COVID-19 Pharmacotherapy Treatment Guidance

March 30, 2021
What's Changed this Version: March
Update of Monoclonal Antibody section to recommend use a combination monoclonal antibody product; removal of bamlanivimab monotherapy.
OVERVIEW

There are many ongoing clinical trials and data is emerging frequently. Use of investigational anti-COVID-19 therapeutics should be done under approved, randomized, controlled trials whenever feasible.

THERAPEUTICS

This information is provided to share information to help guide treatment conversations. State mandates, medication availability/shortages, and access to Infectious Disease resources may impact some of these recommendations at given sites. As additional information becomes available, this information will be updated accordingly.

- **Prophylaxis:** Evidence does not support use of Hydroxychloroquine, or any other agent, for prophylaxis against COVID-19
- **Treatment:** Assessment of Evidence for COVID-19-Related Treatments, updated regularly, is available in the IDSA COVID-19 Guidelines, NIH COVID Treatment Guidelines and within the ASHP COVID resource center: ASHP COVID Evidence Assessment

<table>
<thead>
<tr>
<th>Patient Subset</th>
<th>Therapeutics</th>
<th>Comments</th>
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</table>
| **OUTPATIENT** Mild-Moderate Disease Outpatient with confirmed COVID-19 | Clinical observation & supportive care | **Monoclonal Antibody Comments**
| | < AND, CONSIDER > Monoclonal Antibody For High-Risk Patients (see comments) | • See full Monoclonal Antibody section below for patient criteria, product selection, dose, contraindications, adverse effects and monitoring
| | **Scarcity supply (Monoclonal Antibody)** | • In the setting of limited supplies, consult local COVID command center for equitable allocation process |
| **INPATIENT NON-SEVERE DISEASE** Hospitalized with confirmed or suspected COVID-19 without any severe disease criteria | Clinical observation & supportive care | **Remdesivir Comments**
| | < AND, CONSIDER > Remdesivir for 1-5 days (see comments) | • Consider for patients with at high risk of disease progression
| | **Duration of 5 days or until hospital discharge**, whichever comes first | • See full Remdesivir section below for dose, contraindications, adverse effects, monitoring and drug interactions |
| **INPATIENT SEVERE DISEASE – NOT INTUBATED** Confirmed or suspected COVID plus either of the following: | Supportive Care <AND> | **Corticosteroid Comments**
| | For patients requiring supplemental oxygen: Dexamethasone 6 mg PO/IV Daily X 10 days* | • Duration of 10 days or until hospital discharge
| | < AND > Remdesivir for 1-5 days (see comments) | • If dexamethasone is unavailable, equivalent doses of an alternative glucocorticoid may be used (see corticosteroid section)
| | <AND, CONSIDER > IL-6 inhibitor | **Remdesivir Comments**
| | < AND, CONSIDER > Convalescent Plasma, if available (see comments) | • Treatment with remdesivir earlier in the course of disease has been associated with better outcomes compared to initiation after mechanical ventilation. Also refer remdesivir comments above.
| **INPATIENT SEVERE DISEASE – INTUBATED/ECMO** Confirmed or suspected COVID plus either of the following: | Supportive Care <AND> | **IL-6 Inhibitor Comments**
| | For patients requiring mechanical ventilation | • Consultation with Infectious Diseases and/or Critical Care is recommended prior to treatment
| | Dexamethasone 6 mg PO/IV Daily X 10 days* | • See full IL-6 Inhibitor Section for detailed patient selection, exclusion criteria, dose, adverse effects, and monitoring.
| | <AND, CONSIDER > IL-6 inhibitor | **Convalescent Plasma Comments**
| | **Duration of 5 days or until hospital discharge** whichever comes first | • See Convalescent Plasma Section for patient selection information
| | **Benefit from convalescent plasma is primarily early in disease course, prior to need for mechanical ventilation.** Treatment with convalescent plasma should be approved by Infectious Diseases and/or a Critical Care Provider at sites with these services prior to dispensing | *Other Comments*: Treatment with remdesivir is not recommended for initiation after mechanical ventilation. Courses of remdesivir started prior to need for mechanical ventilation may be completed |

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MONOClonAL ANTIBody THERAPY PATIENT SELECTION, DOSING, AND MONITOrING

- The U.S. Food and Drug Administration (FDA) has issued Emergency Use Authorizations (EUA) for three unapproved monoclonal antibody products including bamlanivimab, the combination of bamlanivimab and etesevimab, and the combination of casirivimab and imdevimab for outpatient treatment of mild to moderate (COVID-19) in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe disease and/or hospitalization.
  - Prior to treatment the parent/caregiver should be educated with the information within, and provided with, the based on product administered.
  - The following information must be documented in the patient's medical record: The patient/caregiver was given the Fact Sheet, informed of alternatives to receiving monoclonal antibody, and informed that monoclonal antibodies are an unapproved drug that is authorized for use under an EUA.
- The NIH and IDSA guidelines recommend use of bamlanivimab/etesevimab among ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease. Circulating SARS-CoV-2 viral variants may be associated with resistance to monoclonal antibodies; please see information in the product selection information below.
- In patients admitted to the hospital for management of conditions other than treatment of COVID-19, who are diagnosed with COVID-19 and experiencing mild-to-moderate symptoms, monoclonal antibody is a reasonable treatment option if the patient meets FDA EUA for high risk. Therapy should be prescribed after informed decision-making for patients that place a high value on the uncertain benefits and a low value on uncertain adverse events.

Limitations of authorized use:
- Monoclonal antibody therapy is not authorized for use in patients who are hospitalized due to COVID-19, who require oxygen therapy due to COVID-19, or 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.
- Benefit of treatment with monoclonal antibody therapy has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

PATIENTS AT HIGH RISK DISEASE PROGRESSION:
High risk is defined as patients who meet at least one of the following criteria:
  - Adult patients (age ≥ 18) AND have any of the following:
    - ≥ 65 years of age
    - Body mass index (BMI) ≥ 35
    - Immunosuppressive disease or who are currently receiving immunosuppressive treatment
    - Chronic kidney disease
    - Diabetes Mellitus
    - ≥ 55 years of age AND have cardiovascular disease, hypertension, or chronic obstructive pulmonary disease/other chronic respiratory disease.
  - Patients that are 12 – 17 years of age, who weigh at least 40 kg, AND have any of the following:
    - BMI ≥85th percentile for their age and gender based on CDC growth charts https://www.cdc.gov/growthcharts/clinical_charts.htm, OR
    - Asthma, reactive airway or other chronic respiratory disease that requires daily medication for control
    - Sickle cell disease
    - Congenital or acquired heart disease
    - Neurodevelopmental disorders (i.e., cerebral palsy)
    - A medical-related technological dependence (i.e. tracheostomy, gastrostomy, or positive pressure ventilation not related to COVID)

MONOClonAL ANTIBody CONTRAINDICATIONS AND PRECAUTIONS:
- No contraindications to therapy currently exist.
- There are limited clinical data available for monoclonal antibody therapy. Serious and unexpected adverse events may occur that have not been previously reported with bamlanivimab use.
- Monoclonal antibodies are administered by intravenous (IV) infusion in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.
MONOCLONAL ANTIBODY NURSING CONSIDERATIONS

Hypersensitivity Including Infusion-Related and Anaphylactic Reactions:

- There is a potential for serious hypersensitivity reaction, including anaphylaxis, with administration of monoclonal antibodies. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive therapy.
- Signs and symptoms of infusion related reactions may include fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, dizziness. If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care.

MONOCLONAL ANTIBODY PRODUCT SELECTION AND DOSING TABLES

- Given the sustained increase in SARS-CoV-2 viral variants that are resistant to bamlanivimab alone, it is recommended to use a combination monoclonal antibody product that is expected to retain activity to some of these variants.
- Circulating SARS-CoV-2 viral variants may be associated with resistance to monoclonal antibodies. Health care providers should use information on the prominent local variant proportions, information from state and local health authorities, and the Antiviral Resistance information in each of the product fact sheets to guide treatment decisions on antibody product selection.

