CMH Guideline for the Therapeutic Management of Hospitalized COVID 19 Adult Patients

The following is a Guideline based on review of available information as of 4.13.22. Please use this reference with the understanding that individual patient care should always be carried out using the best judgements of the clinical team.

Please see the following Flowchart for those patients who are SARS-CoV2 Positive.

All Patients are recommended to have at least VTE prophylaxis, unless contraindicated (See Table 2)
Consider an Infectious Disease Consult

Mild / Moderate

- Supportive care
- Monitor closely, especially in those with risk factors for progression to severe disease as early treatment may improve outcomes. See risk factors and therapeutic options below

Risk factors for progression for severe disease may include but not limited to:

- Cardiovascular disease
- Diabetes
- Age > 60
- Immunocompromising condition or medications
- Structural Lung Disease
- Not fully vaccinated (including not boosted)

Potential treatment options for patients admitted not due to COVID-19 often referred to as "incidental COVID"
See the CMH outpatient therapeutic treatment guidelines

- Remdesivir
- PAXLOVID
- Bebtelovimab
- Molnupiravir

Severe

Meet the following Criteria:

- Oxygen saturation ≤ 94% at rest

Potential Treatment Options
(See Table 1)

- Remdesivir
- Dexamethasone
- Tocilizumab
- Baricitinib

Critical

Meet any of the following Criteria

- Respiratory failure requiring ICU care/ mechanical ventilation
- Shock
- Other system failure(s) that requires ICU care.

Potential Treatment Options
(See Table 1)

- Remdesivir
- Dexamethasone
- Tocilizumab
- Baricitinib

Overview for Severe and Critical Options:

Dexamethasone: Mortality benefit. Initiate in those who require supplemental oxygen or mechanical ventilation

Remdesivir: Initiate within 10 day of symptom onset in those with oxygen saturation (SpO2) ≤ 94% on room air or requiring supplemental oxygen

Tocilizumab and Baricitinib: Add one (not both) to corticosteroids/Remdesivir for those with rapidly increasing oxygen needs and systemic inflammation

Table 1. Treatments to Consider (Infectious Disease should be involved in Treatment Decisions beyond dexamethasone and remdesivir)

Currently Remdesivir is the only FDA approved Treatment for COVID 19. There is an Emergency Use authorization (EUA) for PAXLOVID, Molnupiravir, Bebtelovimab, Tocilizumab, and Baricitinib. Treatment subject to change as more data emerge

Procalcitonin: Decisions regarding antimicrobial therapy should NOT be based solely on Procalcitonin levels, but used in conjunction with clinical judgment. bacterial co-infection is unlikely in a confirmed COVID-19 patient with a low procalcitonin (<0.25). Due to the inflammatory nature of COVID-19, elevated PCT is commonly seen in severe COVID-19 and has been shown to be a prognostic indicator. As PCT may be elevated in severe COVID infection without a defined bacterial infection it should not be used alone to determine if antibiotics are indicated. Patients with chronic or acute renal dysfunction may have falsely elevated PCT levels, and PCT should be interpreted with caution in these settings.

Treatment	Mechanism of Action (MOA) and Dose	Special Considerations and Monitoring

Corticosteroids	• **Dexamethasone** 6 mg IV or PO daily for 10 days
	• If dexamethasone unavailable or alternative needed, consider the following:
	  ○ Hydrocortisone 50mg IV Q8 hours x 10 days**
	  ○ Methylprednisolone 15 mg IV bid x 10 days
	  ○ Prednisone 40 mg daily x 10 days
		• Recommended for use in patients who require supplemental oxygen or mechanical ventilation
		  ○ Based upon results of the RECOVERY trial dexamethasone is recommended by the NIH and IDSA guidelines for its **mortality benefit.**
		• Not recommended for patients with COVID-19 who do not require supplemental oxygen
		  ○ In a sub-group analysis of patients without hypoxia not receiving supplemental oxygen, there was no evidence for benefit and a trend toward harm with dexamethasone in participants who were not on supplemental oxygen
		• https://www.nejm.org/doi/full/10.1056/NEJMoa2021436
		• https://www.covid19treatmentguidelines.nih.gov/dexamethasone/ accessed 1.13.22
		• https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#toc-3 accessed 1.13.22
		• **For patients with **SHOCK** treat with hydrocortisone 50mg IV q6 hours until improvement in shock followed by steroid dosing for COVID-19 treatment for a total of 10 days

Remdesivir (VEKLURY)
 	
