Many COVID-19 patients will require critical care. Based on the China experience\textsuperscript{1-3}, 15.7 percent of admitted patients were critically ill on admission or became critically ill during hospitalization. Critically ill COVID-19 patients have a high mortality rate. Data reported from China found that 61.5% of critically ill patients with COVID-19 had died by day 28 of ICU admission.\textsuperscript{1}

It behooves us to establish evidence-based clinical protocols to pro-actively plan the management of these patients and anticipate high volumes of critically ill patients.

A. Clinical Presentation and course of illness
1. Fever – among 1,099 hospitalized COVID 19 patients, fever was present 44% at hospital admission. 89% developed fever during admission
2. Cough- 46-82%
3. Myalgia or fatigue 11-52%
4. Shortness of breath 3-31%
5. ARDS developed in 17–29% of hospitalized patients, and secondary infection developed in 10%
6. Approximately 20-30% of hospitalized patients with COVID-19 and pneumonia have required intensive care for respiratory support.

B. Principles of Infection Control
1. PUI and Presumed cases should be under airborne, and contact isolation with face shield. 
   Refer to maestro link embedded

A. Diagnostic Workup

<table>
<thead>
<tr>
<th>Suggested Laboratory for Critically Ill Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 1</strong></td>
</tr>
<tr>
<td>● CBC with differential</td>
</tr>
<tr>
<td>● CMP</td>
</tr>
<tr>
<td>● RPP</td>
</tr>
<tr>
<td>● Lactic acid</td>
</tr>
<tr>
<td>● CPK</td>
</tr>
<tr>
<td>● CRP</td>
</tr>
<tr>
<td>● IL-6</td>
</tr>
<tr>
<td>● LDH</td>
</tr>
<tr>
<td>● Ferritin</td>
</tr>
<tr>
<td>● ABG</td>
</tr>
<tr>
<td>● Urinalysis</td>
</tr>
<tr>
<td>● Blood/urine cultures</td>
</tr>
<tr>
<td><strong>Day 2 until symptom resolution</strong></td>
</tr>
<tr>
<td>● CBC</td>
</tr>
<tr>
<td>● CMP</td>
</tr>
<tr>
<td>● Lactic acid</td>
</tr>
<tr>
<td>● LDH</td>
</tr>
<tr>
<td>● CRP</td>
</tr>
<tr>
<td>● IL-6</td>
</tr>
<tr>
<td>● Ferritin</td>
</tr>
<tr>
<td>● ABG</td>
</tr>
</tbody>
</table>

- Prognostic indicators (negative): Lymphopenia and Leukopenia
- Imaging: Consider Chest CT without contrast. Diagnostically helpful but with rapid testing available may not need in all patients.
  - Typical findings are multiple areas of ground glass and consolidation bilaterally
- Diagnose and treat all other conditions. Consider full differential diagnosis until COVID-19 diagnosis is established and continue to consider possible coinfections.
- Continuous monitoring with telemetry and pulse oximetry

C. Pulmonary Tx:
Combine aggressive tx while minimizing aerosolization of respiratory secretions
- Bronchodilators prn: Avoid Nebulized medications. Prefer MDI in non-ventilated patients. To conserve supply, reserve for patients with active wheezing. If giving to a patient on a ventilator, a one way valve must be utilized for nebulized treatments via the vent circuit to avoid aerosolization into the surrounding environment

1. Early ambulation if possible
2. Conservative fluid management
3. O2 supplementation
a. Nasal cannula and facemask O2 as needed 
b. Increase FiO2 as needed and favor 100% non-rebreather over Hi-Flow. 
c. Hi-Flow can be used but use with caution given potential concerns for aerosolization of the virus. Recommend placing a surgical mask on patient over Hi Flow to minimize aerosolization.
4. Avoid BiPAP/CPAP. Associated with high treatment failure rates and increased risk of aerosolization of the virus 
   a. If BiPAP/CPAP used, must use filter on expiratory limb.
5. Early intubation for progressive disease or with severe comorbidities 
   a. COVID-19 patients desaturate quickly
6. Intubation procedure 
   a. Standard: RSI, without BVM, one pass.
   b. Pre-oxygenate with 100% FiO2 for 3-5 minutes
   c. Avoid BVM. If BVM needed to oxygenate, must use BVM filter attachment.
   d. Favor use of video-laryngoscopy
   e. Controlled suctioning.
7. Post intubation: ARDSNET protocol 
   a. Consider early prone positioning without disconnecting from ventilator
   b. Closed suctioning system
8. Consider ECMO for refractory cases 
   a. ECMO referrals to HUMC are made through the transfer center – 855-367-4862 (855-FOR-HUMC)
   b. ECMO referrals to JSUMC are made Dr. Eric Costanzo 732-757-2560
D. Treatment