BAMLANIVIMAB AND ETESevinMAB DOSING TABLE
For full details on dose preparation and infusion times, please refer to the Bamlanivimab and Etesevimab EUA Fact Sheet for Health Care Providers. Prior to treatment the parent/caregiver should be educated with the information within, and provided with, the Fact Sheet for Patients, Parents and Caregivers for Bamlanivimab and Etesevimab.

<table>
<thead>
<tr>
<th>Adult Dosing</th>
<th>Bamlanivimab 700 mg and Etesevimab x 1 dose</th>
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<tbody>
<tr>
<td>Pediatric Dosing</td>
<td>Treatment of high-risk pediatric patients <strong>12 years of age and older and weighing at least 40 kg</strong>. Bamlanivimab and etesevimab is not authorized for patients weighing less than 40 kg.</td>
</tr>
<tr>
<td>Dose Adjustments</td>
<td>Renal: No dosage adjustment is recommended in patients with renal impairment. Hepatic: No dosage adjustment is recommended in patients with mild hepatic impairment. Bamlanivimab and etesevimab has not been studied in patients with moderate or severe hepatic impairment.</td>
</tr>
</tbody>
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CASIRIVIMAB AND IMDEVIMAB DOSING TABLE
For full details on dose preparation and infusion times, please refer to the Casirivimab and Imdevimab EUA Fact Sheet for Health Care Providers. Prior to treatment the parent/caregiver should be educated with the information within, and provided with, the Fact Sheet for Patients And Parent/Caregivers Emergency Use Authorization (EUA) Of Casirivimab and Imdevimab.

<table>
<thead>
<tr>
<th>Adult Dosing</th>
<th>Casirivimab 1200 mg and Imdevimab 1200 mg (combined total dose of 2400 mg) x 1 dose</th>
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<tbody>
<tr>
<td>Pediatric Dosing</td>
<td>Treatment of high-risk pediatric patients <strong>12 years of age and older and weighing at least 40 kg</strong>. Casirivimab and Imdevimab is not authorized for patients weighing less than 40 kg.</td>
</tr>
<tr>
<td>Dose Adjustments</td>
<td>Renal: No dosage adjustment is recommended in patients with renal impairment. Hepatic: The effect of hepatic impairment on casirivimab and imdevimab is unknown.</td>
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REMDesivir Patient Selection, Dosing, and Monitoring

- Remdesivir (Veklury®) is FDA approved for adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization.
  - Based on available clinical data, benefit with remdesivir treatment has been primarily demonstrated for patients early in the course of disease who are in the hospital requiring supplemental oxygen.
  - For hospitalized patients not requiring supplemental oxygen, remdesivir can be considered for patients at risk of disease progression. These include patients that are older (over the age of 65 years), with a BMI above 35, or who have an underlying medical condition increases the risk for severe.
- The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the unapproved emergency use of the remdesivir for pediatric patient less than 40 kg hospitalized with of suspected or
laboratory confirmed coronavirus disease 2019 (COVID-19). For full details please refer to the FACT SHEET FOR HEALTH CARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF VEKLURY® (remdesivir)

- If remdesivir is initiated in a PUI who subsequently tests negative by molecular PCR testing, discontinue remdesivir; consider consultation with Infectious Diseases if COVID-19 still clinically likely
- Prior to treatment for pediatric patients ages less than 12 or weight less than 40 kg the parent/caregiver should be provided information consistent with the "Fact Sheet for Patients And Parent/Caregivers Emergency Use Authorization (EUA) Of Remdesivir For Coronavirus Disease 2019 (COVID-19)"
  - The following information must be documented in the patient’s medical record: The patient/caregiver was given the Fact Sheet, informed of alternatives to receiving remdesivir, and informed that remdesivir is an unapproved drug that is authorized for use under EUA.

REMDESIVIR CONTRAINDICATIONS AND PRECAUTIONS:

- Remdesivir should not be initiated in patients with ALT ≥ 5 times the upper limit of normal at baseline
- Accumulation of the IV vehicle sulfobutyl-ether beta-cyclodextrin sodium (SBECOD) occurs in patients with renal impairment. The FDA approval does not recommend use for adult patients with eGFR less than 30 mL per minute. After consideration of risk and benefit, remdesivir can be used with caution in adults and pediatric patients with eGFR less than 30 mL per minute or in full-term neonates (>2 days) with serum creatinine clearance ≥ 1 mg/dL.

Considerations in pregnancy
- No adverse embryo-fetal events seen in animal models, however there is insufficient data in humans
- Remdesivir should be used only if benefit exceeds the potential risk to the mother and fetus.

REMDESIVIR DOSING TABLE
For full details on dose preparation, please refer to the Remdesivir Package Insert for adults, and for pediatrics the FACT SHEET FOR HEALTH CARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF VEKLURY® (remdesivir)

<table>
<thead>
<tr>
<th>Adult Dosing</th>
<th>Treatment of hospitalized COVID-19 patients (Remdesivir Package Insert)</th>
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<tr>
<td></td>
<td>• Initial: 200 mg IV (over 30-120 minutes) as a single dose on Day 1</td>
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<td>• Maintenance: 100 mg IV (over 30-120 minutes) once daily for a total duration of 5 days</td>
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<tr>
<th>Pediatric Dosing</th>
<th>Treatment of hospitalized COVID-19 patients</th>
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<tbody>
<tr>
<td></td>
<td>• Patients weighing 3.5 to 39.9 kg (EUA, HealthCare Provider Factsheet)</td>
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<tr>
<td></td>
<td>o Must use lyophilized powder formulation</td>
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<td></td>
<td>o Initial: 5 mg/kg IV (over 30-120 minutes) as a single dose on Day 1</td>
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<tr>
<td></td>
<td>o Maintenance: 2.5 mg/kg IV (over 30-120 minutes) once daily for a total duration of 5 days</td>
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<tr>
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<td>• Patients 12 years and older and weighing ≥40 kg: See adult dosing (Remdesivir Package Insert)</td>
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| Duration | Based on current available data, Trinity recommends a 5-day course for all patients
|          | Patients should not be held in the hospital solely for the purpose of completing 5 days of remdesivir therapy. If patient is deemed clinical stable for discharge prior to completion of 5 days course, discontinue the remdesivir and discharge to the appropriate next level of care (per NIH guidelines)
|          | The optimal duration of Remdesivir treatment for COVID-19 is unknown

| Dose Adjustments | Renal: No pharmacokinetic data for mild or moderate renal impairment. Hepatic: No pharmacokinetic data for mild or moderate hepatic impairment. Do not use in patients with AST/ALT elevations >5x the upper limit of normal. |

REMDESIVIR MONITORING

- Prior to initiation, and daily during remdesivir therapy, monitor hepatic function tests (ALT, AST, bilirubin, alkaline phosphatase), prothrombin time (PT/INR) and renal function tests (serum creatinine, CrCl/eGFR). Remdesivir is not recommended in adults and pediatric patients with eGFR less than 30 mL per minute unless the potential benefit outweighs the potential risk. Consider discontinuing remdesivir if ALT levels increase to greater than 10 times the upper limit of normal. Discontinue remdesivir if ALT elevation is accompanied by signs or symptoms of liver inflammation.
- If a serious and unexpected adverse event occurs and appears to be associated with the use of remdesivir, the prescribing health care provider and/or the provider’s designee should complete and submit a MedWatch form to FDA Remdesivir Nursing Considerations.
Hypersensitivity Including Infusion-Related and Anaphylactic Reactions: Hypersensitivity reactions including infusion-related and anaphylactic reactions have been observed during and following administration of remdesivir. See nursing considerations below.

**Remdesivir Nursing Considerations**

- Hypersensitivity Including Infusion-Related and Anaphylactic Reactions: Hypersensitivity reactions including infusion-related and anaphylactic reactions have been observed during and following administration of remdesivir. Signs and symptoms may include hypotension, tachycardia, bradycardia, dyspnea, wheezing, angioedema, rash, nausea, vomiting, diaphoresis, and shivering. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration of remdesivir and initiate appropriate treatment.

**Remdesivir Adverse Reactions**

- An adverse reaction associated with remdesivir in clinical trials in healthy adult subjects was increased liver transaminases. Additional adverse reactions associated with the drug, some of which may be serious, may become apparent with more widespread use.

