2 (2.1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hemorrhage of lower digestive tract</td>
<td>2 (2.1)</td>
<td>1 (1.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>0</td>
<td>0</td>
<td>2 (2.0)</td>
<td>2 (2.0)</td>
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<tr>
<td>Unconsciousness</td>
<td>1 (1.1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
<td>1 (1.1)</td>
<td>0</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0</td>
<td>0</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Acute heart failure</td>
<td>0</td>
<td>0</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
</tr>
</tbody>
</table>
Other points:
- Open label
- Late enrollment
- Likely underpowered (large confidence intervals)
- Sub group started treatment before day 12 → trend toward faster improvement
- Fewer ICU days (6 v 11)
- Mortality trend
- Perhaps “serious adverse events” of respiratory failure/ARDS are actually the better outcomes to look at in subsequent trial
- GI side effects

“negative trial” but wouldn’t rule out additional investigation of Lopinavir/Ritonavir
**HCQ**

- **Lopinavir**

- **Ribavirin**
- **Galidesivir**

**Remdesivir, Favipiravir**

**Additional experimental treatments not covered here:**
- Azithromycin
- IL6 inhibitors
- Convalescent Plasma

**Additional “anti-viral” treatments in progress:**
- **Baricitinib** – JAK inhibitor, inhibits ACE2-mediated endocytosis
- **Meplazumab** – anti-CD147 mAb that competes with S protein – MedRxiv preprint

Anti-virals discussed in detail
An Infectious Diseases consultation is recommended for patients admitted to the hospital with SARS-CoV-2 (COVID-19) infection. All therapies below require approval by an Infectious Diseases physician, but a one-time STAT dose may be given in situations pending infectious diseases evaluation.

The dose of hydroxychloroquine should be 400 mg Q12H for 1 day followed by 400 mg daily for 4 more days for a total duration of 5 days.

Remdesivir can now be considered for treatment of SARS-CoV-2 in pregnancy [the only current compassionate use indication]

Despite reports of efficacy of azithromycin plus hydroxychloroquine to treat SARS-CoV-2, azithromycin should not be added to hydroxychloroquine only to treat SARS-CoV-2.

Clinical Trials at Penn:

Remdesivir:
- NIH: drug v placebo trial ongoing
  - BillShort, Pablow Tebas
  - 14 participants thus far
- Gilead: two trials ongoing
  - Kathleen Degnan, Ian Frank

Hydroxychloroquine:
- Two trials still in planning stages
  - Ravi Amaravadi
  - high v low dose
  - drug v placebo for patients at home
- Wit et al., Nature Reviews Microbiology, 2016 (SARS, MERS)
- Zumla et al., Nature Reviews Drug Discovery, 2016 (SARS, MERS)
- Yang and Wang, Nature Cellular & Molecular Immunology, 2020 (COVID-19)
- Liu et al., Nature Cell Discovery, 2020 (Chloroquine vs Hydroxychloroquine in vitro)
- Wang et al., Nature Cell Research, 2020 (Chloroquine and Remdesivir in vitro)
- McChesney, The American J of Medicine, 1983 (Hydroxychloroquine v Chloroquine)
- Chen et al., MedRxiv preprint, 2020 (Hydroxychloroquine n=62 RCT from China)
- Gautret et al., Int J Antimicrobial Agents, in press, 2020 (HCQ, Azithro from France)
- Cai et al, Engineering, 2020 (WITHDRAWN; Favipiravir)
- Chen et al, medRxiv preprint, 2020 (Favipiravir v Aribdol)
- Cao et al, NEJM, 2020 (RCT Lopinavir/Ritonavir)
ARDS Management with COVID-19

Meeta Prasad Kerlin, MD MSCE
Pulmonary, Allergy and Critical Care Division

April 2, 2020
Objectives

- Review clinical features of ARDS with COVID-19
- Discuss ventilator management strategies
- Discuss adjunctive therapies for ARDS management
- Introduce helmet ventilation (Maurizio Cereda)
- Highlight UPHS strategies to support best practices

- I am NOT going to review
  - Algorithm to escalate respiratory support
  - Best practices for intubation
Disclaimers and acknowledgements

- This talk is meant to be a pragmatic guide
  - But there are a lot of unknowns….

