YNHHS Treatment Guidance for **Hospitalized** ADULTS with COVID-19

**Disclaimer:** Remdesivir is the only FDA-approved agent to date. Updated 11/25/20
Treatment data continues to evolve & clinical judgment is warranted

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 ≤ 95%** on room air and requiring supplemental oxygen
or oxygen requirement above home baseline

**YES**

**Remdesivir x 5 days**
if hospital length of stay is ≤10 days OR ≤10 days from nosocomial acquisition
(or until hospital discharge if length of stay < 5 days)
Use only when benefit may outweigh risk in patients with hepatic dysfunction or pregnant
(See Appendix 2 for exclusion criteria)

**WITH**
**Dexamethasone 6 mg po daily x 7 days**
(or until hospital discharge if length of stay < 7 days)
Can be given IV if NPO
Other steroid equivalent can be considered if dexamethasone is not available. Steroid therapy may not be beneficial when given at late stage of disease

**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, Procalcitonin, BNP
4) Baseline & ICU transfer: Cytokine panel
5) Baseline and with acute kidney injury (AKI):
   urinalysis and urine protein/albumin ratio
6) Baseline EKG
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

**There are no recommended therapies for patients not improving on remdesivir and dexamethasone.**
If no clinical improvement (increasing O2 requirement and/or rising CRP) within 24-48 hours of steroid therapy,
please re-assess patient eligibility for clinical trials
(see Appendices 1, 2, & 3 for trials and exclusion criteria)

Consider MICU evaluation if > 5 Liter O2 requirement or hemodynamic instability
(at YNHH see Appendix 5 for suggested triage guidelines)

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

See Page 2 of treatment guidance for multi-disciplinary management by sub-specialty recommendations
Report suspected adverse events related to therapeutics through RL solutions

Treatment guidance reviewed by YNHHS SAS and YNHH/YSM Ad-Hoc COVID-19 Treatment Team
YNHHS Initial Treatment Guidance 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 confirmed VTE, start **therapeutic dose anticoagulation**; aspirin is NOT recommended unless needed for a non-COVID indication.
- If D-dimer >10mg/L and no confirmed VTE, consider Hematology consult at discretion of primary team.

(*see Appendix 6 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
- **DO NOT ADMINISTER** if patient on therapeutic anticoagulation unless needed for a non-COVID indication
- **Discontinue at discharge**

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

### Cardiac:
- **Baseline EKG**
- If significantly elevated troponin or EKG abnormalities and/or hemodynamic instability, consider POCUS for LV function assessment and cardiology consult

### Obstetrics:
- **Treatment Protocol is similar.**
- D-dimer cutoff for anticoagulation (see Appendix 6b)

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**Treatment guidance** 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

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

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

**Potential Adjunctive Therapeutic Resources**
- Consider convalescent plasma administration under EUA (See Appendix 3)
- Consult Allergy / Immunology to help target immune dysregulation
  - Evaluate for other available clinical trials of immunomodulators
- Cytokine adsorption via ECMO circuit

* Available options are subject to rapid change *

**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

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Treatment guidance 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>
</table>
| **Drug: Remdesivir (RDV)** Broad-spectrum nucleoside prodrug which inhibits RNA polymerase activity against pathogenic coronaviruses. | • Informed consent or assent (depending on age)  
• 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)  
• Requiring > 6L/min supplemental oxygen to maintain SpO2 > 93%  
• Agreement not to participate in another COVID-19 treatment trial while participating  
• Ability for men and women of childbearing potential to adhere to contraception rules | Remdesivir: infusion reactions, elevated LFTs, kidney toxicity (dose-dependent and reversible), possible viral resistance | YNHH PI: Onyema Ogbuagu  
Lead CRC: Laurie Andrews  
laurie.andrews@yale.edu |
| **Remdesivir** (RDV) | • 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 | Tocilizumab: infusion reactions, serious infections and opportunistic infections, GI perforations, hematological malignancies, demyelinating disorders, elevated LFTs | |
| **Tocilizumab (TCZ)** Monoclonal antibody which inhibits soluble and membrane-bound IL-6R | • Infused as an 8 mg/kg 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).

**Convalescent plasma** in COVID-19 patients

**Rationale:** Use of convalescent plasma is a form of passive antibody therapy that involves the administration of antibodies to a given agent to a susceptible individual for the purpose of potentially treating COVID-19.