- Other adverse effects with incidence ≥10%
  - Constipation (14%) [15% in placebo group]; Hypoalbuminemia (13%) [15% in placebo group]; Hypokalemia (12%) [14% in placebo group]; Anemia (12%) [15% in placebo group]; Thrombocytopenia (10%); Increased bilirubin (10%)

**Remdesivir Drug Interactions**

- Risk of Reduced Antiviral Activity When co-administered with Chloroquine or Hydroxychloroquine: coadministration of remdesivir and chloroquine phosphate or hydroxychloroquine sulfate is not recommended based on in vitro data demonstrating an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of Remdesivir.
- In vitro, remdesivir is a substrate for drug metabolizing enzymes CYP2C8, CYP2D6, and CYP3A4, and is a substrate for Organic Anion Transporting Polypeptides 1B1 (OATP1B1) and P-glycoprotein (P-gp) transporters. In vitro, remdesivir is an inhibitor of CYP3A4, OATP1B1, OATP1B3, BSEP, MRP4, and NTCP. The clinical relevance of these in vitro assessments has not been established. Please refer to [http://www.covid19-druginteractions.org/](http://www.covid19-druginteractions.org/)

**Convalescent Plasma**

The FDA has authorized an Emergency Use Authorization (EUA) for emergency use of COVID-19 convalescent plasma (CP) for the treatment of hospitalized patients with COVID-19. The following information highlights the EUA provider information, please see the full EUA document for complete details. Full details on the collection, testing, labeling, and recordkeeping accompanying the use of CP is available here: [Investigational COVID-19 Convalescent Plasma Guidance for Industry](http://www.covid19-druginteractions.org/).

Fact sheets for Convalescent Plasma EUA have been created for both health care providers and patients.

**Convalescent Plasma: Patient Selection**

- The EUA is based on a review of historical evidence using convalescent plasma in prior outbreaks of respiratory viruses, certain preclinical evidence, results from small clinical trials of convalescent plasma conducted during the current outbreak, and data obtained from the ongoing expanded access program indicating that it is reasonable to believe that the known and potential benefits of COVID-19 convalescent plasma outweigh the known and potential risks.
- Evidence suggests that benefit of convalescent plasma is primarily early in disease course, prior to need for mechanical ventilation. Randomized trials of convalescent plasma given to patients later in the course of disease have demonstrated disparate results.
- COVID-19 convalescent plasma should not be considered a new standard of care for the treatment
- Use in specific patient populations:
  - Safety and effectiveness of COVID-19 convalescent plasma in the pediatric population (< 18 years old), pregnant and nursing women has not been evaluated. Convalescent plasma should be used in these patient populations only if the potential benefit justifies the potential risk for the child or mother and the fetus.

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CONVALESCENT PLASMA: ORDERING AND CONSENT

- Orders for convalescent plasma will be entered in the EMR according via local process to order plasma blood products. A notation should be present on the order to denote the requested product is for Convalescent Plasma.
- Whenever possible, prior to administration the health care provider administering COVID-19 convalescent plasma must provide recipients with the Fact Sheet for Patients/Caregivers and must communicate the following information to the recipients:
  1) The FDA has authorized emergency use of COVID-19 convalescent plasma, which is not an FDA-approved biological product; 2) The patient or caregiver has the option to accept or refuse administration of COVID-19 convalescent plasma; 3) The significant known and potential risks and benefits of COVID-19 convalescent plasma and the extent to which such risks and benefits are unknown; and 4) Information on available alternative treatments and the risks and benefits of those alternatives.
- If providing the above information will delay the administration of COVID-19 convalescent plasma to a degree that would endanger the lives of patients, the information must be provided to the patients as soon as practicable after convalescent plasma is administered.
- Consent processes per local policies and procedures for administration of blood products should be followed. If applicable based on local product availability, a modified blood product consent with the following additional information should be used: “You are receiving a non-EUA compliant unit of plasma that was manufactured under the prior Emergency Access Protocol (EAP)”.

CONVALESCENT PLASMA: PRODUCT QUALIFICATIONS

- COVID-19 convalescent plasma is human plasma collected by FDA registered blood establishments from individuals whose plasma contains anti-SARS-CoV-2 antibodies, and who meet federal regulation donor eligibility. Under the EUA, authorized COVID-19 convalescent plasma will be obtained from registered or licensed blood establishments from donors in the United States or its territories in accordance with applicable regulations, policies, and procedures. The ordering physician should collaborate with local blood bank for local product availability.

CONVALESCENT PLASMA: SUGGESTED DOsing AND Administration

- Per the EUA, the initial first dose is suggested as one COVID-19 convalescent plasma unit (about 200 mL). Due to the limited supply, administration of additional COVID-19 convalescent plasma units are currently not recommended.
- Administer COVID-19 convalescent plasma infusion through a peripheral or central venous catheter according to standard institutional medical and nursing practices for the administration of plasma and local policies and procedures.

CONVALESCENT PLASMA: DOCUMENTATION, ADVERSE reactions, AND RISKS

- Side Effects Known side effects and hazards associated with plasma transfusion include transfusion transmitted infections (e.g. HIV, hepatitis B, hepatitis C), allergic reactions, anaphylactic reactions, febrile nonhemolytic reactions, transfusion-related acute lung injury (TRALI), transfusion-associated cardiac overload (TACO), and hemolytic reactions. Hypothermia, metabolic complications, and posttransfusion purpura have also been described.
- A theoretical risk of administration of convalescent plasma is the phenomenon of antibody dependent enhancement of infection (ADE). ADE has been described in other viral infections and involves an enhancement of disease in the presence of certain antibodies. Another theoretical risk is that antibody administration may attenuate the immune response and make patients more susceptible to re-infection.
- Blood banks must maintain records in accordance with federal requirements and local policies. All suspected adverse reactions should be followed with a thorough investigation according to blood product administration policy.

CORTICOSTEROIDS

The IDSA and NIH COVID-19 Treatment Guidelines recommends using dexamethasone (at a dose of 6 mg per day for up to 10 days) in patients with severe COVID-19 who require supplemental oxygen, mechanical ventilation, or ECMO. A large randomized trial, the RECOVERY trial, has reported a significant mortality benefit with dexamethasone 6 mg daily for up to 10 days in patients requiring supplemental oxygen for COVID. In a sub-group analyses of patients without hypoxia not receiving supplemental oxygen, there was no benefit and a trend toward harm with dexamethasone. Dexamethasone is not recommended for patients with non-severe COVID-19 illness, defined as a patient with a SpO2 > 94% not requiring supplemental oxygen.
Dexamethasone has been listed on the FDA drug shortage list since February 2019 and is chronically in sporadic supply. If dexamethasone is unavailable, an equivalent total daily dose of an alternative glucocorticoid such as methylprednisolone 32 mg daily (usually divided as 16 mg BID) and prednisone 40 mg once daily may be used. Systemic glucocorticoids cause a dose-dependent, usually mild, hyperglycemia. Patients with diabetes mellitus or critical illness exhibit higher blood glucose levels while taking glucocorticoids, leading to increased difficulty with glycemic control. Patients receiving corticosteroids should be monitored for hyperglycemia. Clinically significant hyperglycemia that is glucocorticoid-induced are generally treated pharmacologically in the same way that they are in patients with diabetes mellitus or glucose intolerance in the absence of glucocorticoid therapy.

INTERLEUKIN-6 (IL-6) INHIBITORS

Patients with COVID-19 disease may display an exuberant “cytokine storm” reaction. Several randomized clinical trials have evaluated the potential role of IL-6 inhibitors for treatment of COVID-19, producing conflicting results and primarily signifying a lack of benefit on clinical outcomes. The patient selection criteria applied in these trials is highly varied in level of disease severity, concomitant corticosteroid use, and timing of IL-6 therapy in the course of disease. Emerging data from the REMAP-CAP trial has shown a clinical and mortality benefit with the IL-6 inhibitors Tocilizumab and Sarilumab in combination with corticosteroids for treatment of COVID-19 in a carefully selected patient population. The main differentiator in patient selection applied in the REMAP-CAP trial is the use of IL-6 inhibitors early in the course of disease in patients with severe symptoms (defined as invasive or non-invasive mechanical ventilation or via high flow nasal cannula if flow rate >30 L/min and FIO2 >0.4 or need for vasopressor infusion). In contrast, Veiga et al. was stopped early due to lack of clinical benefit and a signal for higher mortality in a patient population receiving supplemental oxygen or mechanical ventilation along with abnormal levels of at least two serum biomarkers (C reactive protein, D dimer, lactate dehydrogenase, or ferritin). The majority of patients in the Veiga trial were receiving respiratory support with supplemental oxygen only, where REMAP-CAP required higher levels of respiratory support. The preliminary report for the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial has demonstrated that the IL-6 inhibitor tocilizumab reduces the risk of death when given to hospitalized patients with severe COVID-19. The study also showed that tocilizumab shortens the time until patients are successfully discharged from hospital and reduces the need for a mechanical ventilator. These benefits were seen in all patient subgroups, including those requiring oxygen via a simple face mask through to those requiring mechanical ventilators in an intensive care unit.