**Most of this section refers to information regarding treatment of Severe and Critical patients. For Mild/Moderate "incidental" COVID-19 see CMH outpatient therapeutic
	• MOA: inhibitor of the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), which is essential for viral replication
	• Inpatient dosing
	• Dosing for Severe and critical patients
	  ○ for adults and pediatric patients 12 years of age and older and weighing at least 40 kg: 200mg IV on day 1 followed by 100mg once daily for 5 days
	  ○ Total of 5-day treatment is suggested. Evidence is lacking regarding benefit of extending beyond 5 days. If non-ventilated patients do not demonstrate
		• Approved by FDA 10-22-20
		• Shown to shorten the time to recovery and faster clinical improvement. Significant mortality benefit has only been demonstrated in a retrospective cohort study (see Efficacy below)
		• https://www.nejm.org/doi/full/10.1056/NEJMoa2007764
		• Recommended Criteria for Use:
		  ○ Confirmed positive SARS-CoV-2 test
		  ○ Hospitalized with COVID 19
		  ○ Benefit is greatest when used early in the course of COVID-19 (within 10 day of symptom onset)
		  ○ oxygen saturation (SpO2) ≤ 94% on room air or requiring supplemental oxygen
		• Mechanical Ventilation and ECMO
		  ○ Recent data support that if benefit is to be derived, Remdesivir should be used primarily in those with severe COVID-19 on supplemental oxygen rather than in patients on mechanical ventilation or ECMO. Per NIH and IDSA guidance, it is suggested that it is not recommended as a new start in patients who require invasive mechanical ventilation or

Treatment	Mechanism of Action (MOA) and Dose	Special Considerations and Monitoring
treatment guidelines**	clinical improvement, treatment *may* be extended for up to 5 additional days (ie total of 10 days). • **Please use Remdesivir order set located in COVID folder in Powerchart.** • Dosing for mild/moderate "incidental COVID" ○ 200 mg (day 1); 100mg (day 2 and day 3) ○ See CMH outpatient therapeutic treatment guidelines for more information	ECMO, however at the present time there remains FDA approval under these circumstances. • Monitoring ○ Baseline and during treatment ▪ Serum creatinine and CrCl ▪ Hepatic laboratory testing ▪ Prothrombin time/INR ▪ Signs and symptoms of infusion reaction ▪ vital signs • Renal Impairment ○ Manufacturers labeling does not recommend use in patients with CrCl < 30 mL/min unless the potential benefit outweighs the potential risk. However, significant toxicity with short duration of therapy (5 to 10 days) is unlikely • Hepatic Impairment ○ Consider discontinuing if ALT levels increase to greater than 10 times the upper limit of normal. Discontinue if ALT elevation is accompanied by signs and symptoms of liver dysfunction • Warnings/Precautions ○ Serious and unexpected adverse events may occur that have not been previously reported. ○ Infusion related reactions: hypotension, nausea, vomiting, diaphoresis, and shivering. ○ Increased risk of transaminase elevations ○ Postmarketing: Cardiovascular: Bradycardia, cardiac failure, hypotension, severe bradycardia • Drug Interactions: ○ Co-administration of Remdesivir and chloroquine phosphate or hydroxychloroquine sulfate is not recommended as it may result in reduced antiviral activity of Remdesivir. • Efficacy ○ Adaptive COVID-19 Treatment Trial (ACTT-1) ▪ Reduced time to recovery compared to placebo (10 days vs. 15 days; RRR 1.29; 95% CI, 1.12–1.49; P < 0.001). ▪ No statistically significant difference in mortality by Day 29 (Kaplan–Meier estimates of mortality were 6.7% with remdesivir vs 11.9% by day 15) ▪ Benefit was most apparent in hospitalized patients on supplemental oxygen. ▪ Benefit was greatest in patients randomized during the first 10 days after symptom onset and those on supplemental oxygen (not powered to detect a difference)