**Description:** Randomized, blinded phase 2 study evaluating the safety and efficacy of convalescent plasma compared to placebo in hospitalized patients with COVID-19

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
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</table>
| • Patients ≥18 years of age  
• Hospitalized with COVID-19 with respiratory symptoms, cough, chest pain, shortness of breath, fever, or oxygen saturation ≤ 94%, or abnormal imaging  
• Hospitalized for less than 72 hours OR within day 3 to 7 days from first signs of illness  
• Laboratory confirmed COVID-19  
• On supplemental oxygen, non-invasive ventilation or high-flow oxygen  
• Patients may be on other randomized controlled trials of pharmaceuticals for COVID-19 and patients who meet eligibility criteria will not be excluded on this basis. | • Receipt of pooled immunoglobulin in past 30 days  
• Contraindication to transfusion or history of prior reactions to transfusion blood products  
• Invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)  
• Volume overload secondary to congestive heart failure or renal failure  
• Intracranial bleed |

**Drug: Tofacitinib**

Selective JAK1 and JAK3 inhibitor

**Rationale:** 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.

**Description:** 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.

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
</table>
| • Hospitalized patients aged 18-65 with lab-confirmed SARS-CoV-2  
• Evidence of pneumonia by radiographic imaging (chest x-ray or chest CT scan) AND Requiring ≥ 3L O2 OR ≥ 2L O2 and hsCRP > 70 mg/L  
• Provide informed consent  
• Willingness to conform to contraceptive guidance | • Require mechanical ventilation or ECMO on day 1 at time of randomization  
• Current or history of VTE (DVT or PE)  
• Personal or first-degree family history of blood clotting disorders  
• Immunocompromised or taking immunosuppressive agents  
• Current malignancy or lymphoproliferative disorders requiring active treatment  
• Females of child bearing potential or pregnant/breastfeeding  
• Other medical/psychiatric conditions which the investigator determines as inappropriate for participation  
• Survival < 72hrs  
• Infection History  
  • Secondary bacterial pneumonia  
  • Active herpes zoster |

Clinical Trial Currently only at YNHH

**Contacts:**

YNHH:

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URTI, viral infections, herpes simplex.  
Joint/muscle/ligament swelling/pain

YNHH PI: Hyung Chun  
hyung.chun@yale.edu

Clinical Research Assistant: Danielle Peterson
### Drugs:
1. Cenicriviroc: CCR2/CCR5 inhibitor
2. Apremilast/Otezla: PDE4 inhibitor
3. Icatibant: B2 receptor inhibitor, with an affinity similar to bradykinin
4. Razuprotafib: inhibition of vascular endothelial-protein tyrosine phosphatase

### Inclusion/Exclusion

#### Inclusion Criteria
- Male or Female, at least 18 years old
- Admitted to the hospital and placed on high flow oxygen (greater than 6L by nasal cannula or mask delivery system) or intubated for the treatment of (established or presumed) COVID-19
- Informed consent provided by the patient or health care proxy
- Confirmation of SARS-CoV-2 infection by PCR prior to randomization

#### Exclusion Criteria
- Pregnant or breastfeeding women
- History of allergic reactions attributed to compounds of similar chemical or biologic composition to study agent based on review of the medical record and patient history;
- Comfort measures only
- Acute or chronic liver disease with a Child-Pugh score > 11
- Resident for more than six months at a skilled nursing facility

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**I-SPY COVID-19**

**Drugs:**
1. Cenicriviroc: CCR2/CCR5 inhibitor
2. Apremilast/Otezla: PDE4 inhibitor
3. Icatibant: B2 receptor inhibitor, with an affinity similar to bradykinin
4. Razuprotafib: inhibition of vascular endothelial-protein tyrosine phosphatase

**Rationale & Description:** SARS-CoV-2 may manifest as ARDS and cytokine release syndrome. I-SPY COVID is an adaptive trial that enrolls severely ill COVID-19 subjects into a “backbone” control arm consisting of standard of therapy until return to their clinical baseline and will subsequently continue on 5 mg PO BID for a total duration of therapy of 14 days.