Given discordant trial results from the REMAP-CAP trial, RECOVERY, and Veiga trials consultation with ID or Critical care is recommended prior to treatment for cautious patient selection.

- It is recommended that IL-6 inhibitor therapy, given in combination with corticosteroids, is considered for patients exhibiting rapid progression of respiratory failure with evidence of inflammatory mediator elevation
- Treatment with the combination of an IL-6 inhibitor with corticosteroids appears to be most effective when given earlier in the course of disease (within 2 days of admission)
- We recommend AGAINST IL-6 therapy based on inflammatory markers levels alone

IL-6 CONTRAINDICATIONS:

- IL-6 inhibitors therapy should not be initiated for the following patients:
  - Co-existing infection that might be worsened by IL-6 inhibitors
  - A pre-existing condition or treatment resulting in ongoing immunosuppression
  - ALT ≥ 5 times the upper limit of normal (ULN) at baseline (caution if hepatic enzymes are >1.5X ULN)
  - Baseline platelet count of less than 50,000/mm3
  - Baseline absolute neutrophil count of less than 2,000/mm3

IL-6 INHIBITOR DOSING

<table>
<thead>
<tr>
<th>Adult Dosing</th>
<th>Tocilizumab should be administered as a single intravenous infusion at a dose of 8 mg per kg, up to a maximum dose of 800 mg (infused over at least 60 min)</th>
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<tr>
<td></td>
<td>Sarilumab should be administered as a single dose of 400mg as an intravenous infusion. No additional doses should be administered.</td>
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</table>
IL-6 INHIBITOR ADVERSE REACTIONS

The rate of serious adverse reactions in patients receiving IL-6 inhibitors in randomized trials to date, including the REMAP-CAP trial, did not differ significantly from standard care/placebo comparators. Known adverse reactions associated with IL-6 inhibitors include (from package insert for non-COVID related indications):

- **Serious Infections**: Serious infections have occurred in patients receiving IL-6 inhibitors. Patients with co-existing infections that might be worsened by IL-6 inhibitors were excluded from REMAP-CAP. Do not use IL-6 inhibitors with known active tuberculosis.
  - US Boxed Warning from **Tocilizumab package insert**: Serious and potentially fatal infections (including active tuberculosis, invasive fungal, bacterial, viral (including Herpes Zoster), protozoal, and other opportunistic infections) have been reported in patients receiving tocilizumab. Prior to treatment initiation, evaluate tuberculosis exposure, history of or current opportunistic infection, underlying conditions predisposing to infection, or patients at risk of endemic tuberculosis or endemic mycosis. Do not administer tocilizumab to a patient with an active infection, including localized infection.

- **Hypersensitivity**: May cause hypersensitivity or anaphylaxis; Medications for the treatment of hypersensitivity reactions should be available for immediate use.

- **GI perforation**: Use with caution in patients at increased risk for GI perforation; perforation has been reported, typically secondary to diverticulitis.

- **Hematologic effects**: Neutropenia and thrombocytopenia may occur. Monitor neutrophils and platelets.

- **Hepatic effects**: Hepatic injury, resulting in liver transplant or death, has been reported. Monitor LFTs prior to therapy initiation and during treatment.

- **Hyperlipidemia**: Therapy is associated with increases in total cholesterol, triglycerides, LDL, and/or HDL; monitor ~4 to 8 weeks after initiation, then subsequently according to current guidelines.

IL-6 INHIBITOR MONITORING

- **Prior to therapy initiation**: Neutrophils, platelets, and liver function (ALT/AST, alkaline phosphatase, and total bilirubin) to evaluate for exclusion criteria. Do not initiate treatment for COVID-19 patients with baseline ALT or AST above 5x the upper limit of normal. Do not initiate treatment in patients with ANC <2,000/mm3 or platelet count <50,000/mm3.

- **Monitor all patients for signs and symptoms of hypersensitivity reactions, infection (prior to, during, and after therapy); and signs and symptoms of CNS demyelinating disorders**

IL-6 INHIBITOR NURSING CONSIDERATIONS

- **Hypersensitivity Reactions, Including Anaphylaxis**: Hypersensitivity reactions including anaphylactic reactions have been observed during and following administration of IL-6 inhibitors. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration and initiate appropriate treatment. Reactions that required treatment discontinuation included generalized erythema, rash, and urticaria. Medications for the treatment of hypersensitivity reactions should be available for immediate use.

IL-6 DRUG INTERACTIONS

- **Tocilizumab** may decrease the serum concentration of CYP3A4 Substrates, however a significant interaction of tocilizumab or sarilumab with either dexamethasone or hydrocortisone is not expected. Please refer to [http://www.covid19-druginteractions.org/](http://www.covid19-druginteractions.org/)
**JANUS KINASE (JAK) INHIBITOR/BARICITINIB**

**BARICITINIB: PATIENT SELECTION**

- There is currently limited information on the use of baricitinib in combination with systemic corticosteroids for treating patients with COVID-19.
  - **Routine use baricitinib is not recommended.** Corticosteroids should be first line therapy for patients requiring supplemental oxygen or mechanical ventilation or ECMO. The EUA states that the use of baricitinib in patients receiving systemic corticosteroids is not precluded however impact of this combination on adverse effects is unknown.
  - Baricitinib may be considered for patients who meet EUA criteria and continue to deteriorate despite remdesivir and corticosteroid therapy after careful consideration of the risks including the adverse effect profile and potential benefits.
- The [U.S. Food and Drug Administration (FDA)](https://www.fda.gov) has issued an Emergency Use Authorization (EUA) for use of baricitinib, in combination with remdesivir, to treat suspected or laboratory-confirmed COVID-19 in hospitalized adults and pediatric patients 2 years or older requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). This is not an FDA-approved use of baricitinib.
  - Prior to treatment the parent/caregiver should be educated with the information within, and provided with, the "Fact Sheet for Patients And Parent/Caregivers. Emergency Use Authorization (EUA) Of Baricitinib" For Coronavirus Disease 2019 (COVID-19)"
  - The following information must be documented in the patient's medical record: The patient/caregiver was given the Fact Sheet, informed of alternatives to baricitinib, and informed that baricitinib is an approved drug that is authorized for the unapproved use under this EUA.
  - Baricitinib is FDA approved for the treatment of Rheumatoid Arthritis. Please see the [package insert](https://www.fda.gov) for more information on the FDA approved indication.

**BARICITINIB CONTRAINDICATIONS AND PRECAUTIONS:**

- There are no known contraindications for baricitinib. However, 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 or for patients with known active tuberculosis.

**BARICITINIB DOSING**

<table>
<thead>
<tr>
<th>Adult Dosing</th>
<th>For adult patients with eGFR ≥60 mL/min/1.73 m2, Baricitinib 4 mg PO/GT once daily for 14 days or until hospital discharge, whichever is first.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric Dosing</td>
<td>The recommended dosage for patients 9 years of age and older is 4 mg PO/GT once daily for 14 days of total treatment or until hospital discharge, whichever is first.</td>
</tr>
<tr>
<td></td>
<td>The recommended dosage for patients ages 2 years through less than 9 years of age is 2 mg PO/GT once daily for 14 days of total treatment or until hospital discharge, whichever is first.</td>
</tr>
<tr>
<td></td>
<td>Baricitinib is not authorized for patients younger than 2 years of age.</td>
</tr>
</tbody>
</table>
| Dose Adjustments | Dose adjustments are required for renal dysfunction, hepatic dysfunction, and drug interactions with strong OAT3 Inhibitors. For full details on dose adjustment, please refer to the "Fact Sheet for Healthcare Providers EUA Of Baricitinib For Coronavirus Disease 2019 (COVID-19)"

**BARICITINIB MONITORING, ADVERSE REACTIONS, AND DRUG INTERACTIONS**

- Prior to initiation, evaluate estimated glomerular filtration rate (eGFR), liver enzymes, and complete blood count at baseline. Repeat testing is thereafter according to local patient management practice. Monitor closely when treating patients with abnormal baseline and post-baseline laboratory values.