- Recommendations formulated with input from many local experts
  - Nuala Meyer
  - Nilam Mangalmurti
  - John Reilly
  - Barry Fuchs
  - Maurizio Cereda
Clinical features of ARDS with COVID-19

‣ Severe hypoxia
‣ Diffuse ground-glass opacities
‣ Initial high lung compliance?
‣ Prolonged course of respiratory failure

‣ Early Seattle experience (n=18)
  • Median duration of MV 10 days (11 days among survivors)
  • Median ICU stay 14 days

<table>
<thead>
<tr>
<th>Characteristics of mechanical ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate or thick and purulent secretions — no./total no. (%)†</td>
</tr>
<tr>
<td>Day 1 median values</td>
</tr>
<tr>
<td>Plateau pressure (IQR) — cm of water‡</td>
</tr>
<tr>
<td>Driving pressure (IQR) — cm of water‡</td>
</tr>
<tr>
<td>Highest FiO₂ — median (IQR)</td>
</tr>
<tr>
<td>Compliance (IQR) — ml/cm of water¶</td>
</tr>
<tr>
<td>Day 2 median values</td>
</tr>
<tr>
<td>Plateau pressure (IQR) — cm of water‡</td>
</tr>
<tr>
<td>Driving pressure (IQR) — cm of water‡</td>
</tr>
<tr>
<td>Highest FiO₂ — median (IQR)</td>
</tr>
<tr>
<td>Compliance (IQR) — ml/cm of water¶</td>
</tr>
<tr>
<td>Day 3 median values</td>
</tr>
<tr>
<td>Plateau pressure (IQR) — cm of water‡</td>
</tr>
<tr>
<td>Driving pressure (IQR) — cm of water‡</td>
</tr>
<tr>
<td>Highest FiO₂ (IQR) — median (IQR)</td>
</tr>
<tr>
<td>Compliance (IQR) — ml/cm of water¶</td>
</tr>
</tbody>
</table>


This official clinical practice guideline of the American Thoracic Society (ATS), European Society of Intensive Care Medicine (ESICM), and Society of Critical Care Medicine (SCCM) was approved by the ATS, ESICM, and SCCM, March 2017

AJRCCM. 2017;195(9):1253-63

▶ Strongly recommended:
  • Low tidal volumes
  • Limit inspiratory pressures
  • Prone positioning for severe ARDS
  • Do not use HFOV

▶ Conditionally recommend
  • Higher PEEP in moderate or severe ARDS
  • Recruitment maneuvers in moderate or severe ARDS

▶ No recommendation re: ECLS
COVID-19 ARDS: Recommend adherence to ARMA protocol

- Ventilator mode: AC/VC
- Target tidal volume: 6 cc/kilogram predicted body weight
- Target $P_{\text{plat}}$: 30
- Permissive hypercapnia: pH $>7.20$ if needed to maintain above settings
Caveat: Optimal PEEP is unclear

- **Rationale for use of PEEP in ARDS**
  - Alveolar recruitment (usually in setting of low compliance)
  - Prevent atelectrauma
  - Reduce lung stress and strain
  - Facilitates weaning of FiO₂

- **Potential risks of PEEP**
  - Overdistension causing lung injury
  - Increased intrapulmonary shunt
  - Increased dead space
  - Higher pulmonary vascular resistance
ARDSnet tables for PEEP titration

- **PEEP table used in ARMA trial**

<table>
<thead>
<tr>
<th>FiO₂</th>
<th>0.3</th>
<th>0.4</th>
<th>0.5</th>
<th>0.6</th>
<th>0.7</th>
<th>0.7</th>
<th>0.8</th>
<th>0.9</th>
<th>0.9</th>
<th>0.9</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP</td>
<td>5</td>
<td>5</td>
<td>8</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>12</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>18-24</td>
</tr>
</tbody>
</table>

- **ARDSnet High PEEP table**

<table>
<thead>
<tr>
<th>FiO₂</th>
<th>0.3</th>
<th>0.3</th>
<th>0.3</th>
<th>0.3</th>
<th>0.4</th>
<th>0.4</th>
<th>0.5</th>
<th>0.5</th>
<th>0.5-0.8</th>
<th>0.8</th>
<th>0.9</th>
<th>1.0</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP</td>
<td>5</td>
<td>8</td>
<td>10</td>
<td>12</td>
<td>14</td>
<td>14</td>
<td>16</td>
<td>16</td>
<td>18</td>
<td>20</td>
<td>22</td>
<td>22</td>
<td>24</td>
</tr>
</tbody>
</table>

Early experience at Penn

- Many patients have improved hypoxia with higher PEEP
- Improved oxygenation may reflect vascular redistribution
- Monitor both oxygenation and driving pressure closely with PEEP titration
Pressures

Driving pressure: \( \Delta P = P_{\text{plat}} - P_{\text{EEP}} \)
Consider selecting PEEP based on optimal driving pressure

- Compliance = slope of the curve
  \[ C_{\text{stat}} = \frac{\Delta V}{\Delta P} \]

- Low compliance (high driving pressure) with atelectasis and overdistension

- **SUGGEST:** Start PEEP around 10, titrate to optimize driving pressure

Source: Jesse B. Hall, Gregory A. Schmidt, John P. Kress; *Principles of Critical Care*, 4th Edition; www.accessmedicine.com
Copyright © McGraw-Hill Education. All rights reserved.
Monitor for potential consequences of ventilation strategy

- Barotrauma with higher PEEP

- Acidemia with low tidal volumes
  - Increase respiratory rate to compensate for low tidal volumes
  - Tolerate pH as low as 7.20

- Breath stacking with high rates to achieve required minute ventilation
  - Reduce rate if able, allowing for permissive hypercapnia
  - Reduce inspiratory time (or increase flow) to extend expiratory time – this will increase peak pressure but NOT plateau pressure
Adjunctive therapies

- Sedation and neuromuscular blockade
- Inhaled vasodilators
- Prone positioning
- Extracorporeal life support
Sedation and Neuromuscular Blockade

- Consider deep sedation early if FiO2 > 50%
  - Goal RASS -4 to -5, synchrony with ventilator, using fentanyl plus sedative

- Consider neuromuscular blockade if P:F ratio <100 on FiO2 >70% or higher
  - Consider bolus dosing rather than continuous infusion
  - Not mandatory even with prone positioning
  - However – if P:F ratio improves with NMB, may consider deferring proning

- Concerns about medication shortages - sedation and NMB protocol forthcoming
Inhaled vasodilators

- Inhaled nitric oxide (iNO) preferred over inhaled prostacyclin
  - iNO is not aerosol generating
  - Flolan can cause clogging of filters in ventilator circuit

- Consider if P:F ratio < 100 despite PEEP > 15, FiO2 > 85% and on NMB
  - Modest increase in risk for AKI
  - Some have postulated antiviral effect – unproven
  - If benefit not observed, recommend titrating off
Prone Positioning

PROSEVA trial: Mortality benefit with daily proning for ~16h per day among patients with ARDS with P:F ratio < 150
  • HUP MICU guidelines for ARDS in general are to prone if P:F<150 despite FiO2 60% and optimized PEEP

Limitations/consideration
  • Resource/staff intensive → PPE intensive

Consider lengthening initial prone to > 24 hours if:
  • FiO2 > 70% despite prone
  • P:F ratio < 120 on 60% or higher (~PaO2 73)
Consider deferring prone positioning if:

- High suspicion cardiomyopathy
  - Troponin rising significantly
  - Adding epinephrine or other inotrope
  - Planning formal echo that day

- Escalating pressor requirements: norepi > 15 plus vasopressin

- Super Obesity with BMI > 50 or habitus: unable to stabilize chest with large belly

- Concern for intra-abdominal pathology
  - Colitis, tense abdomen, bladder pressure > 22 cm and low UOP
ECLS