**Inclusion/Exclusion**
- Male or Female, at least 18 years old
- Admitted to the hospital and placed on high flow oxygen (greater than 6L by nasal cannula or mask delivery system) or intubated for the treatment of (established or presumed) COVID-19
- Informed consent provided by the patient or health care proxy
- Confirmation of SARS-CoV-2 infection by PCR prior to randomization
- 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

**Exclusion Criteria**
- **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

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**YNHH PI:** Jon Koff  
**RC:** Jacqueline Prinz

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[jacqueline.prinz@yale.edu](mailto:jacqueline.prinz@yale.edu)
<table>
<thead>
<tr>
<th>care plus remdesivir and dexamethasone. Each additional study arm is an intervention that is evaluated for safety and efficacy via rolling DSMB review.</th>
</tr>
</thead>
</table>
| • Estimated mortality greater than 50% over the next six months from underlying chronic conditions  
• Time since requirement for high flow oxygen or ventilation greater than 72 hours  
• Anticipated transfer to another hospital which is not a study site within 72 hours  
Patients with either end-stage kidney disease or acute kidney injury who are on dialysis |

**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, please 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, Tocilizumab, COVID-19 Convalescent Plasma and 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: COVID-19 Convalescent Plasma (CP) Inclusion/Exclusion Criteria
Convalescent Plasma is not stocked in any YNHHS hospital and will take 24 hours to obtain

For patients who do not meet criteria for enrollment in the randomized clinical trials (RCT) can receive CP through emergency use authorization (EUA) if they meet the following criteria:

1. Patient has a confirmed positive SARS-CoV-2 PCR Result AND been admitted for ≤ 6 days AND requires ≥ 3 L of oxygen supplementation.

2. Patients who meet the following criteria should be excluded:
   a. Patient meets any of the exclusion criteria outlined in Appendix 2
   b. History of anaphylaxis to blood products or history of IgA deficiency
   c. D-dimer > 10
   d. Evidence or suspicion of thrombosis
   e. Active bleed or high risk for bleeding
   f. Beyond 6 days of hospitalization (from initial admission date)

Any patient who receives CP should receive, at minimum, intermediate dose prophylaxis anticoagulation with enoxaparin for 72 hours, regardless of d-dimer. After 72 hours, the need for intermediate dose prophylaxis can be re-assessed based on d-dimer level and risk for thrombosis. See Appendix 5 with additional anticoagulation recommendations.
Appendix 4: YNHH Acute Respiratory Failure with COVID-19 MICU / SDU Triage Guidelines

1. > 5 liters NC with O2 saturation < 90%
   - RR < 25
     - Obtain ABG
       - pH > 7.32
         - Consider SDU evaluation, reassess in 24 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)

## DOAC Dosing

<table>
<thead>
<tr>
<th>D-dimer</th>
<th>Give Aspirin?</th>
<th>BMI &lt; 40 kg/m²</th>
<th>BMI ≥ 40 kg/m²</th>
</tr>
</thead>
</table>
| < 5 mg/L | Yes | CrCl ≥ 30 mL/min  
Enoxaparin 40mg sq daily  
CrCl < 30 mL/min  
Enoxaparin 30mg sq daily  
Heparin 5000 units sq Q8-12H | CrCl ≥ 30 mL/min  
Enoxaparin 40mg sq Q12H  
CrCl < 30 mL/min  
Enoxaparin 40mg sq Q24H  
Heparin 7500 units sq Q8-12H |

| ≥ 5 mg/L or Receiving convalescent plasma | Yes | CrCl ≥ 30 mL/min  
Enoxaparin 0.5mg/kg sq Q12H*  
DOAC  
CrCl < 30 mL/min  
Enoxaparin 0.5mg/kg sq Q12H*  
DOAC  
Heparin 7500 units sq Q8-12H | CrCl ≥ 30 mL/min  
Enoxaparin 0.5mg/kg sq Q12H*  
DOAC  
CrCl < 30 mL/min  
Enoxaparin 0.5mg/kg sq Q12H*  
DOAC  
Heparin 7500 units sq Q8 |

## Prophylaxis

<table>
<thead>
<tr>
<th>BMI &lt; 40 kg/m²</th>
<th>BMI ≥ 40 kg/m²</th>
</tr>
</thead>
</table>
| < 5 mg/L | Yes | CrCl ≥ 30 mL/min  
Enoxaparin 40mg sq daily  
CrCl < 30 mL/min  
Enoxaparin 30mg sq daily  
Heparin 5000 units sq Q8-12H | CrCl ≥ 30 mL/min  
Enoxaparin 40mg sq Q12H  
CrCl < 30 mL/min  
Enoxaparin 40mg sq Q24H  
Heparin 7500 units sq Q8-12H |

| ≥ 5 mg/L or Receiving convalescent plasma | Yes | CrCl ≥ 30 mL/min  
Enoxaparin 0.5mg/kg sq Q12H*  
DOAC  
CrCl < 30 mL/min  
Enoxaparin 0.5mg/kg sq Q12H*  
DOAC  
Heparin 7500 units sq Q8-12H | CrCl ≥ 30 mL/min  
Enoxaparin 0.5mg/kg sq Q12H*  
DOAC  
CrCl < 30 mL/min  
Enoxaparin 0.5mg/kg sq Q12H*  
DOAC  
Heparin 7500 units sq Q8 |