<table>
<thead>
<tr>
<th>Treatment Guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. There is currently no evidence from RCTs to recommend any specific treatment for patients with suspected or confirmed COVID-19 infection. Treatment should be considered in symptomatic patients requiring hospitalization based on a careful assessment of risk factors.</td>
</tr>
<tr>
<td>2. The majority of treatment is supportive care with prevention of spread of the disease.</td>
</tr>
<tr>
<td>3. Although the patient may be suspected to have COVID-19, administer appropriate empiric antimicrobials within one hour of identification of sepsis. Empiric antibiotic treatment should be based on the clinical diagnosis (CAP, HCAP, or septic shock).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NOT Recommended</th>
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<tbody>
<tr>
<td>• Lopinavir-ritonavir (Kaletra®) is no longer recommended for the treatment of COVID-19 based on a recently published clinical trial conducted in China (3/18/2020 NEJM) demonstrating no benefit over the standard of care in 199 patients infected with SARS CoV-2</td>
</tr>
<tr>
<td>• Corticosteroids should be AVOIDED due of the potential for prolonging viral replication unless indicated for other reasons. Prior studies assessing outcomes in patients receiving systemic corticosteroids for infections due to closely related viruses (SARS-CoV and MERS-CoV) found a lack of effectiveness and possible harm. However, corticosteroids may still be warranted for other medical indications (e.g., CRS, COPD exacerbation) after a careful risk vs benefit assessment</td>
</tr>
<tr>
<td>• Therapies with insufficient evidence for treatment of COVID-19: oseltamivir, baloxavir, interferon, ribavirin, IVIG. As evidence emerges, status will be updated</td>
</tr>
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<table>
<thead>
<tr>
<th>Treatments Under Investigation</th>
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<tbody>
<tr>
<td>• The following therapies are considered for off-label or investigational use. The decision to initiate treatment should be based on a risk assessment including clinical status, co-morbid conditions, acuity of illness, and concomitant medications.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Remdesivir</th>
<th>Please call Research Hotline 551-996-2994 for assistance with IND compassionate use. Refer to research website IND Workflow</th>
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<tbody>
<tr>
<td><strong>Preferred therapy for patients hospitalized due to COVID-19 based on enrollment to clinical trial or compassionate use IND</strong></td>
<td></td>
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<tr>
<td>Adult dosing: (see drug panel in EPIC)</td>
<td></td>
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</tbody>
</table>

<table>
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<tr>
<th>Inclusion Criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hospitalization</td>
</tr>
<tr>
<td>• SARS-CoV-2 by PCR</td>
</tr>
</tbody>
</table>
200 mg IV load, then 100 mg IV q 24 h for 5 – 10 days (depending on trial or IND)

**Exclusion Criteria:**
- Multi-organ failure
- Vasopressor requirement
- ALT > 5x ULN
- CrCl < 30 mL/min or dialysis

Adverse effects: increased liver enzymes. Also potential to have drug-drug interactions with medications metabolized through cytochrome system

**Hydroxychloroquine**
**Preferred therapy for hospitalized patients unable to obtain remdesivir.** Based on limited availability, hydrochloroquine should be reserved for patients based on risk assessment consistent with high risk features. Please discontinue hydroxychloroquine 24 hours prior to starting remdesivir (per the research protocol)

**Adult Dosing:** (see drug panel in EPIC)
400 mg twice daily x 1 day followed 200 mg twice daily for 4 days (5 day total)
(No dose adjustment needed for renal impairment)

Adverse effects: retinopathy rash, nausea, glucose fluctuations
- Use with caution in diabetic patients
- Use with caution in patient at risk for QT prolongation
- Recommend obtaining G6PD test. The package insert contains a warning of potential hemolysis in G6PD deficient patients, but post-marketing studies suggest the risk is very low. It is reasonable to start hydroxychloroquine in most patients while awaiting G6PD testing

**Tocilizumab**
Reserved for patients with worsening pulmonary status with ARDS and signs/symptoms consistent with superimposed delayed pro-inflammatory cytokine release

Informed Consent Required

Will be reviewed for eligibility prior to approval

**Adult Dosing:**
400 mg IV over 30 minutes x 1 dose

The following criteria for use have been developed to identify patients that may benefit from IL-6 inhibition with Tocilizumab:

