YNHHS Treatment Algorithm for Hospitalized ADULTS with COVID-19

Disclaimer: There are no FDA-approved treatments for COVID-19, supportive care is standard of care. Treatment data continues to evolve & clinical judgment is warranted – Algorithm last updated 7/22/20

Patient with confirmed POSITIVE SARS-CoV-2 by PCR
Assess all patients routinely for clinical trial eligibility (see Appendix 1)
* Please refer to page 3 for additional guidance on ECMO patients

Oxygen saturation ≤ 94% on room air and requiring supplemental oxygen (≤ 95% if pregnant), or oxygen requirement above home baseline

YES

Remdesivir x 5 days if hospital length of stay is ≤10 days
Use only when benefit may outweigh risk if eGFR <30 mL/min, hepatic dysfunction, or pregnancy
(See Appendix 2 for exclusion criteria)
Remdesivir has not been FDA approved; remdesivir is authorized by the FDA under and Emergency Use Authorization (EUA)

NO

SUPPORTIVE CARE & EVERY 4 HOUR OXYGEN MONITORING

COVID-SPECIFIC TESTS
1) Baseline & every 12 hours (for 5 days, then daily thereafter): CRP, D-dimer
2) Baseline & every 12 hours x3: Troponin (continue longer if further testing clinically indicated)
3) Baseline & every 24 hours (for 5 days*): CBC with differential, BMP, LFTs, Ferritin, Procalcitonin, BNP, fibrinogen, PT/PTT, Mg
4) Baseline & ICU transfer: Cytokine panel
5) Baseline and with acute kidney injury (AKI): urinalysis and urine protein/albumin ratio
6) Baseline EKG (see Appendix 3 for QTc recommendations)
7) Repeat Chest X-Ray: if clinical deterioration. (CXR not indicated for discharge or to document clinical improvement)
*May extend longer if clinically indicated
Obtain LFTs daily if on remdesivir

YNHH: ID consult is not mandatory for remdesivir or tocilizumab. Make requests for remdesivir and tocilizumab through a non-formulary / restricted medication consult to pharmacy.
BH, GH, LMH, or WH: consult ID for remdesivir and tocilizumab requests

Consider MICU evaluation if > 4 Liter O2 requirement or hemodynamic instability
(at YNHH see Appendix 4 for suggested triage guidelines)

See Page 2 of algorithm for multi-disciplinary management by sub-specialty recommendations

Algorithm reviewed by YNHHS SAS and YNHH/YSM Ad-Hoc COVID-19 Treatment Team
YNHHS Initial Treatment Algorithm for **Hospitalized** ADULTS with COVID-19

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**Hematologic:**
- If D-dimer <5 mg/L: All patients should receive standard prophylactic anticoagulation and aspirin 81mg daily unless contraindicated
- If D-dimer ≥5mg/L or receiving convalescent plasma: use weight-based intermediate prophylactic anticoagulation and aspirin 81mg daily unless contraindicated
- If ferritin >100,000 or D-dimer >10mg/L, consider Hematology consult at discretion of primary team
  (*see Appendix 5 for anticoagulation dosing recommendations)

**Aspirin 81mg PO daily**
- Relative contraindications: recent or risk for CNS bleed, use of other anti-platelet therapy, severe thrombocytopenia, allergy, or history of bleeding disorder
- Discontinue at discharge

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**Cardiac:**
- Monitor electrolytes: Replete Mg >2, K >4
- Baseline EKG and monitor telemetry closely for QTc Prolongation (Appendix 2 for recommendations)
- Caution combining QTc prolonging medications
- If significantly elevated troponin or EKG abnormalities and/or hemodynamic instability, consider POCUS for LV function assessment and cardiology consult

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**Nephrology:**
- If acute kidney injury, check urinalysis and baseline urine protein/albumin.
- If ≥ 1 gram of protein, consider renal input

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**Obstetrics:**
Treatment Protocol is similar.
Alternative cut-offs for:
- Treatment administration with oxygen saturation of ≤ 95%.
- D-dimer cutoff for anticoagulation (see Appendix 5b)

Remdesivir is available to pregnant patients under Expanded Access / Compassionate Use requests. Request only if potential benefits outweigh risks.

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*Immunosuppressed hosts* include: Cancer treatment within 1 year, the use of immunosuppressive drugs (biologics, chronic prednisone ≥20mg daily), solid organ transplant, bone marrow transplantation, HIV/AIDS (regardless of CD4 count), leukemia, lymphoma, SLE, vasculitis, and pregnancy

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Algorithm reviewed by YNHHS SAS and YNHH/YSM Ad-Hoc COVID-19 Treatment Team
Guidance for Patients with Confirmed COVID-19 and Refractory Respiratory Failure Requiring ECMO

Prior to cannulation
- Goals of care discussion
- Follow YNHHS COVID-19 Severe Algorithm for treatment and testing
- Evaluate for secondary causes of respiratory failure
- Order pre-ECMO cytokine panel

ECMO (24-48 hours)
- Order post-ECMO cytokine panel (after ~48 hours)
- Assess eligibility for clinical trials / expanded access protocols

ECMO (48 hours–2 weeks)
- Consider Allergy / Immunology and Infectious Diseases consultation
- Consider adjunctive therapeutic resources

