COVID-19 Pharmacotherapy Treatment Guidance

December 18, 2023

What's Changed this Version:

- Remdesivir monitoring and dose adjustments for renal and hepatic insufficiency have been updated to align with the revised FDA approved package insert

TABLE OF CONTENTS

Therapeutics Overview 3
Clinical Management of COVID-19 in Pediatric Patients 4
Patients at high risk disease progression 4
Molnupiravir Patient Selection, Dosing, and Monitoring 4
Mandatory Requirements for Administration of Molnupiravir Under the EUA: 5
Molnupiravir Contraindications and Precautions: 5
Molnupiravir Dosing Table 5
Molnupiravir Pregnancy and Lactation Considerations 6
Molnupiravir Adverse reactions & Drug Interactions 6
SARS-COV-2 Protease Inhibitor (nirmatrelvir/ritonavir - Paxlovid) Patient Selection, Dosing, and Monitoring 6
Paxlovid Contraindications, Warnings and Precautions 6
Paxlovid Dosing Table 7
Paxlovid Adverse reactions & Drug Interactions 7
Monoclonal Antibody Therapy 8
Remdesivir Patient Selection, Dosing, and Monitoring 8
Remdesivir Dosing Table 8
Remdesivir Contraindications and Precautions: 9
Remdesivir Monitoring 9
Remdesivir Nursing Considerations 9
Remdesivir Adverse reactions & Drug Interactions 9
Convalescent Plasma 9
Convalescent Plasma : Patient Selection 10
Corticosteroids 10
Interleukin-6 (IL-6) Inhibitor Patient Selection, Dosing, and Monitoring 10
IL-6 Contraindications: 11
IL-6 Inhibitor Dosing 11
IL-6 Inhibitor Adverse reactions 11
IL-6 Inhibitor Monitoring 11
IL-6 Inhibitor Nursing Considerations 12
Janus kinase (JAK) inhibitor (Baricitinib) Patient Selection, Dosing, and Monitoring 12
Baricitinib: Patient Selection 12
Baricitinib Contraindications and Precautions: 12
Baricitinib Dosing 12
Baricitinib Monitoring, Adverse Reactions, and Drug Interactions 13
Hydroxychloroquine 13
Azithromycin 13
Ivermectin 13
Considerations for Using Concomitant Medications in Patients With COVID-19 14
COVID And Co-Infection 14
Respiratory Treatments 14
Use of Neuromuscular Blocker Agents and Conservation 14
Special Considerations in Pregnancy 15
Anticoagulation and COVID Related Coagulopathy Guidance 18
Anticoagulation Admission Considerations for Highly Suspected or Confirmed COVID 18
Prevention of Venous Thromboembolism (VTE) in Highly Suspected or Confirmed COVID Patients 18
Figure 1: VTE Prophylaxis 19
Empiric Therapeutic Anticoagulation for COVID related Coagulopathy 19
Empiric Thrombolytic Therapy 19
Treatment of Venous Thromboembolism (VTE) in Highly Suspected or Confirmed COVID Patients 19
Figure 2 : Therapeutic Anticoagulation for Treatment of VTE in COVID Patients 20
Anticoagulation Discharge Considerations 20
Post Hospitalization Considerations for Suspected or Confirmed VTE During COVID Admission 20
Post Hospitalization Considerations - VTE Prophylaxis 20
Overview of Anticoagulation Management In COVID Patients 21
VTE-BLEED Score 21
Modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) VTE-score 21

THERAPEUTICS OVERVIEW

This information is provided 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: Currently available therapies are not approved for post-exposure prophylaxis. Please reference the NIH guidance on Special Considerations in People Who Are Immunocompromised for prevention of COVID-19.
- Treatment: Assessment of Evidence for COVID-19-Related Treatments, updated regularly, is available in the IDSA COVID-19 Guidelines, and NIH COVID Treatment Guidelines.

Patient Subset	Therapeutics	Comments
OUTPATIENT *Mild-Moderate Disease Outpatient with confirmed COVID-19*	Clinical observation & supportive care **< AND >** **For High-Risk Patients (see comments):** **Paxlovid** **<OR>** **Remdesivir for 3 days** **<OR>** **If unable to use alternative COVID-19 treatment options:** **Molnupiravir**	**Patient-specific factors (e.g., symptom duration, renal function, drug interactions) as well as product availability should drive decision-making regarding choice of agent.** Also refer to the **COVID-19 OUTPATIENT TREATMENT ROADMAP** • Paxlovid is preferred for patients **without significant drug interactions or other contraindications** who present within five days of symptom onset. See full Paxlovid section below. • See full Remdesivir section below for dose, contraindications, adverse effects, monitoring and drug interactions • Monoclonal antibody therapies are no longer authorized for use. • Molnupiravir is not recommended as first line. It may be used for adult, nonpregnant patients, whom alternative COVID-19 treatment options (Paxlovid or Remdesivir) are not accessible or clinically appropriate. See full Molnupiravir section.
INPATIENT NON-SEVERE DISEASE *Hospitalized with confirmed COVID-19 not requiring any supplemental oxygen*	Clinical observation & supportive care **< AND, CONSIDER >** **Remdesivir for up to 3 days** (see comments) **<OR>** **(See comments, if available)** **Paxlovid**	**Remdesivir Comments** • Consider for patients at high risk of disease progression • For patients hospitalized for reasons other than COVID-19 with mild-moderate disease, suggest duration of 3 days or until hospital discharge, whichever comes first. • See full Remdesivir section **Paxlovid Comments** • The FDA Paxlovid EUA authorizes use for the treatment of patients hospitalized for conditions other than COVID-19 with mild-to-moderate COVID-19. See full Paxlovid section below.
INPATIENT SEVERE DISEASE – NOT INTUBATED *Confirmed COVID-19 plus requiring a minimal and stable level of conventional supplemental oxygen*	Supportive Care **<AND>** **Dexamethasone 6 mg PO/IV Daily X 10 days*** **< AND >** **Remdesivir for 1- 5 days** (see comments)	**Corticosteroid Comments** • Duration of 10 days or until hospital discharge • If dexamethasone is unavailable, equivalent doses of an alternative glucocorticoid may be used (see corticosteroid section) **Remdesivir Comments** • Treatment with remdesivir earlier in the course of disease has been associated with better outcomes compared to initiation after mechanical ventilation. Also refer to remdesivir comments above. • For patients hospitalized for COVID, duration of 5 days or until hospital discharge, whichever comes first. • See full Remdesivir section
INPATIENT SEVERE DISEASE – NOT INTUBATED ***Patients with any of the following:*** • On conventional oxygen with rapidly increasing requirements • High Flow Nasal Canula • Non-Invasive Ventilation	Supportive Care **<AND>** **Dexamethasone 6 mg PO/IV Daily X 10 days*** **< AND >** **Remdesivir for 1- 5 days** **<AND>** **Immunomodulator (IL-6 Inhibitor or Baricitinib)** (See comments)	**Remdesivir Comments** • See full Remdesivir section **Immunomodulator Comments** • Consultation with Infectious Diseases and/or Critical Care is recommended prior to treatment • See full IL-6 Inhibitor Section for detailed patient selection, exclusion criteria, dose, adverse effects, and monitoring • See full Baricitinib Section for detailed patient selection, exclusion criteria, dose, adverse effects, and monitoring
INPATIENT SEVERE DISEASE – INTUBATED/ECMO *Confirmed COVID plus either of the following:* *a. Requiring mechanical ventilation* *b. Requiring extracorporeal membrane oxygenation (ECMO)*	Supportive Care **< AND >** **Dexamethasone 6 mg PO/IV Daily X 10 days*** **<AND >** **Immunomodulator (IL-6 Inhibitor or Baricitinib)** (See comments)	**Immunomodulator Comments** • Consultation with Infectious Diseases and/or Critical Care is recommended prior to treatment • See full IL-6 Inhibitor Section for detailed patient selection, exclusion criteria, dose, adverse effects, and monitoring • See full Baricitinib Section for detailed patient selection, exclusion criteria, dose, adverse effects, and monitoring • **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