Criteria for consideration of VV ECMO for respiratory failure:
- PaO2 < 80 on FIO2 100% despite proning, hemodynamic instability X 12 hours
- Age < 65
- BMI < 45
- Smoking hx < 30 ppy

Call CT surgery early

Current plan at HUP is to administer ECMO in patient’s home unit, rather than transfer to CT-SICU
Titrating Off Therapy: iNO, NMB, Sedation, Prone

- Suggest order of de-escalation

1. iNO – titrate off when FiO2 60-70%
2. NMB – consider interrupting while proned
3. Sedation – consider liberalizing to RASS -2
4. Prone positioning – may find that patients meet PROSEVA criteria for proning for longer than usual (several days?) – consider risks/costs of proning daily
Extubation considerations

- High rates of failed extubations
  - Consider more challenging SBTs?
    - PS 5 with PEEP 3 at 40% for at least 1 hour?

- Hypoxia seems to drive reintubation

- Consider extubation to helmet ventilation
Tracheostomy for patients with COVID-19

- UPHS guidelines created by multidisciplinary team (I-Pulm, surgery, ENT, anesthesia)

- Key points:
  - Consider at **21 days** of mechanical ventilation
    - Among patients without other significant co-morbidities
    - Consider earlier for pulmonary toilet or high sedation needs
  - Open surgical approach, bedside in negative pressure room
  - **Multidisciplinary decision**: primary team, surgical team, palliative care, and family
  - Direct consults to Dr. Benjamin Braslow at HUP, Dr. James Kearney at PAH, and Dr. Sean Harbison at PPMC
Helmet ventilation

- Non-invasive ventilation administered by helmet compared to face mask resulted in lower risk of intubation for patients with ARDS
  - Transparent helmet with rubber seal at the neck
  - Being used with success in Italy

- Advantages of helmet ventilation
  - Non-invasive positive-pressure ventilation
  - Less aerosolization
  - May eliminate need for intubation among some patients

Patel B et al 2016 JAMA
HEPA Filters

Fresh Gas

PEEP Valve

UPHS educational video
(log into VPN first; also found on UPHS COVID-19 site)
UPHS and PennChart support for ARDS management

- Penn Elert
- COVID-19 Consult Team (HUP)
- ICU board with ARDS alerts
- Low stretch protocol embedded within MV order
- Proning order and flowsheet
ICU Board

- Accessible for all ICUs via UPHS Intranet
Low stretch protocol

Mechanical Ventilation

Priority: Routine  Routine  STAT
Vent Mode: AC/VC  SIMV/VC  AC/PC  SIMV/PC  AC/VC+
PS/CPAP

Order Low Stretch Protocol (if ARDS) Yes  No
Low stretch protocol

Order Low Stretch Protocol (if ARDS)

Yes  No

Tidal Volume

- 4 ml/kg IBW
- 5 ml/kg IBW
- 6 ml/kg IBW
- 7 ml/kg IBW
- 8 ml/kg IBW

Recommended LSP TV at 6mL/kg:

310

Initial PEEP (cm H2O)

RT will titrate FiO2 and PEEP according to low PEEP/FiO2 table to maintain SpO2 goal of 88-96% per Low Stretch Prot...

Process Instructions:

Comments: Add Comments (F6)

Reference Links:
1. PennPathways: Ventilator Liberation Protocol (VLP)
2. PennPathways: Low Stretch Protocol (LSP)

Phase of Care:
Proning protocol order

Proning Protocol for Adult Severe ARDS

Process Inst.: Please prone patient for a minimum of 16 hours a day until discontinued.

Priority: Routine Routine STAT

Frequency: Continuous Continuous

Starting: 4/1/2020 Today Tomorrow At: 1730

First Occurrence: Today 1730
Scheduled Times

04/01/20 1730

Comments: Add Comments (F6)

Phase of Care:

Next Required Link Order
A few more references

- **Surviving sepsis campaign guidelines for COVID19 management**

- **Retrospective cohort of critically ill COVID 19 patients**
Thank you!

- Questions?

prasadm@pennmedicine.upenn.edu