ECMO (2-3 weeks)
- Revisit goals of care discussions if no clinical improvement after addressing potentially reversible processes

Evaluation / Management of Secondary Causes of Respiratory Failure
- Vigorous pulmonary toilette
- Infection – blood and sputum cultures
- Pulmonary embolism
- Heart failure – limited TTE

Potential Adjunctive Therapeutic Resources
- Convalescent plasma administration if eligible
- Consult Allergy / Immunology to help target immune dysregulation
  - Evaluate for other available clinical trials of immunomodulators
  - Possible repeat tocilizumab dosing
- Cytokine adsorption via ECMO circuit

* Available options are subject to rapid change *

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Algorithm reviewed by YNHHS SAS and YNHH/YSM Ad-Hoc COVID-19 Treatment Team
# Appendix 1: Active Coronavirus (SARS-CoV)-2 infection Clinical Trials for Hospitalized Patients

<table>
<thead>
<tr>
<th>Drug, study description and rationale for use</th>
<th>Inclusion and Exclusion Criteria</th>
<th>Notable adverse effects</th>
<th>Primary Investigator(s)/Contact Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug: Sarilumab</strong>&lt;br&gt;Monoclonal antibody to IL6 receptor&lt;br&gt;Rationale: IL-6 receptor antagonist may attenuate cytokine release in patients with severe disease&lt;br&gt;Description: Phase 2/3, Randomized, Double-Blind, Placebo Controlled Study Assessing Efficacy and Safety of Sarilumab for Hospitalized Patients with COVID-19</td>
<td>Inclusion&lt;br&gt;• Aged ≥ 18 years&lt;br&gt;• Evidence of pneumonia and have one of the following disease categories: severe disease, multi-system organ dysfunction or critical disease Laboratory-confirmed SARS-CoV-2 infection</td>
<td>Elevated liver enzymes&lt;br&gt;Leukopenia&lt;br&gt;Infusion reactions (e.g. flushing, chills)</td>
<td>YNHH PI: Geoffrey Chupp Contact: <a href="mailto:Geoffrey.Chupp@yale.edu">Geoffrey.Chupp@yale.edu</a></td>
</tr>
<tr>
<td></td>
<td>Key Exclusion&lt;br&gt;• Low likelihood of survival after 48 hours from screening&lt;br&gt;• Presence of neutropenia less than 2000/mm³&lt;br&gt;• AST or ALT greater than 5 X ULN&lt;br&gt;• Platelets &lt; 50,000/mm³ prior immunosuppressive therapies&lt;br&gt;• Use of chronic oral corticosteroids for non-COVID-19 related condition&lt;br&gt;• Patients who have received IL-6 receptor antagonist within 30 days of study enrollment&lt;br&gt;• Participation in any other clinical trial of an experimental treatment for COVID-19&lt;br&gt;• Known or suspected history of tuberculosis&lt;br&gt;• Suspected or known active systemic bacterial or fungal infection</td>
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<tr>
<td></td>
<td>Relative Exclusion&lt;br&gt;• ≥ 10 days since first positive SARS-CoV-2 PCR&lt;br&gt;• Confirmed or high suspicion for bacterial or fungal infection&lt;br&gt;• D-dimer ≥ 5 mg/L or evidence of/suspicion for thrombosis&lt;br&gt;• Recent bleeding or high risk for bleeding&lt;br&gt;• Known severe IgA deficiency</td>
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<tr>
<td><strong>Expanded access program for use of convalescent plasma in COVID-19 patients</strong></td>
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<tr>
<td><strong>Drug: Ruxolitinib</strong>&lt;br&gt;Selective JAK1 and JAK2 inhibitor</td>
<td>Inclusion&lt;br&gt;• Aged ≥ 18 years&lt;br&gt;• Confirmed positive SARS-CoV-2 infection by PCR&lt;br&gt;• Severe or Life-threatening disease by the following definitions&lt;br&gt;• Severe disease&lt;br&gt;  o Requiring supplemental oxygen with one or more of the following:&lt;br&gt;   ▪ Non-rebreather&lt;br&gt;   ▪ High-flow nasal cannula&lt;br&gt;   ▪ Pulmonary infiltrates with ≥ 3 L via NC with rapid progression&lt;br&gt;   ▪ Mechanical ventilation&lt;br&gt;• Life-threatening disease&lt;br&gt;  o Refractory respiratory failure, or&lt;br&gt;  o Septic shock, or&lt;br&gt;  o Multi-organ dysfunction&lt;br&gt;</td>
<td></td>
<td>YNHH PI: Hyung Chun. Contact: <a href="mailto:hyung.chun@yale.edu">hyung.chun@yale.edu</a></td>
</tr>
<tr>
<td></td>
<td>Relative Exclusion&lt;br&gt;• ≥ 10 days since first positive SARS-CoV-2 PCR&lt;br&gt;• Confirmed or high suspicion for bacterial or fungal infection&lt;br&gt;• D-dimer ≥ 5 mg/L or evidence of/suspicion for thrombosis&lt;br&gt;• Recent bleeding or high risk for bleeding&lt;br&gt;• Known severe IgA deficiency</td>
<td></td>
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<tr>
<td></td>
<td>Inclusion&lt;br&gt;• Aged ≥ 12 years with clinical and/or lab-confirmed SARS-CoV-2 infection.</td>
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</tbody>
</table>