## Intermediate Dose Prophylaxis

<table>
<thead>
<tr>
<th>BMI &lt; 40 kg/m²</th>
<th>BMI ≥ 40 kg/m²</th>
</tr>
</thead>
</table>
| > 5 mg/L or Receiving convalescent plasma | No | CrCl ≥ 30 mL/min  
Enoxaparin 1mg/kg sq Q12H  
DOAC  
CrCl < 30 mL/min  
Enoxaparin 1mg/kg sq Q12H  
DOAC  
Therapeutic heparin | CrCl ≥ 30 mL/min  
Enoxaparin 1mg/kg sq Q12H  
DOAC  
CrCl < 30 mL/min  
Enoxaparin 1mg/kg sq Q12H  
DOAC  
Therapeutic heparin |

## Confirmed VTE with diagnostic imaging

### TREATMENT

<table>
<thead>
<tr>
<th>BMI &lt; 40 kg/m²</th>
<th>BMI ≥ 40 kg/m²</th>
</tr>
</thead>
</table>
| > 5 mg/L or Receiving convalescent plasma | No | CrCl ≥ 30 mL/min  
Enoxaparin 1mg/kg sq Q12H  
DOAC  
CrCl < 30 mL/min  
Enoxaparin 1mg/kg sq Q12H  
DOAC  
Therapeutic heparin | CrCl ≥ 30 mL/min  
Enoxaparin 1mg/kg sq Q12H  
DOAC  
CrCl < 30 mL/min  
Enoxaparin 1mg/kg sq Q12H  
DOAC  
Therapeutic heparin |

### DOAC Dosing

<table>
<thead>
<tr>
<th>DOAC</th>
<th>D-dimer ≥ 5 mg/L</th>
<th>Confirmed VTE treatment with diagnostic imaging</th>
</tr>
</thead>
</table>
| Apixaban | 5mg PO Q12H regardless of renal function | 10mg PO Q12H x 7 days followed by 5mg PO Q12H (limited data for 10mg in CrCl < 25 or Cr > 2.5)  
Do not give loading dose if patient has been on 7 days of therapeutic anticoagulation |
| Rivaroxaban (may favor in BMI ≥ 40 kg/m²) | 20mg Q24H  
Avoid use with CrCl < 30 mL/min | 15mg PO Q12H x 21 days followed by 20mg PO Q24H  
Avoid use with CrCl < 30 mL/min  
Do not give loading dose if patient has been on 21 days of therapeutic anticoagulation |

### Comment

- **Enoxaparin is the preferred form of anticoagulation**
- **Do not give if contraindicated. DO NOT ADMINISTER if patient on therapeutic anticoagulation unless needed for a non-COVID indication**
- **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)

<table>
<thead>
<tr>
<th>D-dimer</th>
<th>Give Aspirin?</th>
<th>BMI &lt; 40 kg/m²</th>
<th>BMI ≥ 40 kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3.5 mg/L Prophylaxis</td>
<td>Yes</td>
<td>CrCl ≥ 30 mL/min&lt;br&gt;• Enoxaparin 40 mg sq daily&lt;br&gt;CrCl &lt; 30 mL/min&lt;br&gt;• Enoxaparin 30 mg sq daily</td>
<td>CrCl ≥ 30 mL/min&lt;br&gt;• Enoxaparin 40 mg sq Q12H&lt;br&gt;CrCl &lt; 30 mL/min&lt;br&gt;• Enoxaparin 40 mg sq Q24H</td>
</tr>
<tr>
<td>≥ 3.5 mg/L or receiving convalescent plasma Intermediate Dose Prophylaxis</td>
<td>Yes</td>
<td>CrCl ≥ 30 mL/min&lt;br&gt;• Enoxaparin 0.5 mg/kg sq Q12H*&lt;br&gt;CrCl &lt; 30 mL/min&lt;br&gt;• Enoxaparin 0.5 mg/kg sq Q12H*</td>
<td>CrCl ≥ 30 mL/min&lt;br&gt;• Enoxaparin 0.5 mg/kg sq Q12H*&lt;br&gt;CrCl &lt; 30 mL/min&lt;br&gt;• Enoxaparin 0.5 mg/kg sq Q12H*</td>
</tr>
<tr>
<td>≥ 7 mg/L Confirmed VTE by diagnostic imaging TREATMENT</td>
<td>No</td>
<td>CrCl ≥ 30 mL/min&lt;br&gt;• Enoxaparin 1 mg/kg sq Q12H&lt;br&gt;CrCl &lt; 30 mL/min&lt;br&gt;• Enoxaparin 1 mg/kg sq Q24H</td>
<td>CrCl ≥ 30 mL/min&lt;br&gt;• Enoxaparin 1 mg/kg sq Q12H&lt;br&gt;CrCl &lt; 30 mL/min&lt;br&gt;• Enoxaparin 1 mg/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