Treatment	Mechanism of Action (MOA) and Dose	Special Considerations and Monitoring
		▪ No observed benefit in those on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, but the study was not powered to detect differences within subgroups ○ World Health Organization Solidarity Trial ▪ Did not decrease in-hospital mortality ▪ WHO suggest against administering remdesivir in addition to usual care. ○ Remdesivir Versus Standard of Care in Hospitalized Patients with Moderate COVID-19 ▪ 5-day Remdesivir had significantly higher odds of better clinical status distribution on Day 11 than standard of care (OR 1.65; 95% CI, 1.09–2.48; P = 0.02). ▪ Clinical status distribution on Day 11 was not significantly different between the 10-day Remdesivir and standard of care arms (P = 0.18). ○ Remdesivir treatment in hospitalized patients with COVID-19: a comparative analysis of in-hospital all-cause mortality in a large multi-center observational cohort ▪ 28,855 remdesivir patients were matched to 16,687 unique non-remdesivir patients. Remdesivir was associated with a reduction in mortality at 14-days (HR[95% CI]: 0.76[0.70–0.83]) and 28-days (0.89[0.82–0.96]).
Actemra (Tocilizumab)	• MOA: Tocilizumab is an antagonist of the interleukin-6 (IL-6) receptor. Endogenous IL-6 is induced by inflammatory stimuli and mediates a variety of immunological responses. Inhibition of IL-6 receptors by tocilizumab leads to a reduction in cytokine and acute phase reactant production • Dose: 60-minute intravenous infusion: ○ Patients less than 30 kg weight: 12 mg/kg ○ Patients at or above 30 kg weight: 8 mg/kg ○ Maximum dosage in COVID-19 patients is 800 mg per infusion ○ subcutaneous administration is not authorized for the treatment of COVID-19 patients Repeat Dosing:	• <u>ID approval required.</u> • <u>Studies show mortality benefit</u> • The FDA has issued an EUA for the emergency use of Actemra (tocilizumab) for the treatment of COVID-19; COMPLIANCE WITH ALL ASPECTS OF EUA IS REQUIRED • Please see the following, for more complete information access protocol on the portal under <u>COVID-19 Clinical Resources:</u> ○ CMH Physician Workflow/Checklist (available on portal) ○ Actemra (Tocilizumab) Treatment Plan at CMH (available on portal) ○ Patient Consent Form for Actemra (Tocilizumab) (available on portal) ○ <u>https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs</u> • <u>Inclusion Criteria</u> ○ Confirmed COVID-19 via laboratory testing (per EUA) ○ Hospitalized Adult or pediatric patient (2 years of age and older) (per EUA) ○ Receiving systemic corticosteroids (per EUA) ○ Laboratory Parameters Checked: Use is not recommended in patients with an absolute neutrophil count (ANC) less than 1000 per mm^3, platelet count below 50,000 per mm^3, or ALT or AST above 10 times the upper limit of the reference range (Per EUA) ○ ID approval required. (CMH)

Treatment	Mechanism of Action (MOA) and Dose	Special Considerations and Monitoring
	• 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 • Although some patients in the REMAP-CAP and RECOVERY trials received a second dose of tocilizumab at the discretion of treating physicians, there are insufficient data to determine which patients, if any, would benefit from an additional dose of the drug.	○ Not receiving concurrent Baricitinib therapy (CMH) ○ ≥1 elevated inflammatory marker **CRP, D-dimer, LDH, ferritin *** (CMH) ○ Require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO (per EUA) ○ Exhibiting rapid respiratory decompensation due to COVID-19 ** Studies suggest Actemra use may be more beneficial in people with early rapidly progressive disease; NIH COVID-19 Treatment guidelines recommend use within 3 days of admission to the hospital or within 24 hours of admission to the ICU*** ○ No known hypersensitivity to Actemra or any of its ingredients (per EUA) ○ Serious Infection: should not be administered if patients have any other concurrent active bacterial, fungal, or non-SARS-CoV-2 viral infection (per EUA) • <u>If all the above Inclusion Criteria are met, assess the following for risk vs benefit (see above resources for more information)</u> ○ Tuberculosis ○ Gastrointestinal perforation ○ Demyelinating Disorder ○ Immunosuppression: Tocilizumab should be avoided in patients who are significantly immunosuppressed, particularly in those with recent use of other biologic immunomodulating drugs ○ Active hepatic disease and hepatic impairment • Healthcare provider per **MUST**: ○ Obtain written consent using CMH drug specific consent form and Complete Patient's Inclusion / Exclusion Checklist (available on the portal) ▪ Fax copy of both to Pharmacy. (FAX 795-5675) ○ As a healthcare practitioner per the EUA, you must communicate to the patient and/or caregiver information consistent with the "FACT SHEET FOR PATIENTS, PARENTS AND CAREGIVERS" https://www.gene.com/download/pdf/actemra_eua_patient_fact_sheet.pdf) ○ Provide them with a copy of this Fact Sheet prior to administration ○ Report of all serious adverse events and medication errors potentially related to Actemra within 7 calendar days from the onset of the event ○ Provide mandatory responses to requests from FDA for information about adverse events and medication errors associated with Actemra • Efficacy ○ RECOVERY and REMAP CAP are the two tocilizumab trials that reported a benefit, and are the basis of its suggested/recommended use in the NIH and IDSA guidelines. there are other trials with that have mixed efficacy outcomes.