**Contacts:**<br>YNHH : Mahalia.desruisseaux@yale.edu<br>BH: Tina.McCurry@bpthosp.org<br>GH: Herbert.Archer@greenwichhospital.org<br>LMH/WH: Christopher.Song@lmhosp.org
<table>
<thead>
<tr>
<th><strong>Rationale:</strong> Severe COVID-19 infection is associated with cytokine storm. Ruxolitinib has the potential to mitigate cytokine storm through its impact on the JAK-STAT pathway, thus potentially improving the clinical outcome of severely ill patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description:</strong> expanded access, open-label design. Patients will begin 5 mg BID by mouth × 7 days. Eligible patients may receive up to a maximum of 14 days as long as clinical benefit is observed and/or treatment withdrawal criteria are not met.</td>
</tr>
<tr>
<td><strong>Inclusion</strong></td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>• Severe shortness of breath (respiratory rate &gt; 24 breaths/minute).</td>
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<tr>
<td>• SpO2 &lt; 90% on ambient air.</td>
</tr>
<tr>
<td>• Need for invasive or noninvasive mechanical ventilation.</td>
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<tr>
<td>• Acute respiratory distress syndrome.</td>
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<tr>
<td>• Multiple organ failure.</td>
</tr>
<tr>
<td>• Be willing to avoid pregnancy. If woman of childbearing potential, must agree to precautions with at least 99% certainty. For men must agree to precautions with up to 99% certainty.</td>
</tr>
<tr>
<td>• Able to provide informed consent</td>
</tr>
<tr>
<td><strong>Exclusion</strong></td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>• Females who are pregnant or breastfeeding, and males and females who cannot comply with requirements to avoid fathering a child or becoming pregnant</td>
</tr>
<tr>
<td>• ALT &gt; 4x ULN or direct bilirubin 4x ULN and lab abnormalities considered to be due to underlying liver function</td>
</tr>
<tr>
<td>• PLT &lt; 50 x 10^9 / L</td>
</tr>
<tr>
<td>• Underlying medical/psychiatric condition that the treating physician would deem to have an unacceptable risk</td>
</tr>
<tr>
<td>• Previous allergy</td>
</tr>
<tr>
<td>• Concomitant use to any other JAK inhibitor</td>
</tr>
<tr>
<td>• Is eligible or able to access ruxolitinib through an Incyte-sponsored clinical study or is eligible for another therapeutic clinical study for cytokine storm</td>
</tr>
<tr>
<td><strong>Drug: Tofacitinib</strong></td>
</tr>
<tr>
<td><strong>Rationale:</strong> SARS-CoV-2 may manifest cytokine release syndrome. Tofacitinib functions as an intracellular JAK1/JAK3 inhibitor, leading to inhibition of a number of downstream inflammatory, thus potentially decreasing clinical severity of cytokine release syndrome</td>
</tr>
<tr>
<td><strong>Description:</strong></td>
</tr>
<tr>
<td><strong>Inclusion</strong></td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>• Evidence of pneumonia by radiographic imaging (chest x-ray or chest CT scan) AND Requiring ≥ 3L O2 OR ≥ 2L O2 and hsCRP &gt; 70 mg/L</td>
</tr>
<tr>
<td>• Provide informed consent</td>
</tr>
<tr>
<td>• Willingness to conform to contraceptive guidance</td>
</tr>
<tr>
<td><strong>Exclusion</strong></td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>• Current or history of VTE (DVT or PE)</td>
</tr>
<tr>
<td>• Personal or first-degree family history of blood clotting disorders</td>
</tr>
<tr>
<td>• Immunocompromised or taking immunosuppressive agents</td>
</tr>
<tr>
<td>• Current malignancy or lymphoproliferative disorders requiring active treatment</td>
</tr>
<tr>
<td>• Females of child bearing potential or pregnant/breastfeeding</td>
</tr>
<tr>
<td><strong>Note:</strong> oral syringe exp in 24hrs.</td>
</tr>
</tbody>
</table>

Thrombocytopenia, anemia and neutropenia, Reactivation of TB, HBV and herpes zoster

URTI, viral infections, herpes simplex.

Joint/muscle/ligament swelling/pain

YNHH PI: Hyung Chun
hyung.chun@yale.edu
Clinical Research Assistant: Danielle Peterson
Randomized, double blinded, placebo controlled Phase 2b study in patients with SARS-CoV-2 and pneumonia who require supplemental oxygen and have serologic markers of inflammation but do not need mechanical ventilation. Will be recruited to tofacitinib or placebo 2:1 and given 10mg PO BID until return to their clinical baseline and will subsequently continue on 5 mg PO BID for a total duration of therapy of 14 days.

