Therapeutics for COVID-19

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Professor of Medicine
Considerations for COVID-19 Treatment

• Our tools are limited
• We have to do our best to learn (and adapt) as we go
• Data are sparse – we should be data driven as much as we can but keep an open mind
COVID-19 is a spectrum of illness

Asymptomatic | Mild | Severe | Critical | Multi-organ system

Inflammation

Supportive care

Antivirals

Anti-inflammatory agents
Treatment Algorithm for COVID-19

SARS-CoV-2 (COVID-19) positive or strongly suspected

Is patient presently hospitalized or requires inpatient management?

No

- Stay home and avoid close contact with others to minimize spread
- Drink plenty of water
- Symptomatic care for fever, cough, congestion, pain
- Avoid corticosteroids unless required for other condition (e.g., COPD exacerbation)
- If shortness of breath develops, seek immediate medical evaluation

Yes

- Consider antibiotics for secondary bacterial pneumonia if concerned
- Avoid corticosteroids unless indicated for separate process (e.g., septic shock, COPD, asthma, ARDS, etc.)

Patient has any of the following AND confirmed SARS-CoV-2?

- Age ≤ 65 years
- Significant history of lung or heart disease
- History of transplantation (solid organ or hematologic)
- Immunocompromising condition or receiving immunosuppressive medications
- Moderate to severe infection: Radiographic evidence of pneumonia requiring supplemental oxygen and/or mechanical ventilation

Supportive Care

No

Clinical Status

Stable supplemental oxygen requirements

Yes

Worsening oxygenation requirements, mechanical ventilation, or expected need for mechanical ventilation within 36 hours

Antiviral therapy may be considered*

Site Specific Criteria

Central Region: ID consult mandatory if initiating therapy.
South Colorado Region: Contact Critical Care boarded providers. Antivirals restricted to critical care boarded or infectious diseases providers
Northern Colorado Region: Contact ID or pulmonology for approval
Contact local antimicrobial stewardship for treatment-related questions

Medications

First-line: Hydroxychloroquine x 5 days

Azithromycin in combination is currently not recommended due to lack of in vitro activity, clinical evidence, and risk of additive adverse events

Second-line: Lopinavir/ritonavir (LPV/r) + Ribavirin x 5 days

Third-line: Nintazoxamide x 5 days

Remdesivir - currently unavailable for most patients (Page 2)

Antibiotics should be discontinued upon diagnosis of COVID-19 and absence of features consistent secondary bacterial pneumonia

Evidence of severe infection, including hyper-inflammatory response*

Consideration of IL-6 inhibition

Assess for agent-specific use criteria

Sarilumab

Clinical Trial

(Azucurma Only)

Criteria Page 5

Tocilizumab

(All UCHealth)

Criteria Page 2

*Agents are not FDA approved for COVID-19, and limited evidence supports possible benefit, weigh risks and benefits prior to initiation. Data is rapidly evolving with therapeutics for COVID-19 and recommendations are subject to change rapidly. Please refrain from printing this document.

Available on The Source
Antiviral potency in tissue culture

<table>
<thead>
<tr>
<th>Rank Order</th>
<th>IC$_{50}$ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. HCQ</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>RDV</td>
</tr>
<tr>
<td>2. CQ</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>1.1-5.4</td>
</tr>
<tr>
<td>3. NTZ</td>
<td>2.1</td>
</tr>
<tr>
<td>4. LPV/r</td>
<td>17</td>
</tr>
<tr>
<td>5. RBV</td>
<td>110</td>
</tr>
</tbody>
</table>

Wang et al. Cell Res 2020
Yao et al. CID 2020
Effects of HCQ on Viral Shedding

• Non-randomized prospective cohort
• N = 36; HCQ 200 mg TID x 10 d

Minimal clinical benefits of Lopinavir/ritonavir

• Randomized open-label controlled trial (N=199)
• LPV/r BID for 14 days vs standard care
• 16% on mechanical ventilation
• 33% received corticosteroids

<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 (15.0 to 17.0)</td>
<td>16.0 (13.0 to 17.0)</td>
<td>16.0 (15.0 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 (≤12 days after onset of symptoms)</td>
<td>21 (23.3)</td>
<td>8 (19.0)</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 (23.1)</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 7</td>
<td>75 (37.7)</td>
<td>45 (45.5)</td>
<td>30 (30.0)</td>
<td>15.5 (2.2 to 28.8)</td>
</tr>
<tr>
<td>Day 14</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>
</tbody>
</table>

Cao et al. NEJM 2020
Tocilizumab

• mAb IL-6R antagonist
• Non-randomized retrospective cohort
• N = 21, (80% severe, 20% critical; 2 mechanical vent)
• Tocilizumab 400 mg IV infusion (3 had a 2nd dose)
Potential Mortality Benefit of Corticosteroids for COVID-19 ARDS

- Non-randomized retrospective cohort
- N = 84 with ARDS
- Methylprednisolone associated with ↓ risk of death (HR, 0.38; 95% CI, 0.20-0.72; P = .003)

Wu et al. JAMA Int Med 2020
Convalescent Plasma

- 5 patients received transfusion with convalescent plasma with a SARS-CoV-2–specific IgG titer >1:1000 (ELISA) and a nAb titer >40, obtained from 5 who recovered from COVID-19
- Convalescent plasma administered 10-22 days after admission
- All 5 on mechanical ventilation at the time of treatment; all treated with antiviral agents and nethyprednisolone
- 3 discharged (53, 51, and 55 days), and 2 in stable condition 37 d after transfusion

Shen et al. JAMA 2020
Current Treatment Status at UCH

• 81 SARS-CoV-2 positive cases
• 54% have received azithromycin
• 45% have received hydroxychloroquine
• 8 enrolled in Sarilumab clinical trial
• 1 Tocilizumab
• 1 Nitazoxanide
• 1 Death
• 21% discharged

Data courtesy of Samuel Windham, MD
Ongoing/Upcoming Clinical Trials

Denver Health
• **NIAID**: Adaptive COVID-19 Treatment Trial (ACTT)

UCH
• **Regeneron**: An Adaptive Phase 2/3, Randomized, Double-Blind, Placebo-Controlled Study Assessing Efficacy and Safety of Sarilumab for Hospitalized Patients with COVID-19
• **Gilead**: A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734TM) in Participants with Severe COVID-19
• **Gilead**: A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734TM) in Participants with Mild COVID-19
• **NHLBI (PETAL)**: Hydroxychloroquine for the Early Treatment of COVID-19 in Hospitalized Adults: A Multicenter Randomized Clinical Trial
• **NIAID (ACTG)**: A Randomized, Controlled, Open-Label, Trial to Evaluate the Efficacy of Hydroxychloroquine (HCQ) and Azithromycin versus Vitamin C to Prevent Hospitalization and Death in Persons with COVID-19
Thank You!