**BARICITINIB ADVERSE REACTIONS**

- Serious venous thrombosis, including pulmonary embolism, and serious infections have been observed in COVID-19 patients treated with baricitinib and are known adverse drug reactions of baricitinib.
- Serious Infections: Serious infections have occurred in patients receiving baricitinib. Avoid the use of baricitinib with known active tuberculosis. Consider if the potential benefits outweigh the potential risks of baricitinib treatment in patients with active serious infections other than COVID-19 or chronic/recurrent infections.
• Thrombosis: In hospitalized patients with COVID-19, prophylaxis for venous thromboembolism is recommended unless contraindicated. If clinical features of deep vein thrombosis or pulmonary embolism occur, patients should be evaluated promptly and treated appropriately.
• Hypersensitivity: If a serious hypersensitivity occurs, discontinue baricitinib while evaluating the potential causes of the reaction.
• Other adverse effects with incidence ≥10%
  o Hypoalbuminemia (13%) [15% in placebo group]; Hypokalemia (12%) [14% in placebo group]; Anemia (12%) [15% in placebo group]; Thrombocytopenia (10%); Increased bilirubin (10%)

**Baricitinib Drug Interactions**
• Vaccinations: Avoid use of live vaccines with baricitinib
• Evaluate for drug interactions with strong OAT3 Inhibitors

**Hydroxychloroquine**
• Current IDSA treatment guidelines do not recommend the use of chloroquine (CQ) or hydroxychloroquine (HCQ) in hospitalized patients with COVID-19 outside of a clinical trial. NIH guidelines now recommend against use outside of a clinical trial.
• Recent data from a large randomized controlled trial showed no evidence of benefit for mortality or other outcomes such as hospital length of stay or need for mechanical ventilation of HCQ treatment in hospitalized patients with COVID-19.
• Based on the continued review of the scientific evidence available for hydroxychloroquine sulfate for the treatment of COVID-19, the FDA has revoked the Emergency Use Authorization (EUA) based on this new information and other information discussed in their memorandum.
  o Specifically, the FDA has determined that CQ and HCQ are unlikely to be effective in treating COVID-19 for the authorized uses in the EUA. Additionally, in light of ongoing serious cardiac adverse events and other serious side effects, the known and potential benefits of CQ and HCQ no longer outweigh the known and potential risks for the authorized use.

**Azithromycin**
• Evidence to support the combination of hydroxychloroquine with azithromycin improves clinical outcomes for treatment of COVID-19 is lacking. However, the combination of these drugs is known to increase the likelihood of QTc prolongation which can lead to life-threatening arrhythmias and sudden cardiac death.
• Because of the potential for toxicity, routine use of this combination for inpatient treatment of COVID-19 in the absence of secondary bacterial infection is not recommended. If used, cardiac monitoring as outlined in the Cardiovascular section above, should be followed.
• For outpatients the use of antimicrobial regimens, including azithromycin, are only encouraged under approved conditions for treatment of bacterial pneumonia. Routine use in COVID is not recommended.

**Protease Inhibitors**
• NIH Treatment Guidelines recommend against using lopinavir/ritonavir, or other HIV protease inhibitors, to treat COVID-19 outside of a clinical trial. A trial of adults hospitalized with severe COVID-19 treated with Lopinavir–Ritonavir (Kaletra®) has shown no benefit over supportive care and is not recommended (Cao et al.). Darunavir/cobisistat activity against COVID-19 has not been confirmed, activity is extrapolated from other coronaviruses (SARS/MERS). In the lopinavir-ritonavir arm of the RECOVERY trial there was not improvement in mortality at 28-days compared to usual care (23% vs 22%), nor did the drugs decrease the duration of hospital stay, or the risk of progressing to invasive mechanical ventilation.
• The triple combination of lopinavir, ritonavir and ribavirin with or without interferon beta-1b, may reduce duration of symptoms among patients who have been admitted to the hospital with COVID-19 based on preliminary data. Use of this triple antiviral regimen, and interferon beta-1b, should only be within the context of a clinical trial.
• Oseltamivir and other neuraminidase inhibitors do not appear to have activity against other coronaviruses (SARS), and should be reserved for treatment of influenza.
IVERMECTIN

The NIH have found insufficient evidence to recommend either for or against the use of ivermectin for the treatment of COVID-19. The IDSA panel suggests against ivermectin use outside of the context of a clinical trial. Current evidence with ivermectin has incomplete data or flawed designs, thus both the NIH panel and IDSA recommend well-designed, adequately powered studies to determine the safety and efficacy of ivermectin to treat COVID-19. A randomized trial of ivermectin in outpatients with mild disease did not significantly improve the time to resolution of symptoms or prevent the need for medical care. The FDA issued a warning in April 2020 that ivermectin intended for use in animals should not be used to treat COVID-19 in humans.

ACE INHIBITORS AND ARBs

There is interest in the potential role of ACE-inhibitors and angiotensin receptor blockers (ARBs) in the pathophysiology of this disease since the SARS-CoV-2 virus binds to the ACE2 receptor for cellular entry. However, current guidance from cardiology organizations (i.e. ACC/AHA/HFSA) state that there is not enough evidence to recommend for or against these medications in the setting of the COVID-19 pandemic.

- The HFSA, ACC, and AHA recommend continuation of RAAS antagonists for those patients who are currently prescribed such agents for indications for which these agents are known to be beneficial, such as heart failure, hypertension, or ischemic heart disease.
- In the event patients with cardiovascular disease are diagnosed with COVID-19, individualized treatment decisions should be made according to each patient’s hemodynamic status and clinical presentation. Therefore, be advised not to add or remove any RAAS-related treatments, beyond actions based on standard clinical practice.

NSAIDS

The FDA is aware of news reports stating the use of non-steroidal anti-inflammatory drugs (NSAIDs) could worsen coronavirus disease (COVID-19). However, there is no scientific evidence to support these claims to date. The agency is investigating this issue and currently does not have any specific recommendations to withhold NSAID therapy in these patients. The European Medicines Agency has also issued guidance that there is not enough data to recommend avoiding NSAIDS in COVID patients.

COVID AND CO-INFECTION

Although the exact incidence of co-infection with bacterial pathogens among patients with COVID-19 is unknown, current data suggests it is uncommon (<5%). Empiric antibiotic therapy in patients with confirmed COVID is not recommended in the absence of highly suspected or confirmed bacterial co-infection.

MANAGEMENT OF INFLUENZA CO-INFECTION

At times of co-circulation of influenza and COVID, hospitalized patients should be started on empiric treatment for influenza with oseltamivir as soon as possible, then antiviral treatment can be tailored based on influenza and COVID testing results. For patients with influenza and COVID co-infection, consultation with an Infectious Disease is recommended. Given the benefit of dexamethasone on reducing mortality for patients with severe COVID disease, use should be considered along with the risks and benefits in a co-infected patient. The role of dual antiviral therapy is unknown, but the combination of oseltamivir and remdesivir is not expected to be detrimental.

RESPIRATORY TREATMENTS

Inhaled medications can be delivered either by Metered Dose Inhalers (MDIs) or by nebulization; when delivered by nebulization, these can be aerosol generating. For COVID positive or patients suspected to have COVID, the use of MDIs is preferred when / if available. Collaboration and communication between physician, nursing, respiratory and pharmacy colleagues is necessary to reduce the risk of aerosolizing respiratory secretions induced through nebulization. Please refer to the COVID-19 Patients and Inhaled Respiratory Meds and ED and Urgent Care Inhaled Respiratory Medications for COVID Patients documents on the Trinity Health COVID Resource page.
**PATIENT POSITIONING**

- For non-intubated patients, please see the "Prone Positioning for the Non-intubated Patient" reference on the Trinity Health COVID site.
- For intubated patients, please see the guidance for "Prone Positioning of the Mechanically Ventilated Patient".

**USE OF NEUROMUSCULAR BLOCKER AGENTS AND CONSERVATION**

Neuromuscular blockade (NMB) is implemented when needed to facilitate mechanical ventilation for treatment of moderate or severe acute respiratory distress syndrome (ARDS). The historical supply shortages with these agents has been augmented by the surge in demand due to treatment of COVID-19. Conservation methods are necessary to avoid complete exhaustion of drug supply.

The Society of Critical Care Medicine (SCCM) does not recommend routine use of continuous infusion of neuromuscular blockade for all mechanically ventilated patients or for treatment of mild ARDS. For mechanically ventilated patients and with moderate to severe ARDS, the recommendation is as follows:

**SCCM Recommendations:**

1. For mechanically ventilated adults with COVID-19 and moderate to severe ARDS: We suggest using, as needed, intermittent boluses of neuromuscular blocking agents (NMB), over continuous NMB infusion, to facilitate protective lung ventilation (weak recommendation, low-quality evidence).
2. In the event of persistent ventilator dyssynchrony, the need for ongoing deep sedation, prone ventilation, or persistently high plateau pressures, we suggest using a continuous NMB infusion for up to 48 hours (weak recommendation, low-quality evidence).

Below are the available Trinity Health Formulary Nondepolarizing NMB agents, suggested dosing, and dose considerations:

<table>
<thead>
<tr>
<th>NMB</th>
<th>Onset of Action (MIN)</th>
<th>Duration after INITIAL dose (MIN)</th>
<th>Usual Dose Range#</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisatracurium</td>
<td>1.5 -2</td>
<td>20-35</td>
<td>Intermittent bolus dosing: 0.1 to 0.2 mg/kg/dose. Continuous infusion: Initial rate of 3 mcg/kg/min; Usual dose range of 1- 10 mcg/kg/min</td>
<td>Drug elimination varies based on renal and hepatic function.</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>2.3-3</td>
<td>20-40</td>
<td>Intermittent bolus dosing: 0.1 to 0.2 mg/kg/dose. Continuous infusion: Initial rate of 0.8 mcg/kg/minute; Usual dose range 0.8 to 1.7 mcg/kg/minute</td>
<td>Vagolytic action can cause dose-dependent tachycardia.</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>1-2</td>
<td>22-67</td>
<td>Intermittent bolus dosing: 50 mg initial dose followed by 25 mg dose as needed. Continuous infusion: Initial rate of 8 mcg/kg/min; Usual dose range 8-12 mcg/kg/min</td>
<td></td>
</tr>
</tbody>
</table>
3. Critical care colleagues should familiarize themselves with alternative agents, dosing, and pharmacodynamic profile in preparation for a potential need to shift to these agents based on availability. Atracurium and Pancuronium are non-formulary alternative NMBA agents. Listed below are the suggested dosing and dose considerations:

<table>
<thead>
<tr>
<th>NMBA</th>
<th>Onset of Action (MIN)</th>
<th>Duration after INITIAL dose (MIN)</th>
<th>Usual Dose Range#</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atracurium</td>
<td>2-3</td>
<td>20-35</td>
<td>Intermittent bolus dosing: 0.4 to 0.5 mg/kg/dose# Continuous infusion: 4 to 20 mcg/kg/minute</td>
<td>Can cause histamine release, however clinical effects unlikely. Histamine release can be reduced by slowing the rate of administration.</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>2-3</td>
<td>60-100</td>
<td>Intermittent bolus dosing: 0.06 to 0.1 mg/kg/dose# Continuous infusion: 0.8 to 2 mcg/kg/minute</td>
<td>Avoid, if possible, if history of coronary artery disease. Vagolytic action and sympathetic stimulation can cause dose dependent tachycardia. Long acting agent. Dose adjustment in renal impairment.</td>
</tr>
</tbody>
</table>

**ANTICOAGULATION AND COVID RELATED COAGULOPATHY GUIDANCE**

- Patients infected with COVID-19 are at increased risk of venous thromboembolism due to hospitalization, immobilization, active infection and inflammation, and possibly due to a hypercoagulable state unique to the virus itself. Arterial thrombosis has also been reported.
- COVID-19 infected patients display multiple coagulation abnormalities which may be more prothrombotic than hemorrhagic
- Lab derangements may include elevated d-dimers, prolonged PT/PTT high fibrinogen and sometimes mild thrombocytopenia
- This document is based on expert clinical guidance and current best available information, which is still evolving. This guidance should be used in conjunction with latest evidence and patient-specific characteristics and should not supersede clinical judgment

**ANTICOAGULATION ADMISSION CONSIDERATIONS FOR HIGHLY SUSPECTED OR CONFIRMED COVID**

- Labs on admission: D-dimer, INR/PT, PTT, fibrinogen and CBC with differential
  - Elevated D-dimer is of unknown clinical significance and should not be used as a lone criterion in care decisions
- Inpatient labs every 2-3 days: CBC, PT, PTT, D-dimer, INR/PT, fibrinogen
  - If worsening parameters, consider more aggressive critical care support
  - Do not use blood products to correct non-bleeding coagulopathy
  - There is no evidence for use of TEG in COVID-19 patients to guide decisions regarding anticoagulation and use is **NOT** recommended

**THERAPEUTIC ANTICOAGULATION PRIOR TO ADMISSION**

- If a patient was receiving anticoagulation therapy prior to admission for a co-morbid disease state, continue anticoagulation therapy during COVID admission if no contraindications exist
  - Monitor renal function daily
- Consider switching to enoxaparin or heparin infusion if severe illness, possible drug-interactions with COVID investigational therapies, inability to take PO medications or anticipated procedures
PREVENTION OF VENOUS THROMBOEMBOLISM (VTE) IN HIGHLY SUSPECTED OR CONFIRMED COVID PATIENTS

- All highly-suspected or confirmed COVID-19 patients not on anticoagulation therapy should receive VTE prophylaxis unless contraindicated (e.g., platelet count <25-30K, active bleeding)
- Low molecular weight heparin (enoxaparin), appropriately dose adjusted for renal function and/or weight is the preferred agent for thromboprophylaxis (see Figure 1)
  - Therapy adjustments are required for impaired renal function and/or extremes of weight (see Figure 1)
  - Fondaparinux may be used as an alternative to enoxaparin for patients with heparin induced thrombocytopenia without contraindications
- If pharmacologic prophylaxis is contraindicated, mechanical prophylaxis with intermittent pneumatic compression (IPC) should be consistently applied
- VTE prevention regimens and recommendations include pregnant COVID+ patients. Close collaboration with OB and anesthesiology is recommended in the event of delivery and/or need for epidural anesthesia during hospitalization

**FIGURE 1: VTE PROPHYLAXIS**

<table>
<thead>
<tr>
<th>CrCl &lt; 30 ml/min</th>
<th>29 – 10 ml/min</th>
<th>&lt; 10 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-Critically III</strong></td>
<td>Enoxaparin SubQ*</td>
<td>Heparin SubQ</td>
</tr>
<tr>
<td>Weight</td>
<td>CrCL &gt; 30 ml/min</td>
<td>Enoxaparin 0.5 mg/kg SubQ q12h*</td>
</tr>
<tr>
<td>50-99 kg</td>
<td>40 Daily</td>
<td>30 Daily</td>
</tr>
<tr>
<td>100-150 kg</td>
<td>40 BID</td>
<td>40 Daily</td>
</tr>
<tr>
<td>&gt;150 kg</td>
<td>60 BID</td>
<td>60 Daily</td>
</tr>
<tr>
<td>*For patients &lt;50 kg and age &gt;80 YO, dose adjustment to Heparin 5000 units SubQ q12 hour</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CRITICALLY III (ICU)**

<table>
<thead>
<tr>
<th>CrCL &gt; 30 ml/min</th>
<th>Enoxaparin 0.5 mg/kg SubQ q24h*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCL 29 – 10 ml/min</td>
<td>Enoxaparin 0.5 mg/kg SubQ q24h*</td>
</tr>
<tr>
<td>CrCL &lt; 10 ml/min</td>
<td>Heparin 7500 Units SubQ q12h*</td>
</tr>
<tr>
<td>*For patients &lt;50 kg and age &gt;80 YO, dose adjustment based on multidisciplinary discussion is necessary</td>
<td></td>
</tr>
</tbody>
</table>

**MONITORING**

Every 2-3 days: CrCl, CBC, PTT, PT/INR, D-dimer, fibrinogen

**MONITORING**

DAILY: CrCl and CBC
Every 2-3 days: PTT, INR/PT, D-dimer, fibrinogen

EMPIRIC THERAPEUTIC ANTICOAGULATION FOR COVID RELATED COAGULOPATHY

- Initiation of therapeutic anticoagulation regimens without confirmed or high clinical suspicion of VTE is controversial is not recommended at this time.
- Suspected VTE should be confirmed with diagnostic imaging whenever feasible if patient is stable to do so.
- Severe COVID-19 infections may be associated with significant coagulopathy. Reported microvascular thrombosis is a distinctly different entity from embolic DVT/PE and when present in other inflammatory conditions such as sepsis, which does not respond to anticoagulant therapy and bleeding risk is high.
- Currently anticoagulants are not recommended to treat suspected microvascular thrombosis. In contrast, embolic VTE, responds to anticoagulant therapy.
- In the setting of persistent clotting of lines/devices/filters despite COVID-appropriate VTE prophylaxis and worsening clinical course, intensified anticoagulation may be considered via multidisciplinary discussion with critical care attending, coagulation specialist, or others (path, heme) where available.

EMPIRIC THROMBOLYTIC THERAPY

- Empiric use of thrombolytic (i.e. alteplase) is NOT recommended for COVID-19 associated coagulopathy (outside of a clinical trial).
• Thrombolysis may be considered for COVID-19 patients with confirmed or high suspicion for indications specific to thrombolytic therapy (i.e., acute ischemic stroke, PE, acute myocardial infarction).

**TREATMENT OF VENOUS THROMBOEMBOLISM (VTE) IN HIGHLY SUSPECTED OR CONFIRMED COVID PATIENTS**

• Suspected VTE should be confirmed with diagnostic imaging whenever feasible if patient is stable to do so.
• Initiate therapeutic anticoagulation (unless contraindicated) only when VTE is confirmed or clinical suspicion is high and diagnostic testing is unavailable or not feasible.
• Anticoagulation regimens that require minimal monitoring and RN exposure are preferred when possible (see Figure 2).
• The PTT may be impacted by the virus and thus not reliable in some COVID-19 patients.
  o If available, recommend a correlation is performed between PTT/Anti-FXa at the time IV Unfractionated Heparin (UFH) is started and again if significant worsening of clinical status. Discuss with local laboratory.
• Limit treatment regimens for VTE in COVID+ pregnant patients to enoxaparin or UFH. DOACs are contraindicated in pregnancy and breastfeeding.

**FIGURE 2 : THERAPEUTIC ANTICOAGULATION FOR TREATMENT OF VTE IN COVID PATIENTS**

<table>
<thead>
<tr>
<th>CrCl</th>
<th>Preferred Treatment Regimen for Highly-suspected or Confirmed VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl &gt; 30 ml/min</td>
<td>Enoxaparin 1 mg/kg SubQ q12h</td>
</tr>
<tr>
<td>CrCl 29 – 10 ml/min</td>
<td>Enoxaparin 1 mg/kg SubQ q24*</td>
</tr>
<tr>
<td>CrCl &lt; 10 ml/min</td>
<td>Heparin Infusion for Venous Thromboembolism</td>
</tr>
</tbody>
</table>

**THERAPEUTIC ANTICOAGULATION MONITORING**
DAILY: CrCl and CBC
Every 2-3 days: PTT, INR/PT, D-dimer, fibrinogen

**THROMBOPROPHYLAXIS AND ANTICOAGULATION NURSING CONSIDERATIONS**

• Goals of care include prevention of ischemic injury and dehydration, absence of hemorrhage and restoration of homeostatic coagulation. Collaborate with pharmacist and medical staff regarding appropriate anticoagulant dose.
• Management of care include:
  o Regular assessment for signs/symptoms of bleeding
    ▪ Assess skin for hematoma or mottling; Monitor lab values; Assess capillary refill
    ▪ Assess vital signs, watching for arrhythmias, tachycardia and hypotension
  o Assess neuro status
  o Keep venipuncture to a minimum

**ANTICOAGULATION DISCHARGE CONSIDERATIONS**

**POST HOSPITALIZATION CONSIDERATIONS FOR PATIENTS TREATED WITH THERAPEUTIC ANTICOAGULATION FOR SUSPECTED OR CONFIRMED VTE DURING COVID ADMISSION**

• If acute VTE was confirmed during admission, continue therapeutic anticoagulation at least 3 months then re-assess.
• If VTE was unconfirmed & treated empirically for a patient with high suspicion, continue therapeutic anticoagulation for at least 3 months then re-assess.

**POST HOSPITALIZATION CONSIDERATIONS - VTE PROPHYLAXIS**

• Severely ill COVID-19+ patients may experience prolonged hospital stay, significant deconditioning, post-ICU syndrome and thus may not fully recover to baseline mobility or health status by time of discharge. Patients being discharged from the Emergency Department (ED) with confirmed COVID-19 diagnosis may also be at risk for VTE.
• While no data specific to COVID-19 exist, extended prophylaxis with LMWH or with direct oral anticoagulants (DOACs) in non-COVID-19 patients can reduce the risk of VTE, at the cost of increase in bleeding events, including major bleeding.
• Each COVID-19 patient should have a careful risk assessment on a case-by-case basis based on the presence ongoing risk factors for VTE at the time of discharge.

• VTE prophylaxis beyond discharge from the hospital, may be reasonable on a case-by-case basis and may include COVID-19+ patients who have:
  o Diminished mobility / weakness
  o Active cancer
  o An ongoing inflammatory state

• Patients considered to be at significant continued risk for VTE AND without elevated bleeding risk factors should be considered (no data exists) for:
  o Short-term use (up to 14 days) of prophylactic dose LMWH or DOAC (dose based on weight, renal function, and drug interaction screening\(^3\)).

• Prophylaxis dosing with enoxaparin or DOAC for up to 14 days and re-evaluation after beyond hospitalization may be reasonable in appropriately selected patients with reduced mobility and increased thrombotic risk factors
  o Patient education on the potential bleeding risk and expected benefit is required prior to prescribing post-discharge VTE prophylaxis.

• For those patients admitted for treatment of COVID-19 who may have been on thromboprophylaxis for conditions that existed prior to admission, consider transition back to the previous regimen (consider changes in renal function) post-hospitalization (if the pre-hospitalization condition still exists).
COVID VTE Treatment Risk and Treatment Algorithm

Clinical Suspicion for VTE

VTE unlikely (Wells score PE ≤ 4, DVT < 2)

- Continue VTE prophylaxis with close monitoring for further signs and symptoms of VTE
- Consider discharge on VTE prophylaxis for up to 14 days (see Discharge Considerations)

VTE likely (Wells Score PE >4, DVT ≥ 2)

Wells score elevated\(^1\)
(PE >4 or DVT ≥ 2)
& clinical picture
(acute change in oxygenation)

Low risk for bleeding (VTE-BLEED Score ≥ 2)

VTE treatment\(^a\)

VTE (+) or presumptive

Assess VTE-BLEED score\(^2\)

High risk for bleeding (VTE-BLEED Score ≥ 2)

Consider PE CT or LE DVT scan as per clinical suspicion

VTE treatment\(^a\)

VTE prophylaxis

VTE prophylaxis

VTE (-)

COVID VTE protocol exclusion criteria
If yes to any of these criteria, no further studies should be performed. Otherwise, continue algorithm
- Patient is end of life or comfort care
- VTE imaging would not change management
- Patient would not consent to therapeutic anticoagulation
- Patient already has dx of VTE from another study or other indications for therapeutic anticoagulation

Consider PE CT or LE DVT scan as per clinical suspicion\(^b\)

Continue current management

VTE (+)

For presumptive VTE therapy, arrange for PE CT or LE DVT scan when clinically appropriate and treat accordingly