**Exclusion Criteria**
- Other medical/psychiatric conditions which the investigator determines as inappropriate for participation
- Survival < 72hrs
- Infection History
  - Secondary bacterial pneumonia
  - Active herpes zoster
  - Known tuberculosis or inadequately treated tuberculosis
  - Known HBV, HCV, or HIV.
- Prior/Concomitant Therapy
  - Within 4 weeks prior to first dose: Prior treatment with any JAK inhibitors, potent immunosuppressants, or any biologic agents including IL-6 inhibitors (eg, tocilizumab) or IL-1 inhibitors (eg, anakinra) within the past 28 days or 5 half-lives, whichever is longer. Prior treatment with any potent cytochrome P450 inducer, such as rifampin, within the past 28 days or 5 half-lives, whichever is longer
  - Within 48hrs prior to first dose: treatment with corticosteroids equivalent to prednisone 20mg/day or treatment with herbal supplements
- Diagnostic Assessment
  - Severe hepatic impairment, defined as Child-Pugh class C.
  - Hgb <8 g/dL
  - WBC < 1000/mm3, absolute lymphocyte count < 500 cells/mm3, absolute neutrophil count <1000 cells/mm3
  - ALT/AST > 5 x ULN
  - eGFR < 40mL/min/1.73m2
- Allergy to tofacitinib
- Enrollment in another clinical trial to study COVID-19

**Drug: Remdesivir (RDV)**
Broad-spectrum nucleotide prodrug which inhibits RNA polymerase activity against pathogenic coronaviruses.

**Tocilizumab (TCZ)**
Monoclonal antibody which inhibits soluble and membrane-bound IL-6R

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Remdesivir: infusion reactions, elevated LFTs, kidney toxicity (dose-dependent and reversible),</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent or assent (depending on age)</td>
<td>YNHH PI: Onyema Ogbuagu</td>
</tr>
<tr>
<td>Aged ≥ 12 years hospitalized with COVID-19 pneumonia confirmed by PCR and evidenced by Chest X-ray to CT scan (PCR must be ≤ 7 days before randomization)</td>
<td>Laurie Andrews</td>
</tr>
<tr>
<td>Requiring &gt; 6L/min supplemental oxygen to maintain SpO2 &gt; 93%</td>
<td><a href="mailto:laurie.andrews@yale.edu">laurie.andrews@yale.edu</a></td>
</tr>
<tr>
<td>Agreement not to participate in another COVID-19 treatment trial while participating</td>
<td></td>
</tr>
</tbody>
</table>
### Rationale
Remdesivir and tocilizumab have been well-tolerated in patients with severe COVID-19 pneumonia. Combined RNA nucleotide antagonism via remdesivir and inhibition of pro-inflammatory states via tocilizumab in patients with severe COVID-19 pneumonia may lend improved effectiveness.

### Description
Phase III, randomized, double-blind trial in which patients will be randomized 2:1 to receive either remdesivir plus tocilizumab or remdesivir plus placebo.

Patients assigned to the RDV + TCZ arm will receive remdesivir as a 200 mg IV loading dose followed by one infusion of tocilizumab 8 mg/kg or placebo (maximum dose of 800 mg) on Day 1. Patients will subsequently be administered a 100 mg once-daily IV maintenance dose of remdesivir from Days 2-10 (or at time of hospital discharge of 10 days have not been completed).

### Exclusion Criteria
- If progression to death is imminent and inevitable within next 24hrs
- Suspected active bacterial, fungal, viral, or other infection besides COVID-19
- Allergy to tocilizumab or other monoclonal antibodies or remdesivir
- Active TB infection
- Treatment with immunosuppressive/modulators in past 3 months
- Participation in another drug clinical trial
- eGFR < 30mL/min/1.73m²
- ALT or AST > 5x ULN
- ANC < 1000/uL
- PLT < 50,000/uL
- Weight < 40kg
- Pregnant/breastfeeding
- Treatment with investigation drug with 5 half-lives or 30 days or randomization

Possible viral resistance

Tocilizumab: infusion reactions, serious infections and opportunistic infections, GI perforations, hematological malignancies, demyelinating disorders, elevated LFTs

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For single patient INDs and emergency use, expanded access may be appropriate when all the following apply:
- Patient has a serious disease or condition, or whose life is immediately threatened by their disease or condition
- There is no comparable or satisfactory alternative therapy to diagnose, monitor, to treat the disease or condition
- Patient enrollment in a clinical trial is not possible
- Potential patient benefit justifies the potential risks of treatment
- Providing the investigational medical product will not interfere with investigational trials that could support a medical product’s development or marketing approval for the treatment indication

There are several steps necessary when undertaking emergency use of a drug including specific investigator, Sponsor, and FDA requirements. If a provider assesses emergency use of a drug is appropriate they should contact the Yale Human Research Protection Program (HRPP) and the Investigational Drug Service (IDS) (203-688-4872) as soon as possible to get assistance in identifying and navigating the applicable requirements.
Appendix 2: Remdesivir and Tocilizumab Exclusion Criteria

a. Anticipated immediate death (≤24 hours) regardless of critical care support

b. Cardiac: NYHA Class IV heart failure; Severe, inoperable multi-vessel coronary artery disease; Cardiac arrest; Recurrent arrests in the current presentation, or unresponsive to defibrillation or pacing, or unwitnessed out-of-hospital cardiac arrest with poor prognosis

c. Hepatic: Cirrhosis with MELD-Na score ≥25 (in patients who are not transplant candidates), alcoholic hepatitis with MELD-Na >30, advanced liver cancer

d. Neurologic: Severe dementia leading to dependence in multiple ADLs; Rapidly progressive or end-stage neuromuscular disease

e. Oncologic: Advanced malignancy or high-grade primary brain tumors receiving only palliative treatment with estimated 3 or fewer month prognosis.

f. Pulmonary: Severe, chronic lung disease with baseline oxygen requirement of ≥ 60% FiO2; Primary pulmonary hypertension with NYHA Class III-IV heart failure (and patient refractory to/not a candidate for pulmonary vasodilators)

g. Trauma: Severe trauma; Severe burns: age >60 and 50% of total body surface area affected

h. Functional Status: Dependent in all ADLs due to a progressive chronic comorbid condition
Appendix 3: Care Pathways for Mitigation of Drug-Induced Malignant Arrhythmias in COVID-19 Patients

Recommendations:
All COVID-19 patients should have the following:

- When ordering an EKG for a COVID 19 patient to monitor their QTc, select the diagnosis “COVID 19” to alert cardiology to expedite the formal reading of the EKG.
- Daily monitoring of electrolytes; maintain K > 4 and Mg > 2
- All unnecessary QT prolonging drugs should be avoided or switched to alternatives whenever possible.

Recommendations:
A flowchart for the monitoring of potential malignant arrhythmias in these patients is shown below.
Appendix 4: YNHH Acute Respiratory Failure with COVID-19 MICU / SDU Triage Guidelines

>4L NC with O2 sat <93%

RR < 25

Obtain ABG

pH>7.32

Consider SDU evaluation, reassess in 2-4 hours

Hypercapnia with pH<7.32

Consult MICU

RR > 25 +/- AMS +/- inability to manage secretions

Obtain ABG and consult MICU
Appendix 5a: Anticoagulation Dosing Guidelines (Non-Pregnant Patients)

Administer aspirin 81mg PO daily to all patients unless contraindicated. Discontinue aspirin at discharge.

<table>
<thead>
<tr>
<th>D-dimer</th>
<th>BMI &lt; 40 kg/m²</th>
<th>BMI ≥ 40 kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 mg/L</td>
<td>CrCl ≥ 30 mL/min</td>
<td></td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>• Enoxaparin 40mg sq daily</td>
<td>CrCl ≥ 30 mL/min</td>
</tr>
<tr>
<td></td>
<td>• Enoxaparin 30mg sq daily</td>
<td>• Enoxaparin 40mg sq Q12H</td>
</tr>
<tr>
<td></td>
<td>• Heparin 5000 units sq Q8-12H</td>
<td>CrCl &lt; 30 mL/min</td>
</tr>
<tr>
<td></td>
<td>• Enoxaparin 40mg sq daily</td>
<td>• Enoxaparin 40mg sq Q24H</td>
</tr>
<tr>
<td></td>
<td>• Heparin 7500 units sq Q8-12H</td>
<td></td>
</tr>
<tr>
<td>≥ 5 mg/L</td>
<td>CrCl ≥ 30 mL/min</td>
<td></td>
</tr>
<tr>
<td>or receiving convalescent plasma</td>
<td>• Enoxaparin 0.5mg/kg sq Q12H*</td>
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</tr>
<tr>
<td>Intermediate Dose Prophylaxis</td>
<td>• DOAC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CrCl &lt; 30 mL/min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Enoxaparin 0.5mg/kg sq Q12H*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• DOAC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Heparin 7500 units sq Q8-12H</td>
<td></td>
</tr>
<tr>
<td>Confirmed VTE, high clinical suspicion, or clotting of dialysis lines/tubing</td>
<td>CrCl ≥ 30 mL/min</td>
<td></td>
</tr>
<tr>
<td>TREATMENT*</td>
<td>• Enoxaparin 1mg/kg sq Q12H</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• DOAC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CrCl &lt; 30 mL/min</td>
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</tr>
<tr>
<td></td>
<td>• Enoxaparin 1mg/kg sq Q24H</td>
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<tr>
<td></td>
<td>• DOAC</td>
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<tr>
<td></td>
<td>Therapeutic heparin</td>
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<tr>
<td>DOAC Dosing</td>
<td></td>
<td></td>
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<tr>
<td>Apixaban</td>
<td>5mg PO Q12H regardless of renal function</td>
<td>10mg PO Q12H x 7 days followed by 5mg PO Q12H (limited data for 10mg in CrCl &lt; 25 or Cr &gt; 2.5)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>20mg Q24H</td>
<td>15mg PO Q12H x 21 days followed by 20mg PO Q24H</td>
</tr>
<tr>
<td>(may favor in BMI ≥ 40 kg/m²)</td>
<td>Avoid use with CrCl &lt; 30 mL/min</td>
<td>Avoid use with CrCl &lt; 30 mL/min</td>
</tr>
</tbody>
</table>

*Enoxaparin is the preferred form of anticoagulation

*Relative contraindications for aspirin: recent or risk for CNS bleed, use of other anti-platelet therapy, severe thrombocytopenia, allergy, or history of bleeding disorder

*Target anti-Xa levels between 0.3 – 0.7 units/mL

*Patients receiving treatment should continue full dose anticoagulation for 3 months

Consult pharmacy for assistance with dosing recommendations, if needed

Seek hematology input for further recommendations on treatment as needed
Appendix 5b: Anticoagulation Dosing Guidelines (Pregnant Patients)

Administer aspirin 81mg PO daily to all patients unless contraindicated. Discontinue aspirin at discharge.