**Patient must meet ALL three criteria:**
1. Acute Respiratory Distress Syndrome with worsening oxygenation defined by one of the following:
   a. P/F ratio < 150
   b. Increasing FiO2 requirement ≥ 70%
   c. Worsening radiographic imaging
2. Persistent fever > 101°F despite scheduled antipyretic therapy for ≥ 24 hours
3. One or more of the following markers of inflammatory:
   a. Elevated IL-6 levels: > 40 pg/mL
   b. CRP > 20 mg/ml (>200 mg/L)
   c. Ferritin > 2000 ng/mL
   d. Increasing vasopressor (NE > 10 mcg/min)
Links:

- Gilead – Remdesivir request [https://rdvcu.gilead.com/](https://rdvcu.gilead.com/)
- HMH Maestro Clinical Alerts [https://hmhmaestro.org/clinical_alerts/covid19/](https://hmhmaestro.org/clinical_alerts/covid19/)
Criteria for Initiating Hydroxychloroquine in Highly-Suspicious or Confirmed COVID-19

Suggested dosing: Hydroxychloroquine 400 mg PO every 12 hours for two doses followed by 200 mg PO every 12 hours

<table>
<thead>
<tr>
<th>Restriction Stages</th>
<th>High-Suspicion of COVID-19 (pending test result)</th>
<th>Positive COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Patients must meet one of the following criteria</td>
<td>Patients must meet one of the following criteria</td>
</tr>
<tr>
<td></td>
<td>1. Requiring ICU care</td>
<td>1. Requiring ICU care</td>
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<td></td>
<td>2. Supplemental O₂ with SpO₂ &lt;94 on room air</td>
<td>2. Supplemental O₂ with SpO₂ &lt;94 on room air</td>
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<tr>
<td></td>
<td>3. Any of the following risk factors</td>
<td>3. Any of the following risk factors</td>
</tr>
<tr>
<td></td>
<td>o Pre-existing pulmonary condition</td>
<td>o Pre-existing pulmonary condition</td>
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<tr>
<td></td>
<td>o Chronic kidney and/or liver disease</td>
<td>o Chronic kidney and/or liver disease</td>
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<td></td>
<td>o Diabetes</td>
<td>o Diabetes</td>
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<td></td>
<td>o Hypertension</td>
<td>o Hypertension</td>
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<td></td>
<td>o Cardiovascular disease</td>
<td>o Cardiovascular disease</td>
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<tr>
<td></td>
<td>o Biologics, immunotherapy, chemotherapy</td>
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<tr>
<td></td>
<td>o Steroids (equivalent of ≥20 mg prednisone per day for 30 days)</td>
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<tr>
<td></td>
<td>o History of transplant</td>
<td>o History of transplant</td>
</tr>
<tr>
<td></td>
<td>o All patients with HIV (regardless of CD4 count)</td>
<td>o All patients with HIV (regardless of CD4 count)</td>
</tr>
</tbody>
</table>

References:


EMERGENCY INDIVIDUAL PATIENT IND WORKFLOW

1. Patient eligible to receive remdesivir
   - CLINICAL TEAM

2. Complete online application on Gilead website
   - CLINICAL TEAM
   - Notify Research Admin Department AND Pharmacy
   - CLINICAL TEAM

3. Email Approval received by Gilead (Letter of Authorization, LOA)
   - CLINICAL TEAM

4. Prepare forms needed for eIND Form 3926, PFS CV
   - CLINICAL TEAM
   - RESEARCH ADMIN TEAM

5. Submit LOA, Form 3926 and CV to DAV and cc research
   - CLINICAL TEAM
   - RESEARCH ADMIN TEAM

6. FDA Approval AND Gilead Approval (agreement signed, shipment confirmation)

7. Notify HUMC pharmacy AND Research Admin Department
   - CLINICAL TEAM

8. Consent patient (or proxy)
   - CLINICAL TEAM
   - Drug administration

9. Provide FDA approval letter and copy of form 3926 (if not provided previously)
   - CLINICAL TEAM

10. IRB submission
    - RESEARCH ADMIN TEAM

11. eCRF
    - CLINICAL TEAM
    - RESEARCH ADMIN TEAM

Gilead
https://rdcvu.gilead.com/
(form completed by patient’s/lead treating physician)

FDA - DAV (Division of Antivirals):
DAVPINDREQUEST@fda.hhs.gov

RESEARCH HOTLINE: 551-996-2994
Research email: emergencyIND@hackensackmeridian.org
Contacts: Cheryl Fittizzi, Elli Gourna
*To report adverse events, study closure, etc.

Version: 17Mar2020 – Office of Research Administration, HMH
REFERENCES: