**Therapeutic Options:**
The following are based on in-vitro or in-vivo studies suggesting potential benefit and are subject to availability. All severity categories are for patients with confirmed SARS-CoV-2 by PCR and PUI.*

### Remdesivir
- **Dosage:** 200 mg IV loading dose on day 1, followed by 100 mg IV once daily x 4 days or until hospital discharge, whichever is sooner.
- **Consider** for patients at high risk of disease progression.
- Clinical trials evaluated remdesivir use in patients with infiltrates on CXR.

### Corticosteroids, Dexamethasone
- **Dosage:** 150 mcg/kg, max dose 6 mg IV or PO daily x 10 days, higher doses permitted if indicated for other diagnoses.
- **Consider** for non-severe disease requiring supplemental oxygen.
- **Recommended in those requiring supplemental O2**
- **Recommended**

### Tocilizumab
- **Dosage:** 400 mg IV x 1 OR Baricitinib 4 mg PO daily up to 14 days while hospitalized OR Sarilumab 400mg IV x 1 (use only if tocilizumab not available)
- **Avoid combination of Tocilizumab or Sarilumab with Baricitinib**
- **Consider** for non-critical disease requiring supplemental oxygen.
- **Recommended in those requiring supplemental O2**
- **Recommended**

### Severe Disease, Critical: Requires Invasive Mechanical Ventilation or ECMO, Septic Shock
- **Use may not be as beneficial in these patients; suggest against routine initiation**

### Exclusion Criteria:
1. ALT levels > 10x ULN
2. Use not recommended > 14 days after symptom onset

### Warnings, Restrictions, & Links
- If dexamethasone is unavailable, equivalent total daily doses of alternative glucocorticoids may be used

### Sotrovimab
- **Dosage:** 19-21
- **Exclusion Criteria:**
  - Risk of serious infections, avoid with concurrent infection
  - Do not initiate if ANC is <1,000/mm3, PLT <50,000/mm3, or if ALT or AST are >10 times ULN

### Eua Tocilizumab
- **Dosage:** 8, 21
- **Exclusion Criteria:**
  - Do not initiate if ANC is <2,000/mm3, PLT <100,000/mm3, or if ALT or AST are >1.5 times ULN

### Eua Baricitinib
- **Dosage:** 4, 8
- **Exclusion Criteria:**
  - Serious thrombosis has occurred, monitor closely

### Monoclonal Antibodies for COVID-19, Eua Requirements Must Be Followed*
- **Dosage:**
  - Baricitinib HCP Facts
  - Sotrovimab P/C Fact Sheet
  - Toci P/C Fact Sheet

### Sotrovimab:
- **Dosage:**
  - Sotrovimab Fact Sheet HCP
  - Sotrovimab P/C Fact Sheet -English
  - Sotrovimab P/C Fact Sheet -Spanish

### Eua Sotrovimab:
- **Dosage:**
  - Sotrovimab Fact Sheet HCP
  - Sotrovimab P/C Fact Sheet -English
  - Sotrovimab P/C Fact Sheet -Spanish

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*PUI: Person Under Investigation

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COVID-19 ANTICOAGULATION GUIDELINE

This document is based on expert clinical guidance and current available evidence, which is still evolving
This guidance should be used in conjunction with latest evidence, patient-specific characteristics and should not supercede clinical judgment

Background: Patients hospitalized with COVID-19 are at increased risk for thromboembolism due to immobility and inflammation which may cause injury to vascular endothelium. There is clinical evidence to suggest that COVID-19 is associated with increased coagulopathy including elevated D-dimer, fibrinogen, prothrombin time, and fibrin degradation products such as LDH.

VTE prophylaxis for ALL hospitalized patients with COVID-19 unless contraindication (active bleeding or platelet count < 25 x 10⁹)

Decision to initiate anticoagulation should be based on a patient-specific, risk:benefit analysis

Admitted to Intensive Care Unit (ICU)?

- NO
- YES

D-dimer level ≥ 3 mcg/mL?

Any decision to increase the intensity of anticoagulation should take into account patient specific bleeding risk.

STANDARD VTE PROPHYLAXIS DOSING:

| BMI < 40 kg/m²: | - CrCl ≥ 30 mL/min: enoxaparin 0.5 mg/kg SubQ BID |
|               | - CrCl 15 - 29 mL/min: enoxaparin 0.5 mg/kg SubQ daily |
|               | - CrCL < 15 mL/min: heparin 5000 units SubQ q8hr |
| BMI ≥ 40 kg/m²: | - CrCL ≥ 30 mL/min: enoxaparin 0.4 mg/kg SubQ q12h |
|               | - CrCL 15 - 29 mL/min: enoxaparin 0.4 mg/kg SubQ daily |
|               | - CrCL < 15 mL/min: heparin 7500 units SubQ q8hr |

INTERMEDIATE-INTENSITY VTE PROPHYLAXIS DOSING:

| CrCL ≥ 30 mL/min: | enoxaparin 0.5 mg/kg SubQ BID |
| CrCL 15 - 29 mL/min: | enoxaparin 0.5 mg/kg SubQ daily |
| CrCL < 15 mL/min: | heparin 7500 units SubQ q12h |

- If patient transfers out of ICU and D-dimer was never ≥ 3 mcg/mL, consider step-down to standard VTE prophylaxis dosing
- If D-dimer ≥ 3 mcg/mL at any point, consider continuing intermediate-intensity VTE prophylaxis dosing for the duration of the hospital admission

High clinical suspicion or confirmed VTE?

Consider increasing intensity of anticoagulation if recurrent clotting of vascular access devices despite VTE prophylaxis.

Consider the possibility of pulmonary thromboembolism in patients with sudden onset of oxygenation deterioration, reduced blood pressure, tachycardia with imaging not consistent with worsening COVID-19 pneumonia. Evaluate for elevated BNP, troponin, and/or markedly elevated D-dimer. If unable to obtain confirmatory CTA, consider bedside cardiac ultrasound to evaluate for right ventricular strain or thrombus.

Yes

VTE TREATMENT DOSING:

| CrCL ≥ 30 mL/min: | enoxaparin 1 mg/kg SubQ q12hr |
| CrCL < 30 mL/min: | heparin IV continuous infusion |

- Daily D-dimer may be valuable to identify rapidly rising level
- Daily CBC to identify bleeding or severe thrombocytopenia
- aPTT may be elevated in patients with COVID-19 and may be unreliable for heparin infusion monitoring which may necessitate anti-Xa monitoring for confirmation

- Goal anti-Xa levels: (Note: this is a send out laboratory test)
  - Prophylactic dose enoxaparin: 0.1 – 0.4 IU/mL
  - Treatment dose enoxaparin: 0.5 – 1 IU/mL
  - Treatment dose heparin: 0.3 – 0.7 IU/mL

Discharge Considerations for Anticoagulation:

- If VTE confirmed or treated empirically discharge with oral therapeutic anticoagulation for 3 months
- Severely ill COVID-19 patients may experience continued thrombotic risk post-hospital discharge, consideration for VTE prophylaxis in appropriately selected patients (IMPROVE VTE score ≥ 4 or ≥ 2 AND D-dimer > 2x ULN) without high bleed risk (gastric ulcer, dual antiplatelet, recent bleed)

<table>
<thead>
<tr>
<th>IMPROVE VTE Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous VTE</td>
<td>3</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>2</td>
</tr>
<tr>
<td>Lower limb paresis</td>
<td>2</td>
</tr>
<tr>
<td>Cancer history</td>
<td>2</td>
</tr>
<tr>
<td>ICU stay</td>
<td>1</td>
</tr>
<tr>
<td>Immobilized ≥ 1d</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 60 y</td>
<td>1</td>
</tr>
</tbody>
</table>

If decision for discharge VTE prophylaxis consider:

- Rivaroxaban 10 mg PO daily for 14 – 30 days (caution if CrCL < 30; avoid if CrCL < 15 mL/min)
Anticoagulation References:


Therapeutic Options References:

13. Gilead Website: Remdesivir Use in Renal impairment, accessed 6-3-2020
APPENDIX A: Restrictions, Additional Treatment Considerations and Requirements

GENERAL CONSIDERATIONS:
- High risk of drug interactions exists with any of the suggested therapies for management. Please see link below for table of drug interactions, especially those receiving immunosuppressive therapy. [http://www.covid19-druginteractions.org/](http://www.covid19-druginteractions.org/)

REMDESIVIR:
Laboratory: Testing prior to and during treatment: Perform eGFR, and hepatic laboratory testing prior to initiating remdesivir (VEKLURY) and during use as clinically appropriate. Evaluate for signs/symptoms of infusion reaction.

Recommended Daily Labs: CMP

Remdesivir Warnings and Adverse Effects:
- Hypersensitivity and Infusion-Related Reactions, discontinue remdesivir immediately if a severe infusion-related hypersensitivity reaction occurs.
- Hypotension / Hypertension / Tachycardia / Bradycardia
- Nausea
- Diaphoresis / Shivering / Fever
- Hypoxia / Dyspnea / Wheezing
- Angioedema / Rash
- Increased Risk of Transaminase Elevations
- **Remdesivir should be discontinued** in patients who develop:
  - ALT > 10 times the upper limit of normal during treatment with remdesivir
  - ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR.

Risk of reduced antiviral activity when coadministered with chloroquine or hydroxychloroquine

Pregnancy and lactation considerations:
- Pregnancy: There is limited data on the use of remdesivir during pregnancy. Remdesivir should not be withheld from pregnant patients if it is otherwise indicated.
- Lactation: It is not known whether remdesivir can pass into breast milk. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19

TOCILIZUMAB (ACTEMRA): Restricted
Use is restricted to the following:
- **Infectious Disease physicians (confirmed or presumptive positive COVID-19 patients)**
- **Critical Care providers (confirmed COVID-19 patients) when the patient meets the criteria outlined in MCHS COVID-19 Inpatient Treatment Guideline**

Mechanism: Humanized monoclonal antibody; interleukin 6 (IL-6) receptor antagonist; used for cytokine storm related to COVID-19

Administration: infuse over 60 min in dedicated IV line

Warnings and Adverse Effects:
- Serious and potentially fatal infections including reactivation of latent TB (if benefit outweighs risk in treatment of COVID-19, prescriber may defer TB testing), monitor for signs and symptoms of infection during and after treatment
  - Infection has been reported at a higher incidence in elderly patients compared with younger adults
- Neutropenia and thrombocytopenia (platelet count < 50,000 per mm$^3$ and ANC < 1,000 per mm$^3$)
- Hypersensitivity reactions including anaphylaxis
- Hepatic injury, avoid with ALT or AST > 10 times the upper limit of normal, use not recommended in patients with active hepatic disease; initiation in rheumatoid arthritis (RA) and giant cell arteritis (GCA) patients with baseline ALT or AST > 1.5 × ULN is not recommended.
- Gastrointestinal perforation, use with caution in those at increased risk
- Demyelinating CNS disease: Use with caution in patients with preexisting or recent onset CNS demyelinating disorders; rare cases of CNS demyelinating disorders (multiple sclerosis and chronic inflammatory demyelinating polyneuropathy) have occurred
- Hyperlipidemia - Therapy has been associated with increases in total cholesterol, triglycerides, low-density lipoprotein, and/or high-density lipoprotein.
Pregnancy considerations: There are insufficient data to determine whether there is a tocilizumab-associated risk for major birth defects or miscarriage. Monoclonal antibodies are actively transported across the placenta as pregnancy progresses (with greatest transfer during the third trimester) and may affect immune responses in utero in the exposed fetus. Decisions about tocilizumab administration during pregnancy must include shared decision-making between the pregnant individual and their health care provider, considering potential maternal benefit and fetal risks. Pregnancy registry available, providers are encouraged to call.

**SARILUMAB (KEVZARA): Restricted**

**Use is restricted to the following:**
- Infectious Disease physicians (confirmed or presumptive positive COVID-19 patients)
- Critical Care providers (confirmed COVID-19 patients) when the patient meets the criteria outlined in MCHS COVID-19 Inpatient Treatment Guideline
- Use only if tocilizumab not available

**Mechanism:** humanized monoclonal antibody; an interleukin 6 (IL-6) receptor antagonist; approved for treatment of rheumatoid arthritis (RA)

**Administration:** infuse over 60 min in dedicated IV line, with a 0.2-micron filter

**Warnings and Adverse Effects:**
- Serious and potentially fatal infections including reactivation of latent TB (if benefit outweighs risk in treatment of COVID-19, prescriber may defer TB testing), monitor for signs and symptoms of infection during and after treatment
  - Infection has been reported at a higher incidence in elderly patients compared with younger adults
- Avoid use of sarilumab in patients with an active infection.
- Do not initiate if ANC is <2,000/mm³, platelets are <150,000/mm³, or if ALT or AST are >1.5 times ULN
- Hepatic impairment: Use is not recommended in patients with active hepatic disease or hepatic impairment.
- Hypersensitivity reactions including anaphylaxis
- Gastrointestinal perforation, use with caution in those at increased risk
- Hyperlipidemia - Therapy has been associated with increases in triglycerides, LDL, and/or HDL
- The effectiveness of oral contraceptives may be decreased during therapy and for several weeks after sarilumab is discontinued.

**Pregnancy considerations:**
Sarilumab is a humanized monoclonal antibody (IgG1). Potential placental transfer of human IgG is dependent upon the IgG subclass and gestational age, generally increasing as pregnancy progresses. A pregnancy registry has been established to monitor outcomes of women exposed to sarilumab during pregnancy. Health care providers or pregnant patients are encouraged to register.

**BARICITINIB (OLUMIANT): Restricted**

- Infectious Disease physicians (confirmed or presumptive positive COVID-19 patients)

**Mechanism:** inhibits Janus kinase (JAK) enzymes, resulting in a reduction of serum IgG, IgM, IgA, and C-reactive protein; approved for treatment of rheumatoid arthritis (RA)

**Administration:** Oral or per tube, see table for dosing, duration up to 14 days or until hospital discharge, whichever is sooner

<table>
<thead>
<tr>
<th>Lab</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR &gt; 60 mL/min/1.73 m²</td>
<td>4 mg once daily</td>
</tr>
<tr>
<td>eGFR 30 - 60 mL/min/1.73 m²</td>
<td>2 mg once daily</td>
</tr>
<tr>
<td>eGFR 15 - &lt;30 mL/min/1.73 m²</td>
<td>1 mg once daily</td>
</tr>
<tr>
<td>eGFR &lt;15 mL/min/1.73 m²</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Absolute Lymphocyte Count (ALC)</td>
<td>&lt;200 cells/µL = hold until ALC ≥ 200 cells/µL</td>
</tr>
<tr>
<td>Absolute Neutrophil Count (ANC)</td>
<td>&lt;500 cells/µL = hold until ANC ≥ 500 cells/µL</td>
</tr>
</tbody>
</table>

- Drug Interactions: Strong OAT3 Inhibitors: reduce starting dose by one-half
- Avoid use of live vaccines with baricitinib
Warnings and Adverse Effects:

- Baricitinib is not recommended for:
  - Patients who are on dialysis, have end-stage renal disease (ESRD), EGFR <15 mL/min/1.73 m², or have acute kidney injury (AKI)
  - Patients with known active tuberculosis
- Serious venous thrombosis, including pulmonary embolism and arterial thrombosis, have been observed in patients treated with baricitinib. Avoid use in patients with a history of VTE (deep vein thrombosis [DVT] and/or pulmonary embolism [PE]) within the last 12 weeks or have a history of recurrent (>1) VTE (DVT/PE).
  - Prophylaxis for VTE is recommended unless contraindicated
- Serious and potentially fatal infections including reactivation of latent TB (if benefit outweighs risk in treatment of COVID-19, prescriber may defer TB testing), monitor for signs and symptoms of infection during and after treatment
  - Discontinue baricitinib if drug-induced liver injury is suspected while on therapy
  - Hypersensitivity reactions including angioedema, urticaria, and rash
  - Hyperlipidemia - Dose-dependent increases in lipid parameters (eg, total, LDL, and HDL cholesterol) were observed in patients receiving baricitinib
  - Gastrointestinal perforation, use with caution in those at increased risk
  - Hematologic toxicity, including lymphopenia, anemia, and neutropenia, may occur and is generally reversible and managed by treatment interruption
  - Increased incidence of liver enzyme elevation (≥5 × ULN for ALT and ≥10 × ULN for AST) was observed in patients taking baricitinib. Monitor LFTs as clinically indicated; interrupt therapy if LFTs are increased and drug-induced liver injury is suspected.

Pregnancy considerations:
Baricitinib should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus. Consistent with the mechanism of action, embryo-fetal toxicities including skeletal anomalies and reduced fertility have been observed in animals dosed in excess of the maximum human exposure. The limited human data on use of baricitinib in pregnant women are not sufficient to inform a drug-associated risk for major birth defects or miscarriage.

Corticosteroids:
Pregnancy considerations:
- Given the potential benefit of decreased maternal mortality, and the low risk of fetal adverse effects for this short course of therapy, the NIH Panel recommends using dexamethasone in pregnant women with COVID-19 who are mechanically ventilated (AIII) or who require supplemental oxygen but who are not mechanically ventilated (BIII).
- Corticosteroid therapy in pregnancy is considered appropriate to control clinically active maternal illness. Fetal considerations may guide steroid choice.

Additional considerations:
- It is unknown whether other corticosteroids, such as methylprednisolone, prednisone, or hydrocortisone, have a similar benefit as dexamethasone. Dexamethasone lacks mineralocorticoid activity.
- The equivalent doses of other corticosteroids to dexamethasone 6mg are:
  - methylprednisolone 32mg which may be administered once daily or in two divided doses daily
  - prednisone 40mg once daily
  - hydrocortisone 80mg twice daily

Hydroxychloroquine (Plaquenil): The FDA has withdrawn the EUA for use in COVID-19.
- Coadministration of remdesivir and hydroxychloroquine is not recommended based on an antagonistic effect on the antiviral activity of remdesivir.

Sotrovimab:
Treatment: The U.S. FDA has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product, sotrovimab, for the treatment of mild to moderate COVID-19 in adult and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. The authorized dosage is one IV infusion of 500mg administered as soon as possible after a positive test and within 10 days of symptom onset.
sotrovimab is not authorized for use in patients:
  o who are hospitalized due to COVID-19, OR
  o who require oxygen therapy due to COVID-19, OR
  o who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.

- monoclonal antibodies, such as sotrovimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation

**Monoclonal antibodies and COVID-19 Vaccine:** The Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices (ACIP) recommends:

- Passive antibody product used for post-exposure prophylaxis: defer COVID-19 vaccination for 30 days
- Passive antibody product used for COVID-19 treatment: defer COVID-19 vaccination for 90 days

This is a precautionary measure to avoid potential interference of monoclonal antibody treatment specifically with vaccine-induced immune responses.

Vaccines other than COVID-19 vaccines, including inactivated and live vaccines, may be administered without regard to timing of anti-SARS-CoV-2 monoclonal antibodies.

**Vaccinated people who subsequently develop COVID-19**

For vaccinated people who subsequently experience COVID-19, prior receipt of a COVID-19 vaccine should not affect treatment decisions (including use of monoclonal antibodies, convalescent plasma, antiviral treatment, or corticosteroid administration) or timing of such treatments.
COVID-19 Disease Course

**WEEK ONE (can extend through day 10):**
- Viral replication phase
  - Incubation period (exposure to symptoms) = 2-14 days, Delta and Omicron variant symptom onset typically shorter

**WARNING:** steroids during this phase and prior to respiratory symptoms do not decrease mortality and may cause harm

**WEEK TWO, 7-14 days from symptom onset:**
- Early inflammatory phase, earlier onset in elderly and with comorbidities
  - Hypoxemia, coagulation dysfunction
  - Virus enters lung → pneumonia and related symptoms start to develop
  - Immune system may begin to hyper-respond. WBC release chemokines to kill virus-infected cells making it difficult for gas exchange. Patients may need oxygen supplementation.
  - Persistent or worsening hypoxemia despite improving CXR, consider PE

**WEEKS THREE AND FOUR:**
- Hyper-inflammatory phase
  - Immune system hyper-responds and proinflammatory cytokines released, hypercoagulability
  - Patients can develop ARDS and other organ failures
  - If patient worsening, look for potential secondary bacterial/ fungal infections
  - Persistent or worsening hypoxemia despite improving CXR, consider PE

**Treatments:**
- monoclonal antibodies, antivirals (remdesivir)
- dexamethasone, remdesivir, tocilizumab (IL-6 inhibitor), anticoagulation