Treatment	Mechanism of Action (MOA) and Dose	Special Considerations and Monitoring
		○ Both RECOVERY and REMAP CAP initiated treatment early (randomization at median of two days of hospitalization in RECOVERY; <24 hours in the ICU for REMAP-CAP), suggesting tocilizumab may be more beneficial in people with early rapidly progressive disease ○ RECOVERY ▪ tocilizumab reduced all-cause mortality through 28 days (29% of tocilizumab recipients vs. 33% of usual care recipients died by Day 28; RR 0.86; 95% CI, 0.77–0.96), as well as the median time to being discharged alive (20 days for the tocilizumab recipients vs. >28 days for the usual care recipients). In the subgroup analysis, the mortality benefit was restricted to participants who were also receiving corticosteroids (RR 0.80; 95% CI, 0.70–0.90); no benefit was seen among those receiving tocilizumab without corticosteroids ○ REMAP-CAP ▪ Adults with suspected or confirmed COVID19 following admission to an ICU for respiratory (invasive or noninvasive mechanical ventilation) or cardiovascular organ support. Tocilizumab or sarilumab vs control. ▪ Compared to usual care, tocilizumab use reduced both in-hospital mortality (28% of the tocilizumab recipients vs. 36% of the usual care recipients died) and time to hospital discharge (HR 1.41; 95% credible interval [CrI], 1.18–1.70) and increased the number of organ support-free days (10 days in the tocilizumab arm vs. 0 days in the usual care arm; OR 1.64; 95% CrI, 1.25–2.14).
Barcitinib (Olumiant) Use in adults	• MOA: a selective Janus kinase 1 and 2 inhibitor The proposed benefits may be two-fold as it has both anti-inflammatory and potential antiviral activity. ○ Janus kinase mediates cytokine signaling, which contributes to inflammation; Janus kinase inhibitors, therefore, may decrease cytokine-mediated inflammation. ○ Inhibits host intracellular membrane proteins AP2-associated protein kinase 1 (AAK1) and also binds cyclin G-associated kinase (GAK), both thought to play a role in receptor mediated endocytosis of many viruses including Ebola, dengue, Hepatitis C, and SARS CoV-2	• ID approval required. • Studies show mortality benefit • Alternative to Actemra, may not use in combination • The FDA has issued an EUA for the emergency use of baricitinib for the treatment of COVID-19; COMPLIANCE WITH ALL ASPECTS OF EUA IS REQUIRED • Please see the following, for more complete information located on the portal under COVID-19 Clinical Resources: ○ CMH Physician Workflow/Checklist (available on portal) ○ Baricitinib Treatment Plan at CMH (available on portal) ○ Patient Consent Form for Baricitinib (available on portal) ○ https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs • Inclusion Criteria ○ Confirmed COVID-19 via laboratory testing (per EUA) ○ Hospitalized Adult or pediatric patient (2 years of age and older) (per EUA) ○ ID approval required

Treatment	Mechanism of Action (MOA) and Dose	Special Considerations and Monitoring
	• Dosing ○ Adults and pediatric patients 9 years of age and older: 4 mg by mouth once daily ○ Dosage adjustments are recommended for laboratory abnormalities, including renal impairment and drug interactions. See FDA EUA fact sheet for more information and Table 4 at end of this document ○ The recommended total treatment duration is 14 days or until hospital discharge, whichever comes first	○ Not receiving concurrent Actemra (tocilizumab) therapy ○ Laboratory parameters: Patients must have an eGFR, aminotransferases, and CBC with differential determined prior to first administration to determine treatment suitability and dose. (Use not recommended with eGFR < 15 mL/min/1.73 m2 or dialysis. Please note there are dose adjustments required based upon eGFR. There is limited information regarding use in patients with COVID-19 and any of the following: ALC <200 cells/uL, ANC < 1000 cells/uL, and Hemoglobin <8 g/dL) ○ ≥1 elevated inflammatory marker **CRP, D-dimer, LDH, ferritin*** ○ Not recommended for patients with known active tuberculosis ○ Able to take medication enterally/ no absorption issues (This is an oral medication) ○ Requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO. (per EUA) **Not well studied in patients who are already requiring invasive mechanical ventilation or ECMO at baseline, for these patients recommend use of Actemra (tocilizumab) if available**** ○ Exhibiting rapid respiratory decompensation due to COVID-19 • If all the above Inclusion Criteria are met, assess the following for risk vs benefit (see above resources for more information) ○ Thrombosis ○ Gastrointestinal perforation ○ Active hepatic disease and hepatic impairment ○ Serious Infection ○ Immunosuppression ○ Hematologic toxicity ○ Malignancy • Monitoring ○ Monitor ALT, AST, ANC, ALC, hemoglobin, eGFR, signs and symptoms of infection (prior to, during, and after therapy), new onset abdominal symptoms, signs of thrombosis ○ See Table 4 at end of this document for required dose adjustments • Efficacy ○ ACTT-2 (Adaptive COVID-19 Treatment Trial 2) ▪ A randomized, double-blind, placebo-controlled clinical trial of hospitalized adults with confirmed SARS-CoV-2 infection compared treatment with baricitinib (BAR) plus remdesivir (RMV) with placebo plus remdesivir ▪ Data for 1033 patients in the intent-to-treat population (515 in RMV group and 518 in the RMV + BAR group) ▪ Primary end point time to recovery through day 29 : the median time to recovery was 7 days for BAR + RMV compared to 8 days for control group rate ratio for recovery, 1.16; 95% CI 1.01 to 1.32; P = 0.03

Treatment	Mechanism of Action (MOA) and Dose	Special Considerations and Monitoring
		▪ Key secondary outcome measure was clinical status at day 15: Patients assigned to BAR + RMV were more likely to have a better clinical status at Day 15 compared to patients assigned to control group. odds ratio: 1.26 (95% CI 1.01, 1.57); p=0.044 ▪ The BAR + RMV showed a trend towards lower mortality at day 28 but was not statistically significant: 5.1% vs. 7.8%; rate ratio: 0.65; 95% CI 0.39, 1.09 ○ COV-BARRIER (preliminary results not yet peer-reviewed) ▪ Multi-center, randomized, double-blind, placebo controlled, phase 3 international trial of oral BAR or placebo in addition to the local standard of care (SOC) ▪ 1525 participants (SOC N = 761 or BAR + SOC N = 764) ▪ The primary endpoint was the proportion of patients who died or progressed to non-invasive ventilation/high-flow oxygen or invasive mechanical ventilation within the first 28-days of the study. ▪ Lower in patients treated with baricitinib (27.8%) compared to placebo (30.5%), but this effect was not statistically significant [odds ratio:0.85 (95% CI 0.67, 1.08); p=0.180]. ▪ key secondary endpoint was all-cause mortality by Day 28: Mortality was 8.1% in the baricitinib group and 13.1% in the placebo group, corresponding to a 38.2% mortality reduction (HR 0.57, 95% CI 0.41-0.78; nominal p=0.002)

Table 2. VTE prophylaxis and Anticoagulation

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- https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation
- https://www.hematology.org/covid-19/covid-19-and-d-dimer
- https://www.hematology.org/education/clinicians/guidelines-and-quality-care/clinical-practice-guidelines/venous-thromboembolism-guidelines/ash-guidelines-on-use-of-anticoagulation-in-patients-with-covid-19
- Statement on Anticoagulation in Hospitalized Patients | COVID-19 Treatment Guidelines (nih.gov)

Background

- At a minimum, hospitalized COVID-19 patients should receive prophylactic doses of anticoagulants for the duration of their hospitalization.
- COVID-19 has been associated with inflammation and a prothrombotic state, with increases in fibrin, fibrin degradation products, fibrinogen, and D-dimer levels. In some studies, elevations in these markers have been associated with worse clinical outcomes
- An individualized risk to benefit assessment should be performed for each patient with regard to anticoagulant dosing.
- It is important to note that clinical trials available to date were performed prior to Omicron and most instances prior to Delta strain outbreaks. Given apparent differences in Omicron severity and target organs, it is possible that current results may not apply, and more research is urgently needed. It is also important to point out that these recommendations apply only to patients hospitalized due to COVID-19 disease, not to those discovered incidentally to have asymptomatic or mild SARS-CoV-2 infection on routine screening at the time of hospital admission for another indication, as is currently very common for many patients found to be infected with the Omicron strain.
- In patients for whom anticoagulants are contraindicated or unavailable, use mechanical thromboprophylaxis (e.g., pneumatic compression devices). Combined pharmacologic and mechanical prophylaxis is not generally recommended
- Patients with COVID-19 who require extracorporeal membrane oxygenation or continuous renal replacement therapy or who have thrombosis of catheters or extracorporeal filters should be treated with antithrombotic therapy per the standard institutional protocols for those without COVID-19.