*Do not give if contraindicated. DO NOT ADMINISTER if patient on therapeutic anticoagulation unless needed for a non-COVID indication

◊ 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>Current lower limb paralysis or paresis**</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
<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>• In-vitro 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 approved by the FDA on 10/22/20 for COVID-19 treatment. • Although there is a FDA-warning regarding remdesivir use in patients with CrCl&lt;30 ml/min due to the accumulation of cyclodextrin, there is a lack of clinical data to suggest this is problematic in this population. Other medications with cyclodextrin have been given in this population without any adverse effects. • Therapy should be started with dexamethasone if patients meet criteria as defined on page one.</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 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> (13) • 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. • Patients on steroids at home should be administered dexamethasone at the recommended dose of 6 mg in place of their chronic steroid for the recommended duration and then be re-started on their home steroid. There is a lack of data to support higher dose of steroid in patients on therapy chronically who develop COVID-19.</td>
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<tr>
<td>Available Therapy through Clinical Trial or Emergency Use Authorization (EUA)</td>
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<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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<tr>
<td>(Subject to change as more data becomes available and based on medication availability)</td>
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<tr>
<td><strong>Convalescent Plasma (14-18)</strong></td>
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<td>One ABO compatible unit</td>
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<tr>
<td>• Individual (not pooled) plasma from a recovered COVID19 patient</td>
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<td>• Transfer of potentially neutralizing antibodies which could diminish viral pathogenesis</td>
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<td>• Transfusion reactions</td>
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<td>• Potential to increase hypercoagulability</td>
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<td>• Each unit may contain variable titers of anti-SARS-CoV-2 antibodies with differing avidity</td>
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<tr>
<td>• Cannot be used in patients with IgA deficiency due to risk of anaphylaxis</td>
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<td>• Use with intermediate dosing anticoagulation (see Appendix 5 above)</td>
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<td>• See Appendix 3</td>
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</table>

| Therapy with conflicting data                                                                                                                                           |
| (Current use is recommended by NIH/IDSA only under clinical trials)                                                                                                 |
| **Tocilizumab (19-27)**                                                                                                                                               |
| 8mg/kg IV x 1 dose (actual body weight; dose max 800 mg)                                                                                                               |
| • Monoclonal antibody to IL6 receptor                                                                                                                                     |
| • IL-6 receptor antagonist may attenuate cytokine release in patients with severe disease                                                                             |
| • Retrospective data suggest possible benefit (clinical trials ongoing)                                                                                                   |
| • Headache                                                                                                                                                                |
| • Elevated liver enzymes                                                                                                                                                 |
| • Infusion reactions (e.g. flushing, chills)                                                                                                                               |
| • The use of IL-6 levels should NOT guide decision to administer tocilizumab at this time                                                                             |
| • Additional doses not indicated at this time                                                                                                                             |
| • Can be considered 48 hours after remdesivir and dexamethasone if there is no clinical improvement (increasing O2 requirement and/or rising CRP) AND no available clinical trial or patient is ineligible for clinical trial. |

| Therapy with limited data                                                                                                                                           |
| (Current use is preferred to be given under clinical trials)                                                                                                       |
| **Baricitinib (28, 29)**                                                                                                                                              |
| 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 |
| • Risk of severe infections with use and possible increase of thrombosis                                                                                             |
| • Not available for off label use                                                                                                                                       |
| • No published data                                                                                                                                                     |
| • FDA issued EUA of remdesivir and baricitinib but data of its safety and efficacy are not available.                                                                 |
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.