<table>
<thead>
<tr>
<th>D-dimer</th>
<th>BMI &lt; 40 kg/m²</th>
<th>BMI ≥ 40 kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3.5 mg/L&lt;br&gt;Prophylaxis &lt;br&gt;CrCl ≥ 30 mL/min&lt;br&gt;CrCl &lt; 30 mL/min</td>
<td>- Enoxaparin 40mg sq daily&lt;br&gt;- Enoxaparin 30mg sq daily</td>
<td>- Enoxaparin 40mg sq daily&lt;br&gt;- Enoxaparin 40mg sq Q24H</td>
</tr>
<tr>
<td>≥ 3.5 mg/L or receiving convalescent plasma&lt;br&gt;Intermediate Dose Prophylaxis&lt;br&gt;CrCl ≥ 30 mL/min&lt;br&gt;CrCl &lt; 30 mL/min</td>
<td>- Enoxaparin 0.5mg/kg sq Q12H&lt;br&gt;- Enoxaparin 0.5mg/kg sq Q12H*</td>
<td>- Enoxaparin 0.5mg/kg sq Q12H&lt;br&gt;- Enoxaparin 0.5mg/kg sq Q12H*</td>
</tr>
<tr>
<td>≥ 7 mg/L&lt;br&gt;Confirmed VTE or high clinical suspicion&lt;br&gt;TREATMENT&lt;br&gt;CrCl ≥ 30 mL/min&lt;br&gt;CrCl &lt; 30 mL/min</td>
<td>- Enoxaparin 1mg/kg sq Q12H&lt;br&gt;- Enoxaparin 1mg/kg sq Q24H</td>
<td>- Enoxaparin 1mg/kg sq Q12H&lt;br&gt;- Enoxaparin 1mg/kg sq Q24H</td>
</tr>
</tbody>
</table>

Dosing weight for PREGNANT patients should be actual body weight and POST-PARTUM dosing should be PRE-PREGNANCY weight.

 Relative contraindications for aspirin: recent or risk for CNS bleed, use of other anti-platelet therapy, severe thrombocytopenia, allergy, or history of bleeding disorder

 *Target anti-Xa levels between 0.3 – 0.7 units/mL

Consult pharmacy for assistance with dosing recommendations, if needed
Seek hematology input for further recommendations on treatment as needed, including duration
Appendix 5c: Anticoagulation Discharge Recommendations

1. Patients who had initiation of treatment doses during the hospital stay for either presumed or objectively documented venous thrombosis should be discharged on full dose anticoagulation therapy (Direct oral anticoagulant (DOAC), LMWH, warfarin) for a minimum treatment period of three months.
   - We recommend that these patients have follow up with their primary care physician or specialty physician within six weeks of discharge to assess ongoing risk benefit ratio of anticoagulation.

2. Patients who received standard dose VTE prophylaxis in hospital should not ordinarily continue with VTE prophylaxis. If, however, they are being discharged to another medical care facility, standards of care at that facility should prevail.

3. Patients who received escalated dose (intermediate dose) VTE prophylaxis could be considered for extended VTE prophylaxis with rivaroxaban 10 mg daily for 35 days or LMWH if rivaroxaban cannot be used. The following conditions can be used to determine if a patient is eligible to receive extended duration VTE prophylaxis:
   - Patient should have either:
     1. Modified IMPROVE VTE Risk Score is \( \geq 4 \)
     2. Modified IMPROVE VTE Risk Score is 2 or 3 and a D-dimer is > 2x ULN. (D-dimer measured within 24 hours of discharge should be used for this determination)
   - Patient should **NOT** have any of the following:
     1. Major bleeding during hospital stay or during the three months prior to index hospital stay
     2. Major surgery within the last four weeks
     3. Prolonged PT (INR > 1.5- measured within 24 hours of discharge)
     4. Known bleeding disorder
     5. Current use of anti-platelet therapy
     6. CrCl of < 30 mL/min
     7. Discharge platelet count < 100,000/ul (measured within 24 hours of discharge)
     8. Other contraindications to anticoagulation with a DOAC

Calculating the Modified IMPROVE VTE Risk Score

<table>
<thead>
<tr>
<th>VTE Risk Factor</th>
<th>VTE Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous VTE</td>
<td>3</td>
</tr>
<tr>
<td>Known thrombophilia*</td>
<td>2</td>
</tr>
<tr>
<td><strong>Current lower limb paralysis or paresis</strong></td>
<td>2</td>
</tr>
<tr>
<td>History of cancer†</td>
<td>2</td>
</tr>
<tr>
<td>ICU/CCU Stay</td>
<td>1</td>
</tr>
<tr>
<td>Complete immobilization ( \geq 1 ) day†</td>
<td>1</td>
</tr>
<tr>
<td>Age ( \geq 60 ) years</td>
<td>1</td>
</tr>
</tbody>
</table>

* A congenital or acquired condition leading to excess risk of thrombosis (factor V Leiden, lupus anticoagulant, factor C or S deficiency)
** Leg falls to bed by 5 seconds, but has some effort against gravity (taken from the NIH stroke scale)
† Cancer (excluding non-melanoma skin cancer) present at any time in the last 5 years (cancer must be in remission to meet criteria)
‡ Immobilization is being confined to bed or chair with or without bathroom privileges
### Appendix 6

**Possible medications for COVID-19**

(Subject to change as more data becomes available and based on medication availability)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Mechanism</th>
<th>Rationale for use</th>
<th>Notable Adverse Reactions</th>
<th>Other considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remdesivir</td>
<td>200mg IV once followed by 100mg IV daily for 5 days</td>
<td>Viral RNA dependent RNA polymerase inhibitor</td>
<td><em>In-vitro</em> data reveals potent SARS-COV-2 inhibition and early clinical data shows possible benefit</td>
<td>• Nausea, vomiting, • Elevated liver enzymes • Rectal bleeding</td>
<td>• Remdesivir was authorized (not approved) by the FDA through an Emergency Use Authorization (EUA). Availability under the EUA is limited. • Available for pregnant patients and patients on ECMO under Expanded Access; request only if benefits outweigh risks • Hydroxychloroquine is not recommended with remdesivir given concern for possible drug-drug interaction which may reduce remdesivir’s effectiveness.</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Dexamethasone 6 mg daily for 7 days</td>
<td>Inhibit production of inflammatory cytokines that regulate neutrophil and T-cell responses leading to immune suppression</td>
<td>Can attenuate cytokine release in patients in patients with severe disease</td>
<td>• Hyperglycemia • Adrenal suppression and myopathy if given in high doses for long periods • Psychiatric disturbances in certain patients • Perforation risk in patients with GI disease • Fluid retention and hypertension</td>
<td>• Lower 28-day mortality was observed in patients receiving invasive mechanical ventilation or oxygen but <strong>NOT</strong> among those receiving <strong>NO respiratory support</strong> (12) • Corticosteroids should be used if clinically indicated as part of standard of care such as for an asthma or COPD exacerbation, or shock with history of chronic steroid use</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>8mg/kg IV x 1 dose (actual body weight; dose max 800 mg)</td>
<td>Monoclonal antibody to IL6 receptor</td>
<td>IL-6 receptor antagonist may attenuate cytokine release in patients with severe disease</td>
<td>• Headache • Elevated liver enzymes • Infusion reactions (e.g. flushing, chills)</td>
<td>• The use of IL-6 levels should NOT guide decision to administer tocilizumab at this time • Additional doses not indicated at this time</td>
</tr>
</tbody>
</table>
### Medications which may be available through Clinical Trials or Expanded Access

*(Subject to change as more data becomes available and based on medication availability)*

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Mechanism</th>
<th>Rationale for possible efficacy</th>
<th>Rationale for NOT including as first line agent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Convalescent Plasma (20-24)</strong></td>
<td>One ABO compatible unit</td>
<td>- Individual (not pooled) plasma from a recovered COVID19 patient</td>
<td>- Transfer of potentially neutralizing antibodies which could diminish viral pathogenesis</td>
<td>- Available through expanded access, not a trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Transfusion reactions</td>
<td>- Each unit may contain variable titers of anti-SARS-CoV-2 antibodies with differing avidity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Potential to increase hypercoagulability</td>
<td>- Cannot be used in patients with IgA deficiency due to risk of anaphylaxis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Use with intermediate dosing anticoagulation (see Appendix 5 above)</td>
</tr>
<tr>
<td><strong>Sarilumab (25-27)</strong></td>
<td>Clinical Trial dosing</td>
<td>- Monoclonal antibody to IL6 receptor</td>
<td>- IL-6 receptor antagonist may attenuate cytokine release in patients with severe disease</td>
<td>- Available through clinical trial only at this time</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Elevated liver enzymes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Leukopenia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Infusion reactions (e.g. flushing, chills)</td>
<td></td>
</tr>
</tbody>
</table>