Discharge with therapeutic anticoagulation and follow-up as appropriate

VTE prophylaxis

No

Yes

a. See Figure 2. Enoxaparin preferred to IV UFH to minimize need for lab monitoring and RN exposure.
b. If imaging can’t be done but suspicion for VTE is high, may consider cautious use of presumptive therapeutic anticoagulation with close monitoring for bleeding
**Modified Wells Score for Assessment of Clinical Likelihood of VTE**

*Not validated in COVID but no other score available*

<table>
<thead>
<tr>
<th>PE Criteria</th>
<th>Pt</th>
<th>DVT Criteria</th>
<th>Pt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs and symptoms of DVT (objectively measured calf swelling and pain with palpation in the deep vein region)</td>
<td>3</td>
<td>Active cancer (patient receiving treatment for cancer within the previous 6 months or currently receiving palliative treatment)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paralysis, paresis, or recent casting or immobilization of the lower extremities</td>
<td>1</td>
</tr>
<tr>
<td>An alternative diagnosis is less likely than PE</td>
<td>3</td>
<td>Recently bedridden for 3 days or more, or major surgery within the previous 12 weeks requiring general or regional anesthesia</td>
<td>1</td>
</tr>
<tr>
<td>Heart rate &gt; 100 beats per minute</td>
<td>1.5</td>
<td>Localized tenderness along the distribution of the deep venous system</td>
<td>1</td>
</tr>
<tr>
<td>Immobilization or surgery in the previous four weeks</td>
<td>1.5</td>
<td>Entire leg swollen</td>
<td></td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>1.5</td>
<td>Calf swelling at least 3 cm larger than that on the asymptomatic side(measured 10 cm below the tibial tuberosity)</td>
<td>1</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1</td>
<td>Pitting edema confined to the symptomatic leg</td>
<td>1</td>
</tr>
<tr>
<td>Malignancy (on treatment, treated in the past six months, or palliative care)</td>
<td>1</td>
<td>Previously documented DVT</td>
<td>1</td>
</tr>
<tr>
<td>OR acute change in O2 req</td>
<td></td>
<td>Collateral non-varicose superficial veins</td>
<td>1</td>
</tr>
<tr>
<td>Alternative diagnosis at least as clinically likely as DVT</td>
<td></td>
<td>Other factors that contribute to bleeding:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cirrhosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Other anti-thrombotic use (e.g. aspirin, clopidogrel, ticagrelor)</td>
<td></td>
</tr>
</tbody>
</table>

**VTE-BLEED Score**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Score</th>
<th>Other factors that contribute to bleeding:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Male with uncontrolled arterial hypertension</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>History of bleeding</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Age ≥ 60 years old</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

**Anticoagulation References:**

REFERENCES:


15. https://rdvcu.gilead.com/


34. Veiga et al. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial; *BMJ* 2021;372:n84; doi: https://doi.org/10.1136/bmj.n84


72. Peter Horby, Wei Shen Lim, Jonathan Emberson, Marion Mafham, Jennifer Bell, Louise Linsell, Natalie Staplin, Christopher Brightling, Andrew Ustianowski, Einas Elmahi, Benjamin Prudon, Christopher Green, Timothy Felton, David Chadwick, Kanchan Rege, Christopher Fegan, Lucy C Chappell, Saul N Faust, Thomas Jaki, Katie Jeffery, Alan Montgomery, Kathryn Rowan, Edmund Juszczak, J Kenneth Baillie, Richard Haynes, Martin J Landray, RECOVERY Collaborative Group medRxiv 2020.06.22.20137273; doi: https://doi.org/10.1101/2020.06.22.20137273


## Version History

<table>
<thead>
<tr>
<th>Version Date</th>
<th>Revisions Made</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/30/2020</td>
<td>Updated Remdesivir compassionate use information.</td>
</tr>
<tr>
<td>4/4/2020</td>
<td>Updated to reflect new FDA released FACT SHEET FOR HEALTH CARE PROVIDERS and expanded information in 'Use of Hydroxychloroquine: Patient Selection, Dosing, and Monitoring&quot; section</td>
</tr>
<tr>
<td>4/28/2020</td>
<td>Added reference to FDA Drug Safety Communication that cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. Added information on Discharging Patients on Hydroxychloroquine</td>
</tr>
<tr>
<td>05/4/2020</td>
<td>Added outpatient pharmacotherapy guidance.</td>
</tr>
<tr>
<td>05/6/2020</td>
<td>Updated patient categories and therapy guidance for Remdesivir and Hydroxychloroquine. Includes updates for Remdesivir based on FDA emergency use authorization for Remdesivir.</td>
</tr>
<tr>
<td>05/13/2020</td>
<td>Recommendation added to limit use of triple antiviral therapy and interferon beta to use in a clinical trial only</td>
</tr>
<tr>
<td>5/20/2020</td>
<td>Updated recommendations on use of Remdesivir in renal impairment and duration of therapy. Nursing considerations comment added.</td>
</tr>
<tr>
<td>5/28/2020</td>
<td>Hydroxychloroquine no longer recommended</td>
</tr>
<tr>
<td>6/4/2020</td>
<td>Revised criteria for use of IL-6 inhibitors</td>
</tr>
<tr>
<td>Date</td>
<td>Description</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>6/16/2020</td>
<td>Information regarding FDA revocation of emergency approval of Hydroxychloroquine added. Remdesivir information updated with revised warnings for drug interactions and hypersensitivity and anaphylactic reactions.</td>
</tr>
<tr>
<td>6/24/2020</td>
<td>Addition of recommendation for dexamethasone/corticosteroid therapy for patients requiring oxygen therapy</td>
</tr>
<tr>
<td>7/13/2020</td>
<td>Convalescent Plasma guidance is updated and added to guidance document. Updated IL-6 section with results of sarilumab trial. NMBA guidance incorporated into the document. Addition of recommendation for glucose monitoring with corticosteroid use.</td>
</tr>
<tr>
<td>8/27/2020</td>
<td>Removal of option to extend Remdesivir duration from the recommended 5 day to a 10-day duration.</td>
</tr>
<tr>
<td>9/14/2020</td>
<td>Information added on new FDA EUA for convalescent plasma. Remdesivir EUA information updated to reflect the expansion of EUA to all hospitalized patients. Updated IL-6 information; routine use of IL-6 agents is not recommended based on new data. Co-infection (bacterial and influenza) recommendations added.</td>
</tr>
<tr>
<td>9/22/2020</td>
<td>Remdesivir treatment for suspected or confirmed non-severe disease updated &quot;Remdesivir is recommended for hospitalized patients not requiring supplemental oxygen with clinical symptoms of COVID-19 and a positive molecular (PCR) test&quot;</td>
</tr>
<tr>
<td>10/6/2020</td>
<td>Corticosteroid guidance updated with IDSA recommendations.</td>
</tr>
<tr>
<td>10/27/2020</td>
<td>Remdesivir EUA information for adults removed; Remdesivir FDA approved package insert information and updated monitoring (including addition of PT to daily labs) added. Updated influenza co-infection information to include empiric oseltamivir use pending testing results.</td>
</tr>
<tr>
<td>11/23/2020</td>
<td>Clarification that patients deemed stable for discharges should not be held in the hospital to complete a 5-day course of Remdesivir. Addition of monoclonal antibody EUA approval information. Addition of JAK inhibitor/Baricitinib EAU information.</td>
</tr>
<tr>
<td>12/3/2020</td>
<td>Update to Convalescent plasma recommendation and associated new publications.</td>
</tr>
<tr>
<td>12/10/2020</td>
<td>Update to Remdesivir recommendations and associated new publications.</td>
</tr>
<tr>
<td>1/26/2021</td>
<td>Update to IL-6 Inhibitor recommendation and associated new publications. Addition of Ivermectin recommendation.</td>
</tr>
<tr>
<td>2/18/2021</td>
<td>Update of Bamlanivimab administration information and addition of Bamlanivimab and Etsevimab to monoclonal antibody options. Revision of IL6 recommendation.</td>
</tr>
<tr>
<td>3/19/21</td>
<td>Update of Monoclonal Antibody section to provide guidance on impact of variants on product selection.</td>
</tr>
</tbody>
</table>