Clinical Management of COVID-19 in Pediatric Patients

There is limited data from observational studies for treatment of COVID-19 in children. The NIH has provided treatment recommendations for children based largely on safety and efficacy data from clinical trials in adults.
NIH Clinical Management of COVID-19 in Children

Therapy For Mild to Moderate Disease

- Treatment of mild to moderate COVID-19 without risk factors for disease progression are managed with supportive care.
- For patients who are at high risk of disease progression, the addition of pharmacologic therapy with either Paxlovid, Monoclonal Antibody, or Molnupiravir is recommended. Patient-specific factors (e.g., symptom duration, renal function, drug interactions) as well as product availability and local viral variant susceptibility should drive decision-making regarding choice of agent.

Patients at High Risk Disease Progression

- Health care providers should consider the benefit-risk for an individual patient. Examples of a patient with mild-to-moderate COVID-19 at increased risk for disease progression or death is below; information about conditions can be found at the Centers for Disease Control and Prevention's People with Certain Medical Conditions website.

Examples of Adult and Pediatric patients (including neonates) at high risk for severe disease progression:

- Older age (for example, age ≥ 65 years of age)
- Less than 1 year old (including neonates)
- Obesity or being overweight
- Pregnancy or recent pregnancy (within last 6 months)
- Chronic kidney disease
- Chronic liver disease (cirrhosis, non-alcoholic fatty liver disease, alcoholic liver disease, autoimmune hepatitis)
- Neurological disorders, including dementia
- Diabetes Mellitus (Type 1 & Type 2)
- Immunosuppressive disease or immunosuppressive treatment (including HIV, solid organ or blood stem cell transplantation)
- Cardiovascular disease (including congenital heart disease, heart failure, coronary artery disease, or cardiomyopathies) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Smokers (current and former)
- Sickle cell disease or thalassemia
- Neurodevelopmental disorders (for example, cerebral palsy, Down Syndrome) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Mental health disorders (mood disorders, including depression, and schizophrenia spectrum disorders)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19)
- Tuberculosis

Molnupiravir Patient Selection, Dosing, and Monitoring

- The U.S. Food and Drug Administration (FDA) has issued an EUA for the emergency use of molnupiravir for the treatment of mild-to-moderate COVID- 19 in adults with positive results of direct SARS-CoV-2 viral testing who are at high risk for progressing to severe disease including hospitalization or death, **presenting within 5 days of symptom onset, and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.** For full details please refer to the Fact Sheet for Healthcare Providers: Emergency Use Authorization For Molnupiravir.
- Molnupiravir is NOT authorized:
  - For use in patients less than 18 years of age.
  - For initiation of treatment in patients requiring hospitalization due to COVID-19
    - Molnupiravir is authorized for patients hospitalized for reasons other than COVID-19 if the patient reports mild-to-moderate symptoms of COVID-19 with a confirmed with positive result. It may be appropriate to treat the patient with molnupiravir if the patient is also at high risk for progression to severe COVID-19 and alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.
  - For use longer than five consecutive days.
  - For pre-exposure or post-exposure prophylaxis for prevention of COVID-19

MANDATORY REQUIREMENTS FOR ADMINISTRATION OF MOLNUPIRAVIR UNDER THE EUA:

- **Prior to initiation of therapy, prescribers should complete the "Molnupiravir Checklist Tool for Prescribers".**
- Mandatory prescriber requirements prior to the patient receiving molnupiravir include:
  - Review the information contained within the "Molnupiravir Fact Sheet for Patients and Caregivers" with the patient or caregiver
  - Healthcare providers must provide an electronic or hard copy of the "Molnupiravir Fact Sheet for Patients and Caregivers" and must document that it has been given to the patient or caregiver.
  - The prescribing healthcare providers must inform the patient/caregiver that:
    a) Molnupiravir is an unapproved drug that is authorized for use under this Emergency Use Authorization.
    b) There are no adequate, approved, available products for the treatment of COVID-19 in adults who have mild-to-moderate COVID-19 and are at high risk for progressing to severe COVID-19, including hospitalization or death.
    c) Other therapeutics are currently authorized for the same use as molnupiravir.
    d) For additional information on all products authorized for treatment or prevention of COVID-19, please see https://www.fda.gov/emergencypreparedness-and-response/mcm-legal-regulatory-and-policyframework/emergency-use-authorization.
    e) There are benefits and risks of taking molnupiravir as outlined in the "Molnupiravir Fact Sheet for Patients and Caregivers"
    f) Merck Sharp & Dohme has established a pregnancy surveillance program.
    g) Females of childbearing potential should use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of molnupiravir.
    h) Males of reproductive potential who are sexually active with females of childbearing potential should use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose
    i) The prescribing healthcare provider and/or the provider's designee are/is responsible for mandatory reporting of all serious adverse events and medication errors potentially related to molnupiravir within 7 calendar days from the healthcare provider's awareness of the event. Refer to full Molnupiravir EUA for reporting requirements.

MOLNUPIRAVIR CONTRAINDICATIONS AND PRECAUTIONS:

- **Use of Molnupiravir in Pregnancy and During Lactation And In Individuals of Childbearing Potential:**
  - **Molnupiravir may cause fetal harm when administered to pregnant individuals. Therefore, molnupiravir is not recommended for use during pregnancy.**
  - Advise patients on need for contraception use as appropriate:
    - Females of childbearing potential treated: should use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of molnupiravir
    - Males of reproductive potential treated: if sexually active with females of childbearing potential, should use a reliable method of contraception correctly and consistently during treatment and **for at least 3 months** after the last dose
- Bone and Cartilage Toxicity: Molnupiravir is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth.

MOLNUPIRAVIR DOSING TABLE

For full details please refer to the Molnupiravir EUA.

Adult Dosing	**Treatment of mild-moderate COVID-19 adult patients (18 years and older) at high risk of disease progression whom alternative COVID-19 treatment options (Paxlovid or Monoclonal Antibody) are not accessible or clinically appropriate, presenting within 5 days of symptom onset:** • **Prior to initiation of therapy, perform the mandatory requirements for administration and complete the "Molnupiravir Checklist Tool for Prescribers: Prescriber Requirements"** • Molnupiravir 800 mg (four x 200 mg capsules) taken orally every 12 hours for 5 days, with or without food. • Missed doses within 10 hours should be taken as soon as possible and normal dosing schedule should be resumed; if dose is missed by >10 hours, skip the missed dose and take the next dose at the regularly scheduled time
Pediatric Dosing	• **Molnupiravir is not authorized for use in patients less than 18 years**
Duration	• Molnupiravir is not authorized for use for longer than 5 consecutive days because the safety and efficacy have not been established.

	• If a patient requires hospitalization after starting treatment with molnupiravir, the patient may complete the full 5 day treatment course per the healthcare provider's discretion.
Dose Adjustments	No dosage adjustment is recommended based on renal or hepatic impairment or in geriatric patients

MOLNUPIRAVIR PREGNANCY AND LACTATION CONSIDERATIONS

- **Not recommended for use during pregnancy – see Contraindications and Precautions**
  - **Pregnancy status should be confirmed prior to initiating therapy – see "Molnupiravir Checklist Tool for Prescribers: Prescriber Requirements"**
- Advise females of childbearing potential to use an effective method of contraception during treatment with molnupiravir and for 4 days after the final dose
- Advise sexually active males with partners of childbearing potential to use a reliable method of contraception during treatment and for at least 3 months after the last dose
- **Breastfeeding not recommended during treatment and for 4 days after the final dose**

MOLNUPIRAVIR ADVERSE REACTIONS

- Most common adverse reactions (incidence ≥ 1%) are diarrhea, nausea, and dizziness. Additional adverse events associated with molnupiravir may become apparent with more widespread use.

MOLNUPIRAVIR DRUG INTERACTIONS

- No drug interactions have been identified based on the limited available data on the emergency use of Molnupiravir authorized under this EUA. No clinical drug-drug interaction trials of molnupiravir with concomitant medications, including other treatments for mild-to-moderate COVID-19, have been conducted

SARS-COV-2 PROTEASE INHIBITOR (NIRMATRELVIR/RITONAVIR - PAXLOVID) PATIENT SELECTION, DOSING, AND MONITORING

- The U.S. Food and Drug Administration has approved Paxlovid which includes nirmatrelvir, a SARS-CoV-2 main protease inhibitor, co—packaged with ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor, for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. The 5-day treatment course of PAXLOVID should be initiated as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset even if baseline COVID-19 symptoms are mild.
- The U.S. Food and Drug Administration has issued an EUA for the emergency use of the unapproved Paxlovid **for pediatric patients (12 years of age and older weighing at least 40 kg)** with mild-to-moderate coronavirus disease 2019 (COVID-19) and who are at high risk for progression to severe COVID-19, including hospitalization or death
- Paxlovid can be considered for the treatment of patients hospitalized with mild-to-moderate COVID19, such as patients admitted for monitoring of drug-drug interactions. Paxlovid can be considered for patients hospitalized for conditions other than COVID-19. Patients initiated on Paxlovid as an outpatient, who require hospitalization due to severe or critical COVID-19 after starting treatment with Paxlovid should complete the full 5-day treatment course per the healthcare provider's discretion.
- Paxlovid should not be initiated for:
  - For initiation of treatment of patients requiring hospitalization due to SEVERE OR CRITICAL COVID-19
  - For use longer than five consecutive days
  - For pre-exposure or post-exposure prophylaxis for prevention of COVID-19

PAXLOVID CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

- **Before prescribing, patients should be evaluated for contraindications and for drug interactions. Drug interactions can be evaluated using available drug information tools, or by the manufacturer provided Paxlovid Drug Interaction Tool is a tool provided to perform this review.**
- **Paxlovid is contraindicated with drugs that are highly dependent on CYP3A for clearance. These interactions may lead to:**
  - **Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medications**
  - **Clinically significant adverse reactions from greater exposures of Paxlovid.**

- **Loss of therapeutic effect of Paxlovid and possible development of viral resistance and for which elevated concentrations are associated either a potential for serious and/or life- threatening reactions, or loss of efficacy**

- **Paxlovid for the Treatment of COVID-19: Considerations for People With HIV and Hepatitis C treating patients with HIV and Hepatitis C (HCV)**
  - One of the components of Paxlovid -- ritonavir -- is also part of many HIV and HCV treatment regimens and may result in significant drug interactions with other commonly used comedications used in these patients. Please refer to the IDSA reference for considerations for treatment with Paxlovid in these patients.

PAXLOVID WARNINGS AND PRECAUTIONS:

- **Drug Interactions: Nirmatrelvir and ritonavir, which comprise Paxlovid, and certain other drugs may result in potentially significant drug interactions, which may lead to serious or life-threatening adverse reactions. See contraindications section above.**
- **Patients' medications must be screened for serious drug interactions (i.e., medication reconciliation).**
- **Dosing in Patients with Renal Impairment: Patients with estimated GFR 60 or below require dose adjustment and the dose pack should be modified by the pharmacist prior to dispensing.**
- Hepatotoxicity: Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir
- HIV-1 Drug Resistance: Paxlovid use may lead to a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection. Patients on ritonavir- or cobicistat-containing HIV or HCV regimens should continue their treatment as indicated.

PAXLOVID DOSING TABLE

For full details please refer to the Paxlovid Package Insert

Adult Dosing	**PAXLOVID is indicated for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.** • The dosage for Paxlovid is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) with all three tablets taken together orally twice daily for 5 days. • Missed doses within 8 hours should be taken as soon as possible and normal dosing schedule should be resumed; if dose is missed by >8 hours, skip the missed dose and take the next dose at the regularly scheduled time
Pediatric Dosing	• The U.S. Food and Drug Administration has issued an EUA for the emergency use of the unapproved Paxlovid **for pediatric patients (12 years of age and older weighing at least 40 kg. Paxlovid is not authorized for use in patients less than 12 years of age or less than 40 kg**
Duration	• Paxlovid should not be used for longer than 5 consecutive days. Completion of the full 5-day treatment course and continued isolation in accordance with public health recommendations are important to maximize viral clearance and minimize transmission of SARS-CoV-2.

Dose Adjustments	**Dosing Information in Patients with Renal Impairment:**
	• **Paxlovid requires dose reduction in moderate renal impairment and is not recommended for use in severe renal impairment**
	Dose should be adjusted as below for patients with an estimated GFR of ≤60:
	  • Estimated glomerular filtration rate (eGFR) > 60 ml/min: 300 mg nirmatrelvir/100 ritonavir every 12 hours for five days
	  • eGFR ≤60 and ≥30 mL/min: 150 mg nirmatrelvir/100 mg ritonavir every 12 hours for five days
	  • eGFR <30 mL/min: Paxlovid is not recommended
	Hepatic Impairment:
	  • No dosage adjustment is needed in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.
	  • Paxlovid is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C)

PAXLOVID ADVERSE REACTIONS

- Rare anaphylaxis, serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson syndrome), and other hypersensitivity reactions have been reported. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue Paxloivid. The most common adverse reactions (≥1% incidence in the PAXLOVID group and occurring at a greater frequency than in the placebo group) were dysgeusia (5% and <1%, respectively) and diarrhea (3% and 2%, respectively).

PAXLOVID DRUG INTERACTIONS

- **Paxlovid is contraindicated with drugs that are highly dependent on CYP3A for clearance. These interactions may lead to:**
  - **Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medications**
  - **Clinically significant adverse reactions from greater exposures of Paxlovid.**
- **Before prescribing, patients should be evaluated for contraindications and for drug interactions. Drug interactions can be evaluated using available drug information tools, or by the manufacturer provided Paxlovid Drug Interaction Tool is a tool provided to perform this review.**
- Less severe but clinically meaningful drug interactions may also occur when nirmatrelvir/ritonavir is co-administered with other agents. Levels of immunosuppressive agents such as tacrolimus, cyclosporine, or sirolimus can be increased when administered with nirmatrelvir/ritonavir. Hormonal contraceptives containing ethinyl estradiol may possibly have reduced effectiveness due to lowered ethinyl estradiol levels when administered with nirmatrelvir/ritonavir. Women of childbearing potential should be counseled to use a back-up, non-hormonal method of contraception.

MONOCLONAL ANTIBODY THERAPY

- Due to the high frequency of resistant baSARS-CoV-2 viral variants, the monoclonal antibody (MAB) products bebtelovimab, sotrovimab, bamlanivimab/etesevimab and casirivimab/imdevimab are no longer authorized by the U.S. Food and Drug Administration (FDA) for use in treatment of COVID-19. Alternative treatments should be selected (see Therapeutics section).

REMDESIVIR PATIENT SELECTION, DOSING, AND MONITORING

- Remdesivir (Veklury®) is FDA approved for the treatment of coronavirus disease 2019 (COVID-19) in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) with positive results of direct SARS-CoV-2 viral testing, who are: Hospitalized, or not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.

REMDESIVIR DOSING TABLE

For full details on dose preparation, please refer to the Remdesivir Package Insert.

Adult Dosing	**Treatment of hospitalized COVID-19 patients (Remdesivir Package Insert)** • Initial: 200 mg IV (over • 30-120 minutes) as a single dose on Day 1; Maintenance: 100 mg IV once daily up to 5 days **Treatment of non-hospitalized patients with mild to moderate COVID-19** • Initial: 200 mg IV (over 30-120 minutes) as a single dose on Day 1 ; Maintenance: 100 mg IV once daily for 3 days
Pediatric Dosing	**Treatment of hospitalized pediatric COVID-19 patients** • *Patients 28 days of age and older and weighing at least 3 kg* **(Remdesivir Package Insert)** ○ Must use lyophilized powder formulation ○ Initial: 5 mg/kg IV (over 30-120 minutes) as a single dose on Day 1 ○ Maintenance: 2.5 mg/kg IV (over 30-120 minutes) once daily for a total duration of 5 days **Treatment of non-hospitalized pediatric patients with mild to moderate COVID-19** ○ Must use lyophilized powder formulation ○ Initial: 5 mg/kg IV (over 30-120 minutes) as a single dose on Day 1 ○ Maintenance: 2.5 mg/kg IV (over 30-120 minutes) once daily for a total duration 3 days
Duration	• Outpatients: 3 days • Inpatients: Maximum of 5 days. For patients hospitalized for reasons other than COVID-19 with mild-moderate disease, suggest duration of 3 days or until hospital discharge, whichever comes first. For patients hospitalized for COVID, duration of 5 days or until hospital discharge, whichever comes first. ○ **Patients should not be held in the hospital solely for the purpose of completing a 3 or 5 day course of remdesivir therapy.** If patient is deemed clinical stable for discharge prior to completion of 3 or 5 days, 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 dosage adjustment is recommended in patients with any degree of renal impairment, including patients on dialysis. Remdesivir may be administered without regard to the timing of dialysis Hepatic: No dosage adjustment necessary. For ALT > 10 times the normal limit, consider discontinuation of remdesivir.

REMDESIVIR CONTRAINDICATIONS AND PRECAUTIONS:

- Perform hepatic laboratory testing in all patients before starting remdesivir and while receiving, as clinically appropriate. Consider discontinuing treatment 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.

REMDESIVIR MONITORING

- Monitor hepatic function tests (ALT, AST, bilirubin, alkaline phosphatase), and prothrombin time (PT/INR) prior to initiation, and every 1-2 days during remdesivir therapy. Trials excluded patients with baseline ALT/AST ≥5 times normal, however remdesivir has been successfully used in a limited number of these patients. 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. Elevated transaminases are a known clinical feature of COVID-19 infection, and therefore, use of remdesivir should not be avoided solely based on the presence of elevated liver chemistries.
- 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
- 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/

CONVALESCENT PLASMA

- The FDA has authorized an Emergency Use Authorization (EUA) for emergency use of high-titer COVID-19 convalescent plasma (CP) for the treatment of hospitalized patients with COVID-19 that are early in the course of disease or who have impaired humoral immunity. Refer to the full EUA document for complete details. Details on the collection, testing, labeling, and recordkeeping accompanying the use of CP is available here: Investigational COVID-19 Convalescent Plasma Guidance for Industry. Fact sheets for Convalescent Plasma EUA have been created for both health care providers and patients.

CONVALESCENT PLASMA : PATIENT SELECTION

- Despite the EUA, convalescent plasma is not recommended for treatment of immunocompetent COVID-19 patients given the lack of conclusive evidence. The National Institutes of Health (NIH) Guidelines and Infectious Diseases Society of America Guidelines recommend against use for immunocompetent patients.
- Given societal recommendations against use, alternative treatment availability including monoclonal antibodies, and the lack of availability to high quality COVID-19 convalescent plasma product, the use of convalescent plasma is no longer recommended.

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.[33-39]
- 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.
    - Persistent hyperglycemia is a risk factor for infection and death in critically ill patients. Glycemic control with careful monitoring of blood glucose is necessary to achieve glycemic control while avoiding hypoglycemia.

INTERLEUKIN-6 (IL-6) INHIBITOR PATIENT SELECTION, DOSING, AND MONITORING

Tocilizumab is approved by the U.S. Food and Drug Administration (FDA) for the treatment of hospitalized adult patients with coronavirus disease 2019 (COVID-19) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

For the treatment of hospitalized pediatric patients ages 2 to less than 18 years of age use of has Emergency Use Authorization (EUA) for Tocilizumab for the treatment of COVID-19. 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 Tocilizumab For Coronavirus Disease 2019 (COVID-19)" For Coronavirus Disease 2019 (COVID-19)". However, if providing this information will delay the administration of treatment to a degree that would endanger the life of a patient, the information must be provided to the parent and/or caregiver as soon as feasible after administration.

Based on the totality of evidence and recommendations from societal guidelines (IDSA and NIH):

- It is recommended that immunomodulator therapy, given in combination with corticosteroids, is considered for patients exhibiting rapid progression of respiratory failure with evidence of inflammatory mediator elevation.
    - Tocilizumab may be used in combination with dexamethasone plus remdesivir for the patients with severe disease requiring mechanical ventilation.
    - Either Tocilizumab or Baricitinib or may be used in combination with dexamethasone plus remdesivir for the patients with severe disease not requiring mechanical ventilation. Baricitinib should be avoided in patients with recent or recurrent VTE. Tocilizumab should NOT be used in combination with baricitinib.
    - Sarilumab 400 mg administered as a single intravenous infusion (infused over at least 60 min) may be used as an alternative to IV tocilizumab, only when IV tocilizumab is not available or not feasible to use.
- 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:

- Refer to tocilizumab package insert for full information. IL-6 inhibitors therapy should not be initiated for the following patients:
    - Serious Infections: do not administer tocilizumab during any other concurrent active infection
    - Tocilizumab treatment is not recommended in patients with active hepatic disease or hepatic impairment. Do not administer tocilizumab when ALT or AST are elevated above 10 times the upper limit of the normal (ULN) reference range (caution if the ALT ≥ 5 times ULN at baseline
    - Baseline platelet count of less than 50,000/mm3
    - Baseline absolute neutrophil count of less than 1,000/mm3
    - Gastrointestinal (GI) perforation – use with caution in patients who may be at increased risk

IL-6 Inhibitor Dosing

Adult Dosing	• Tocilizumab 8 mg/kg - up to a maximum dose of 800 mg administered as a single intravenous infusion (infused over at least 60 min)
Pediatric Dosing	• The FDA EAU is approved for pediatric patients 2 years and older only. Tocilizumab should be administered as a single intravenous infusion (infused over at least 60 min). • Patients at or above 30 kg weight: Tocilizumab 8 mg/kg up to a maximum dose of 800 mg • Patients less than 30 kg weight: Tocilizumab 12 mg/kg
Duration	• The package insert states that if clinical signs or symptoms worsen or do not improve after the first dose, one additional infusion of tocilizumab may be administered at least 8 hours after the initial infusion. • There is a lack of clarity on criteria for when a repeated dose is needed.
Dose Adjustments	Renal: No dose adjustment is required in elderly patients >65 years of age or in patients with mild or moderate renal impairment. There are no dosage adjustments provided in the EUA or manufacturer's labeling for severe renal impairment (has not been studied). Hepatic: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied). Do not use in patients with AST/ALT elevations >10x the upper limit of normal. Use with caution if hepatic enzymes are >5X the upper limit of normal.

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):

- Most common adverse reactions (incidence ≥ 3%) are constipation, anxiety, diarrhea, insomnia, hypertension, and nausea
- Serious Infections: Serious infections have occurred in patients receiving IL- Inhibitors. 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 10x the upper limit of normal. Do not initiate treatment in patients with ANC <1,000/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 Tocilizumab package insert and/or http://www.covid19-druginteractions.org/

Janus kinase (JAK) inhibitor (Baricitinib) Patient Selection, Dosing, and Monitoring

Baricitinib: Patient Selection

- Either Baricitinib or Tocilizumab may be used in combination with dexamethasone plus remdesivir for the patients with severe disease not requiring mechanical ventilation who are exhibiting rapid progression of respiratory failure with evidence of inflammatory mediator elevation.
    - The adverse effect profile of each agent should be considered prior to use. Baricitinib should NOT be used in combination with tocilizumab.
- Baricitinib with or without remdesivir may be considered for hospitalized patients who require oxygen supplementation when corticosteroids cannot be used
- Tofacitinib may be used as an alternative to baricitinib, only when baricitinib is not available
- The U.S. Food and Drug Administration (FDA) has approved baricitinib, for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).
- The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of baricitinib for treatment of coronavirus disease 2019 (COVID-19) in hospitalized pediatric patients 2 to less than 18 years of age requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).
    - 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 Contraindications and Precautions:

- Baricitinib treatment for COVID should be interrupted if Absolute Lymphocyte Count (ALC) is LESS THAN 200 cells/μL OR if Absolute Neutrophil Count (ANC) is LESS THAN 500 cells/μL.
- 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. Co-existing infection can be worsened by baricitinib therapy.

Baricitinib Dosing

Adult Dosing	• 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.

Pediatric Dosing	• The recommended dosage is :
	  • Patients 9 years of age and older with eGFR ≥60 mL/min/1.73 m2: Baricitinib 4 mg PO/GT once daily for 14 days of total treatment or until hospital discharge, whichever is first.
	  • Patients 2 years through less than 9 years of age with eGFR ≥60 mL/min/1.73 m2: Baricitinib 2 mg PO/GT once daily for 14 days of total treatment or until hospital discharge, whichever is first.
	• **Baricitinib is not authorized for patients younger than 2 years of age.**

Dose Adjustments	• **Dose adjustments are required for renal dysfunction, hepatic dysfunction, and drug interactions with strong OAT3 Inhibitors**. Baricitinib is not recommended for eGFR LESS THAN 15 mL/min/1.73 m^2: • For full details on dose adjustment, please refer to the package insert for adult patients and for pediatric patients review 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. 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).**
- 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%
    - 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 NIH and 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
- 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.
    - 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.
- 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.

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.

Considerations for Using Concomitant Medications in Patients With COVID-19

Patients with COVID-19 who are receiving concomitant medications (e.g., angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], HMG-CoA reductase inhibitors [statins], systemic or inhaled corticosteroids, nonsteroidal anti-inflammatory drugs, acid-suppressive therapy) for underlying medical conditions should not discontinue these medications during acute management of COVID-19 unless discontinuation is otherwise warranted by their clinical condition.

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.

Use of Neuromuscular Blocker Agents and Conservation

Neuromuscular blockade (NMBA) 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 have 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 (NMBA), over continuous NMBA 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 NMBA infusion for up to 48 hours (weak recommendation, low-quality evidence).

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

NMBA	Onset of Action (MIN)	Duration after INITIAL dose (MIN)	Usual Dose Range# #For obese patients (BMI ≥ 30), use ideal body weight when calculating NMBA doses)	Comments
Cisatracurium	1.5 -2	20-35	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	
Vecuronium	2.3-3	20-40	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	Drug elimination varies based on renal and hepatic function.
Rocuronium	1-2	22-67 (dose dependent)	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	Vagolytic action can cause dose-dependent tachycardia.

USE OF NMBA FOR COVID RECOMMENDATIONS:

1. Implement conservation strategies to mitigate NMBA drug supply exhaustion including:
    a. Limit use of NMBA agents for patients with Severe ARDS (P/F <= 100) or who have failed prone ventilation
    b. Attempt intermittent boluses prior to continuous infusion when appropriated based on SCCM recommendations criteria
        i. Recommend 24 hours of intermittent dosing use prior to converting to continuous infusions
        ii. Local assessment with pharmacy regarding medication supply, available presentations, and dose dispensing should occur with bolus dose strategy to minimize waste
    c. If continuous infusion of a NMBA is required, use the lowest dose to achieve clinical goal and reassess the need for infusion at least twice a day. If train of 4 (TOF) monitoring is used, discontinue infusion if TOF reaches 0/4 and reassess need for infusion.
        i. For obese patients (body mass index (BMI) ≥ 30 kg/m2), use ideal body when calculating NMBA doses
2. Use succinylcholine preferentially, when appropriate, for rapid sequence intubations (RSI) to preserve rocuronium supply. Ensure that a NMBA supply is available for emergent surgeries (succinylcholine or rocuronium).
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:

NMBA	Onset of Action (MIN)	Duration after INITIAL dose (MIN)	Usual Dose Range# #For obese patients (BMI ≥ 30), use ideal body weight when calculating NMBA doses)	Comments
Atracurium	2-3	20-35	Intermittent bolus dosing: 0.4 to 0.5 mg/kg/dose# Continuous infusion: 4 to 20 mcg/kg/minute	Can cause histamine release, however clinical effects unlikely. Histamine release can be reduced by slowing the rate of administration.
Pancuronium	2-3	60-100	Intermittent bolus dosing: 0.06 to 0.1 mg/kg/dose# Continuous infusion: 0.8 to 2 mcg/kg/minute	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.

SPECIAL CONSIDERATIONS IN PREGNANCY

For detailed information, please see the guidance from the National Institutes of Health NIH, the Centers for Disease Control and Prevention, the American College of Obstetricians and Gynecologists, and the Society for Maternal-Fetal Medicine and the Trinity Health Inpatient Obstetrical Care reference on the management of pregnant patients with COVID-19. This section summarizes key considerations regarding the management of COVID-19 in pregnancy.

- If hospitalization for COVID-19 is indicated for a pregnant patient, care should be provided in a facility that can conduct maternal and fetal monitoring, when appropriate.
- Management of COVID-19 in pregnant patients should include:
    - Fetal and uterine contraction monitoring based on gestational age, when appropriate

- Individualized delivery planning
- Providers should treat pregnant COVID positive patients in collaboration with Maternal Fetal Medicine specialists.
  - A multispecialty, team-based approach that may include consultation with obstetric, maternal-fetal medicine, infectious disease, pulmonary-critical care, and pediatric specialists, as appropriate

- Fetal monitoring should be determined on a case-by-case basis using gestational age and clinical judgement.
- In general, the therapeutic management of pregnant patients with COVID-19 should be the same as for nonpregnant patients.
  - Pregnant or lactating patients with COVID-19 and their clinical teams should discuss the use of investigational drugs or drugs that are approved for other indications as treatments for COVID-19. During this shared decision-making process, the patient and the clinical team should consider the safety of the medication for the pregnant or lactating individual and the fetus and the severity of maternal disease.

Oxygenation Goals and Proning in Pregnancy

In pregnant patients, SpO2 should be maintained at 95% or above on room air at sea level; therefore, the threshold for monitoring pregnant patients in an inpatient setting may be lower than in nonpregnant patients. Consult with a Maternal Fetal Medicine specialist prior to proning a pregnant patient.

COVID-19 Pharmacotherapy in Pregnancy

Summary of COVID-19 pharmacotherapy treatment options in pregnant patients:

- **Corticosteroids, and Remdesivir** should be used in same manner for the therapeutic management of patients with COVID-19 regardless of pregnancy status
- **Paxlovid** has no human data to evaluate for a drug-associated risk of adverse maternal or fetal outcomes. Based on data from use of ritonavir in HIV and animal studies, ritonavir-boosted nirmatrelvir should be offered to pregnant and recently pregnant patients with COVID-19 who qualify for this therapy based on the results of a risk-benefit assessment.
- **Molnupiravir is NOT recommended** for use during pregnancy
- The decision to use **IL-6 inhibitors (Tocilizumab or Sarilumab) or JAK inhibitors (Baricitinib or Tofacitinib)** during pregnancy should be a collaborative effort between pregnant individuals and their health care providers, and the decision-making process should include a discussion of the potential risks and benefits.

Please see below for further information on the considerations for specific therapeutics for COVID treatment in pregnancy (summarized from NIH guidance):

Monoclonal Antibody Considerations in Pregnancy

Due to the high frequency of resistant baSARS-CoV-2 viral variants, the monoclonal antibody (MAB) products bebtelovimab, sotrovimab, bamlanivimab/etesevimab and casirivimab/imdevimab are no longer authorized by the U.S. Food and Drug Administration (FDA) for use in treatment of COVID-19. Alternative treatments should be selected.

Corticosteroid Considerations in Pregnancy

A short course of betamethasone or dexamethasone, which are known to cross the placenta, is routinely used to decrease neonatal complications of prematurity in women with threatened preterm delivery. Given the potential benefit of decreased maternal mortality and the low risk of fetal adverse effects for a short course of dexamethasone therapy, dexamethasone for hospitalized pregnant patients with COVID-19 who require supplemental oxygen or who are mechanically ventilated. However, for pregnant patients being treated for COVID where delivery is being considered and fetal lung maturity is a concern, dosing regimen should be modified to dexamethasone 6mg IM every 12 hours x 48 hours (4 doses) then dexamethasone 6 mg daily for next 8 days (10 days total treatment).

Remdesivir Considerations in Pregnancy

Pregnant patients were excluded from the clinical trials that evaluated the safety and efficacy of remdesivir for the treatment of COVID-19, but preliminary reports of remdesivir use in pregnant patients from the remdesivir compassionate use program are reassuring. Among 86 pregnant and postpartum hospitalized patients with severe COVID-19 who received compassionate use remdesivir, the therapy was well tolerated, with a low rate of serious adverse events. Remdesivir should not be withheld from pregnant patients if it is otherwise indicated."

Interleukin-6 inhibitors (Tocilizumab Or Sarilumab) Considerations in Pregnancy

There are insufficient data to determine whether there is a tocilizumab-associated risk for major birth defects or miscarriage. mAbs are actively transported across the placenta as pregnancy progresses (with the greatest transfer occurring during the third trimester), and this may affect immune responses in utero in the exposed fetus. Given the paucity of data, current recommendations advise against the use of tocilizumab during pregnancy. The decision to use tocilizumab during pregnancy should be a collaborative effort between pregnant individuals and their health care providers, and the decision-making process should include a discussion of the potential risks and benefits.

JAK inhibitors (Baricitinib or Tofacitinib) Considerations in Pregnancy

There is a paucity of data on the use of Baricitinib (JAK inhibitors) in pregnancy. As small molecule-drugs, JAK inhibitors are likely to pass through the placenta, and therefore fetal risk cannot be ruled out. Decisions regarding the administration of JAK inhibitors must include shared decision-making between the pregnant individual and their health care provider, considering potential maternal benefit and fetal risks. Factors that may weigh into the decision-making process include maternal COVID-19 severity, comorbidities, and gestational age. Pregnancy registries provide some outcome data on tofacitinib use during pregnancy for other conditions (e.g., ulcerative colitis, rheumatoid arthritis, psoriasis). Among the 33 cases reported, pregnancy outcomes were similar to those among the general population.

Paxlovid Considerations In Pregnancy and Lactation

- There are no available human data on the use of nirmatrelvir during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Published observational studies on ritonavir use in pregnant women have not identified an increase in the risk of major birth defects. Ritonavir has been used extensively during pregnancy in people with HIV and has a documented safety profile during pregnancy.
- Based on available data, the NIH guidelines recommend that ritonavir-boosted nirmatrelvir should be offered to pregnant and recently pregnant patients with COVID-19 who qualify for this therapy based on the results of a risk-benefit assessment.
    - The risk-benefit assessment for using ritonavir-boosted nirmatrelvir in pregnant patients may include factors such as medical comorbidities, body mass index, and vaccination status. Obstetricians should be aware of potential drug-drug interactions when prescribing this agent.
    - Published observational studies on ritonavir use in pregnant women have not identified an increase in the risk of major birth defects. Published studies with ritonavir are insufficient to identify a drug-associated risk of miscarriage.
- There are no available data on the presence of nirmatrelvir in human or animal milk, the effects on the breastfed infant, or the effects on milk production. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

Molnupiravir Considerations In Pregnancy and Lactation

- **Not recommended for use during pregnancy – see Molnupiravir Contraindications and Precautions**
    - **Pregnancy status should be confirmed prior to initiating therapy – see "Molnupiravir Checklist Tool for Prescribers: Prescriber Requirements"**
- Advise females of childbearing potential to use an effective method of contraception during treatment with molnupiravir and for 4 days after the final dose
- Advise sexually active males with partners of childbearing potential to use a reliable method of contraception during treatment and for at least 3 months after the last dose
- **Breastfeeding not recommended during treatment and for 4 days after the final dose**

Anticoagulation and COVID Related Coagulopathy Guidance

- 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 severe sepsis, 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.
- 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 continues to evolve. 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) – see Figure 1.**
    - It is reasonable to consider full dose anticoagulation in selected COVID patients not in the ICU (see below)
    - In the event 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 and other available specialists (pathology, hematology).
- 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

VTE PROPHYLAXIS FOR ALL HOSPITALIZED HIGHLY-SUSPECTED OR CONFIRMED COVID-19 PATIENTS WITHOUT CONTRAINDICATIONS

CrCL	≥30 ml/min	29 – 10 ml/min	< 10 ml/min
	Enoxaparin		Heparin
BMI less than 40	40 QD	30 QD	5000 U q8h
BMI 40 or greater	40 BID	40 QD	7500 U q8h

*For patients <50 kg and age >80 YO, dose adjustment to Heparin 5000 units SubQ q12 hour
If pharmacologic prophylaxis contraindicated (active bleeding, PLT <25-30K): SCDs

MONITORING:
CrCL and CBC: Daily for critically ill, or every 2-3 days for other hospitalized
PTT, PT/INR, D-Dimer, fibrionogen: Every 2-3 days

EMPIRIC THERAPEUTIC ANTICOAGULATION FOR COVID RELATED COAGULOPATHY

- Full dose anticoagulation should be considered in selected non-critically ill, non-pregnant COVID patients and requiring minimal supplemental oxygen after careful consideration of potential benefit and risk. The benefit of therapeutic-intensity anticoagulation has been demonstrated primarily in patients hospitalized with COVID-19 who do not require ICU-level care and are at lower risk for bleeding.
    - There was not a consistent validated bleed risk score used in COVID anticoagulation trials. Although the VTE-BLEED Score (see below) was not specifically used, it may serve as a reference to the main risk factors for bleeding risk for use during patient risk to benefit evaluation.
- Critically ill patients with COVID-19 requiring high-flow oxygen, ventilatory support, or vasopressors should receive standard-dose VTE prophylaxis rather than therapeutic anticoagulation unless another indication for anticoagulation exists
    - Suspected VTE should be confirmed with diagnostic imaging whenever feasible if patient is stable to do so

Summary of Guidelines

- NIH COVID guidelines give a CIIa rated recommendation for a therapeutic dose of SubQ LMWH or IV Heparin administered for 14 days or until hospital discharge for patients who are: not pregnant, have D-dimer levels above the upper limit of normal, require low-flow oxygen, and have no increased bleeding risk. The C rating is an "optional recommendation for the statement" reflecting the high heterogeneity of data reviewed with the NIH cautioning that the data reviewed may not be generalizable to all hospitalized patients with COVID-19
- The International Society on Thrombosis and Haemostasis (ISTH) guidelines recommend that for select non-critically ill patients hospitalized for COVID-19, therapeutic dose LMWH or UFH is beneficial in preference to prophylactic dose to reduce risk of thromboembolism and end organ failure. Patients with low bleed risk criteria were selected across trials, and selection criteria for two of the trials specified patients with elevated D-dimer and increased oxygen requirements.
- The American Society of Hematology (ASH) guideline also have a conditional recommendation based on very low certainty in the evidence for use of therapeutic-intensity over prophylactic-intensity anticoagulation for hospitalized non-critically ill patients COVID-19 who do not have suspected or confirmed VTE or another indication for anticoagulation

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.
    - 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

Preferred Treatment Regimens for Therapeutic Anticoagulation in COVID Patients	
CrCL	**Preferred Therapeutic Anticoagulant Regimen**
CrCL ABOVE 30 mL/min	Enoxaparin 1 mg/kg SubQ every 12 hours
CrCL 10-29 mL/min	Enoxaparin 1 mg/kg SubQ every 24 hours
CrCL LESS THAN 10 mL/min	Heparin Infusion for Venous Thromboembolism*

Therapeutic Anticoagulation Monitoring

Daily: CrCL and CBC

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

*Heparin infusion: PTT or Xa per institution nomogram or pharmacist dosing

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:
    - 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
    - Assess neuro status
    - Keep venipuncture to a minimum

ANTICOAGULATION DISCHARGE CONSIDERATIONS

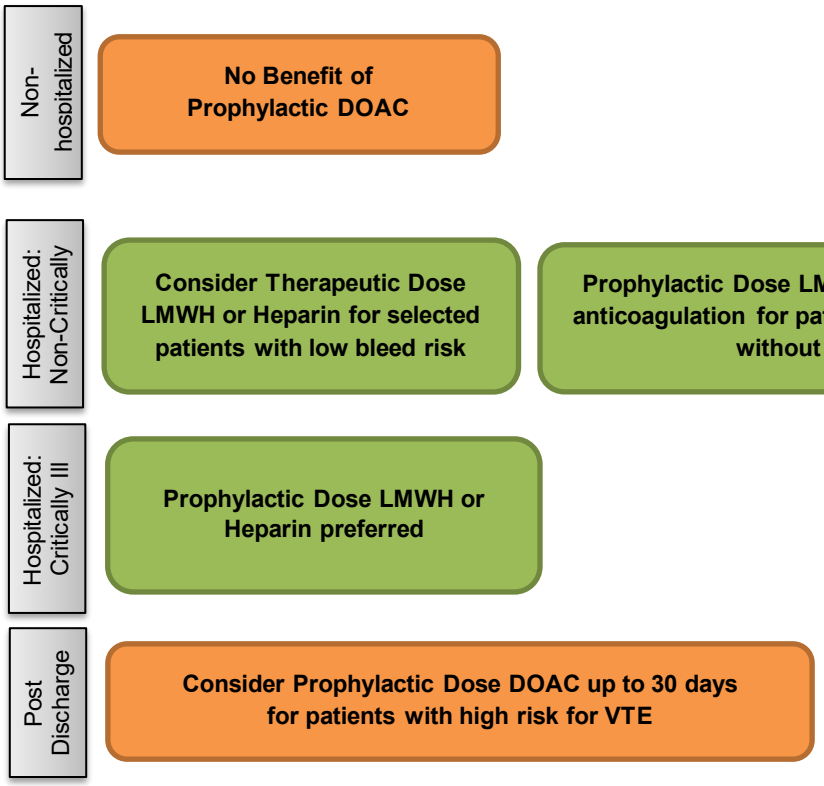
POST HOSPITALIZATION CONSIDERATIONS FOR PATIENTS TREATED WITH THERAPEUTIC ANTICOAGULATION FOR SUSPECTED OR CONFIRMED VTE DURING COVID ADMISSION

- 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

- 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.
    - Patients considered to be at significant continued risk for VTE AND without elevated bleeding risk factors should be **considered** for short-term use (up to 30 days) of prophylactic dose direct oral anticoagulants (DOAC)
    - Increased risk of thrombosis in COVID patients after discharge was defined in a randomized controlled trial as:
        - A modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) VTE-score of 2-3 with D-dimer level more than two times the upper limit of normal at discharge
            OR
        - A modified IMPROVE VTE score of 4 or greater
    - 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).

Overview of Anticoagulation Management In COVID Patients



VTE-BLEED Score

Bleeding Risk Factor	Score
Active cancer	2
Male with uncontrolled arterial hypertension	1
Anemia	1
History of bleeding	1
Age ≥ 60 years old	1
Renal dysfunction	1

Other factors that contribute to bleeding:
- Thrombocytopenia
- Cirrhosis
- Other anti-thrombotic use (e.g. aspirin, clopidogrel, ticagrelor)

Modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) VTE-score

VTE Risk Factor	Score
Previous VTE	3
Known Thrombophilia[a]	2
Paralysis or paresis of the lower limb[b]	2
History of cancer[c]	2
ICU/UTC admission	1
Complete immobilization ≥1 day[d]	1
Age ≥ 60 years	1

a. A congenital or acquired disease that leads to excessive risk of thrombosis (e.g., Leiden factor V, anticoagulant lupus, factor C or Factor S deficiency).
b. The leg falls to bed in five seconds, but makes some effort against gravity
c. Cancer (excluding non-melanoma skin cancer) present at any time in the last five years (the cancer needs to be in remission to meet the eligibility criteria)
d. Immobilization consists of being confined to the bed or chair, with or without sanitary privilege

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VERSION HISTORY

Version Date	Revisions Made
3/30/2020	Updated Remdesivir compassionate use information.
4/4/2020	Updated to reflect new FDA released FACT SHEET FOR HEALTH CARE PROVIDERS and expanded information in 'Use of Hydroxychloroquine: Patient Selection, Dosing, and Monitoring" section
4/14/2020	Updated information on Remdesivir access. Removal of azithromycin from recommendations. Added ASHP evidence summary reference. Added IDSA guidelines reference. Updated patient positioning/prone references.

4/28/2020	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
05/4/2020	Added outpatient pharmacotherapy guidance.
05/6/2020	Updated patient categories and therapy guidance for Remdesivir and Hydroxychloroquine. Includes updates for Remdesivir based on FDA emergency use authorization for Remdesivir.
05/13/2020	Recommendation added to limit use of triple antiviral therapy and interferon beta to use in a clinical trial only
5/20/2020	Updated recommendations on use of Remdesivir in renal impairment and duration of therapy. Nursing considerations comment added.
5/28/2020	Hydroxychloroquine no longer recommended
6/4/2020	Revised criteria for use of IL-6 inhibitors
6/16/2020/	Information regarding FDA revocation of emergency approval of Hydroxychloroquine added. Remdesivir information updated with revised warnings for drug interactions and hypersensitivity and anaphylactic reactions.
6/24/2020	Addition of recommendation for dexamethasone/corticosteroid therapy for patients requiring oxygen therapy
6/29/2020	Extensive inpatient anticoagulation updates. Consolidation of discharge thromboprophylaxis into the treatment guide. Formatting changes.
7/13/2020	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.
8/27/2020	Removal of option to extend Remdesivir duration from the recommended 5 day to a 10-day duration.
9/14/2020	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.
9/22/2020	Remdesivir treatment for suspected or confirmed non-severe disease updated "Remdesivir is recommended for hospitalized patients not requiring supplemental oxygen with clinical symptoms of COVID -19 and a positive molecular (PCR) test"
10/6/2020	Corticosteroid guidance updated with IDSA recommendations.
10/27/2020	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.
11/23/2020	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.
12/3/2020	Update to Convalescent plasma recommendation and associated new publications.
12/10/2020	Update to Remdesivir recommendations and associated new publications.
1/26/2021	Update to IL-6 Inhibitor recommendation and associated new publications. Addition of Ivermectin recommendation.
2/18/2021	Update of Bamlanivimab administration information and addition of Bamlanivimab and Etesevimab to monoclonal antibody options. Revision of IL6 recommendation.
3/19/21	Update of Monoclonal Antibody section to provide guidance on impact of variants on product selection.
4/30/21	Update to Convalescent Plasma guidance to consider use of high-titer only for patients with impaired immunity.
5/25/21	Update to definition of high risk for disease progression for monoclonal antibody therapy
6/9/21	Updated Casirivimab and Imdevimab (REGEN-COV™) dose and route options. Updated recommendation for Immunomodulators in severe disease: either Tocilizumab or Baricitinib in addition to corticosteroids for patients not requiring mechanical ventilation.
6/25/21	Removal of Bamlanivimab/Etesevimab from monoclonal antibody product selection options. Updated Tocilizumab section with new EUA information.
8/9/21	Updated Casivirimab and Imdevimab links to the revised Emergency Use Authorization (EUA) and Fact Sheets. Inserted link to new guidance for Casivirimab and Imdevimab use for post-exposure prophylaxis.

	Updated Baricitinib guidance to reflect new EUA that authorizing use as a stand alone treatment instead of only in combination with Remdesivir
9/7/21	Removed Convalescent Plasma from recommendations; updated Bamlanivimab and Etesevimab recommendation to include use for areas approved by the FDA where the combined frequency of variants resistance does not exceed 5%; Added IV Sarilumab as an alternative IL-6 inhibitor if tociluzimab is not available, and tofacitinib as an alternative JAK inhibitor if baricitinib is unavailable; Revised VTE prophylaxis recommendations for use of standard prophylaxis dose instead of moderate dose
9/24/21	Updated to reflect EUA changes for Bamlanivimab and Etesevimab prophylactic use post high risk exposure.
12/03/2021	Update includes guidance for pregnant patients being treated for COVID
12/03/2021	Addition of PAXLOVID and Molnupirivir
01/11/2022	Addition of Remdesivir for outpatient treatment of mild to moderate disease
02/04/2022	Update to duration of Remdesivir for inpatients.
02/15/2022	Update to add bebtelovimab to treatment options
03/02/2022	Update to Sotrovimab time from symptoms to treatment and infusion time. Updated anticoagulation guidance and references.
4/6/2022	Removal of Sotrovimab due to prevalence of variant resistance.
4/28/22	Addition of FDA approval for Remdesivir to include pediatric patients 28 days of age and older weighing at least 3 kilograms
5/10/22	Addition of link to the patient eligibility checklist for Paxlovid (nirmatrelvir/ritonavir) treatment
5/17/22	Information added on FDA approval of Baracitinib
5/24/22	Paxlovid added as an option for certain hospitalized patients
8/18/2022	Update to immunomodulator recommendations for patients hospitalized requiring supplemental oxygen and in severe disease. Update to guidance on recommendation for use of Paxlovid in pregnancy Reference added to the NIH guidance for treatment of children hospitalized with COVID Removal of patient positioning guidance (prone positioning guidance that was referenced has been retired) Reference added to the NIH guidance for Special Considerations in People Who Are Immunocompromised
9/1/22	Updated anticoagulation guidance
12/1/22	Removal of Bebtelovimab due to prevalence of variant resistance.
1/10/23	Tocilizumab FDA approval for treatment of COVID19
1/20/23	Reference for treatment with Paxlovid for patients with HIV and Hepatitis C
12/18/23	Remdesivir monitoring and dose adjustments for renal and hepatic insufficiency have been updated to align with the revised FDA approved package insert