### Medications NOT currently recommended as first line for COVID-19

*(Can be considered in certain cases after discussion with Infectious Diseases and Pharmacy)*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Mechanism</th>
<th>Rationale for possible efficacy</th>
<th>Rationale for NOT including as first line agent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hydroxychloroquine (HCQ)</strong></td>
<td>400mg PO q12h x 24h, then 200mg q12h x 4 days for a 5 day total duration</td>
<td>- Prevents acidification of endosomes interrupting cellular functions and replication</td>
<td>- In-vitro data shows potent SARS-COV-2 inhibition and early clinical data shows possible benefit</td>
<td>- Available data from clinical trials does not demonstrate benefit, and some studies suggest risk. Risks outweigh benefits given theoretic risk for cardiac arrhythmia.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Prevents viral entry via ACE2 binding</td>
<td>- HCQ was found more potent than chloroquine in inhibiting SARS-CoV-2 in vitro</td>
<td>- Not recommended with remdesivir given concern for possible drug-drug interaction which may reduce remdesivir’s effectiveness (43).</td>
</tr>
<tr>
<td>Drug</td>
<td>Availability</td>
<td>Type</td>
<td>Effectiveness</td>
<td>Side Effects or Interactions</td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------------</td>
<td>---------------------</td>
<td>---------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Lopinavir/ Ritonavir (44-47)</td>
<td>N/A</td>
<td>Viral protease inhibitor</td>
<td>In-vitro data reveals potent SARS-COV-2 inhibition</td>
<td>Limited availability, poor tolerability (such as GI side effects) and recent data demonstrated questionable clinical efficacy</td>
</tr>
<tr>
<td>Atazanavir (48)</td>
<td>N/A</td>
<td>Viral protease inhibitor</td>
<td>More potent binding to the virus compared to other protease inhibitors <em>in vitro</em> (lower than lopinavir)</td>
<td>Mild indirect hyperbilirubinemia is common and not indicative of hepatic dysfunction. CYP enzyme inhibitor (3A4, 2C8) monitor/discuss with pharmacy potential for drug-drug interactions. For patients with NG/OG/NJ open capsules for enteral administration. Atazanavir needs an acidic environment for absorption and therefore <em>antacids, H2 blockers, proton pump inhibitors (PPIs)</em> should be avoided. If these agents must be given the administration should be separated as below: o Atazanavir should be given 2 hours before or 1 hour after antacids o Atazanavir should be given at the same time as the H2 blocker or the atazanavir should be given 10 hours after or 2 hours before the H2 blocker. For PPIs avoid concomitant use</td>
</tr>
<tr>
<td>Azithromycin (49)</td>
<td>500 mg x 1, followed by 250 mg q24h x 4 days</td>
<td>Not well defined; possible immunomodulator</td>
<td>In a small study, combination of HCQ and azithromycin was associated with significant a reduction in SARS-CoV-2 viral load</td>
<td>Very limited data on use of azithromycin alone or in combination with other agents o Gautret, et al. study is limited by small sample size (only 6 patients received HCQ &amp; azithromycin combination) and those patients had lower viral loads than other included patients. Combination of HCQ and azithromycin and atazanavir can increase the risk for QTc prolongation</td>
</tr>
<tr>
<td>Darunavir/ Cobicistat (50)</td>
<td>N/A</td>
<td>Viral protease inhibitor</td>
<td>In-vitro data shows SARS-COV-2 inhibition</td>
<td>Decreased binding to viral protease compared to atazanavir. No clinical data at this time</td>
</tr>
</tbody>
</table>
| **Ribavirin**  
(51, 52) | N/A | • Viral RNA polymerase inhibitor and inhibition of elongation of RNA fragments  
• *In vitro* data for use in SARS-CoV and MERS-CoV indicates possible activity | • Limited evidence for SARS-CoV-2 and toxicity risk outweighs benefit of use  
• Typically used with interferon  
• Studied in patients with other coronaviruses with mixed results |
| **Oseltamivir**  
(53) | N/A | • Inhibits influenza virus neuraminidase blocking viral release  
• Activity against influenza virus | • No current data to support use of this drug.  
• Additionally, **SARS-CoV-2 does not use neuraminidase in the replication cycle** so mechanistically there would be no benefit |
| **Nitazoxanide**  
(54) | N/A | • Augments host antiviral response  
• *In-vitro* data reveals SARS-COV-2 inhibition | • No clinical data available |

**IMMUNOMODULATING AGENTS**

| **Interferon-beta**  
(45-47, 55) | N/A | • Immunomodulator  
• Possible activity against SARS-CoV and MERS-CoV  
• Typically used in combination with ribavirin | • Limited data with SARS-CoV-2, toxicity risk outweighs benefit of use. Have been studied for patients with other coronaviruses with mixed results  
• Not interferon-alpha or interferon-gamma |
| **Intravenous immunoglobulin**  
(IVIG)  
(56, 57) | N/A | • Neutralizing antibodies against the virus  
• May have both antiviral and immunomodulatory effects  
• A recent observational study reported clinical and radiographic improvement in 3 patients who received high dose IVIG at time of respiratory distress | • Drug is on **critical national shortage** and has an unclear role as current preparations will not contain antibodies against SARS-CoV-2 at this time |
| **Baricitinib**  
(58, 59) | N/A | • Janus Kinase (JAK) inhibitor binding cyclin G-associated kinase, may inhibit viral entry via endocytosis  
• May have targeted antiviral and immunomodulatory effect with less side-effects at an effective dose than other JAK inhibitors | • Not available for off label use  
• No clinical data available  
• Risk of severe infections with use |
<table>
<thead>
<tr>
<th>Zinc (60, 61)</th>
<th>N/A</th>
<th>- Directly impairs RNA synthesis in SARS-CoV by inhibiting the replication and transcription complex, as well as RNA-dependent RNA polymerase. Chloroquine has been demonstrated to be a zinc ionophore. All data is based on in vitro studies only.</th>
<th>- Increasing intracellular zinc concentrations may inhibit RNA synthesis</th>
<th>- No clinical data is available to demonstrate efficacy in vivo. - No in vitro studies have evaluated the effect of zinc on SARS-CoV-2 replication, or hydroxychloroquine as a zinc ionophore</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascorbic acid &amp; Thiamine (62-65)</td>
<td>N/A</td>
<td>- Unclear; ?role in septic shock/ARDS</td>
<td>- ? benefit in septic shock/ARDS</td>
<td>- No published peer reviewed studies in the medical literature were found to support the usage of these vitamins for COVID-19. There are ongoing clinical trials assessing possible benefit. - Two recently published open-label studies evaluating the use of vitamin C alone and in combination in other types of infections, associated with septic shock and acute respiratory distress syndrome (ARDS) showed no clear evidence of benefit. It cannot be concluded that intravenous vitamin C or thiamine is an effective treatment of ARDS (resulting from COVID-19, or otherwise).</td>
</tr>
</tbody>
</table>

References:

4. Sciences G. Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Moderate Coronavirus Disease (COVID-19) Compared to Standard of Care Treatment. NCT042927302020.