D-dimer:

- Based on available COVID-19 experience a cut off of >1 µg/mL may stratify patients at higher risk of poor outcomes. For hospitalized patients, there is no consensus regarding how often D-dimer should be measured, or how results should be acted upon with respect to anticoagulation. Although a relationship between markedly elevated D-dimer levels and mortality has been shown, whether this can be applied to predicting or managing VTE risk is not known
- The value of D-dimer testing is the ability to effectively rule out PE/DVT when the level is normal, given low false negative rates. It is important to realize that D-dimer levels are higher in patients with COVID-19, especially those with severe or critical disease. VTE may be suspected if D-dimer levels change from normal to abnormal, there is a rapid increase in D-dimer on serial monitoring, and/or clinical signs or symptoms occur. Imaging studies to diagnose PE or DVT should be pursued in these scenarios.

Choosing a Dose:

- **For hospitalized patients NOT requiring ICU level care**
  - American Society of Hematology (ASH)
    - Suggests using therapeutic-intensity over prophylactic-intensity anticoagulation for patients with COVID-19–related acute illness who do not have suspected or confirmed VTE or another indication for anticoagulation
  - NIH COVID-19 Guidelines

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- NIH recommends therapeutic dose heparin for patients who have D-dimer above the upper limit of normal (ULN), require lower flow oxygen, and have no increased bleeding risk
  - Based on clinical trial exclusion criteria, contraindications for use of therapeutic anticoagulation for patients with COVID-19 are a platelet count <50 x 109/L, hemoglobin <8 g/dL, the need for dual antiplatelet therapy, bleeding within the past 30 days that required an emergency department visit or hospitalization, history of a bleeding disorder, or an inherited or active, acquired bleeding disorder.
  - In patients without VTE who have begun a therapeutic dose of heparin, treatment should continue for 14 days or until hospital discharge, whichever comes first
  - The Panel recommends against the use of a therapeutic dose of oral anticoagulants for VTE prophylaxis or prevention of COVID-19 progression, except in a clinical trial

- **For hospitalized patients <u>requiring ICU level care</u>**
  - American Society of Hematology
    - Advise that critically ill patients receive standard prophylactic doses of anticoagulants, since increased doses of heparin do not confer a benefit for preventing progression of COVID-19 or death. The ASH guideline panel currently suggests using prophylactic-intensity over intermediate-intensity or therapeutic-intensity anticoagulation in patients with COVID-19–related critical illness who do not have suspected or confirmed VTE
  - NIH COVID-19 Guidelines
    - NIH recommends using prophylactic dose anticoagulation as VTE prophylaxis and against the use of intermediate-dose and therapeutic dose anticoagulation for VTE prophylaxis. For patients who started on therapeutic dose anticoagulation for COVID and then transferred to the ICU, NIH recommends switching to prophylactic dosing unless VTE is confirmed.
    - The Panel recommends against the use of an intermediate dose (e.g., enoxaparin 1 mg/kg daily) or a therapeutic dose of anticoagulation for VTE prophylaxis, except in a clinical trial
- Consideration of anticoagulation on <u>Discharge</u>
  - ASH guideline panel do not recommend routine VTE prophylaxis post discharge (See ACTION trial and MICHELLE trial Below)
    - The risk of VTE following hospital discharge appears low and similar to risks following hospital discharge for other medical conditions, based on observational studies. However, an assessment can be performed to determine risk for VTE, using scores such as <u>IMPROVE-DD</u>, to determine whether an individual patient may merit post-discharge prophylaxis, also considering bleeding risk and feasibility.
  - NIH Guidelines
    - For certain high-VTE risk patients without COVID-19, post-discharge prophylaxis has been shown to be beneficial. Inclusion criteria for the trials that studied post-discharge VTE prophylaxis included:
      - A VTE risk score of ≥4 on the modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) tool, or
      - A VTE risk score ≥2 on the modified IMPROVE tool and a D-dimer level >2 times ULN.
    - Any decision to use post-discharge VTE prophylaxis for patients with COVID-19 should include consideration of the individual patient's risk factors for VTE, bleeding risks, and feasibility. The MICHELLE trial of post-discharge prophylaxis in patients with COVID-19 was recently published and is being reviewed by the Panel

<u>Dose and Drug Choices</u>

- To reduce patient contact LMWH is preferred over UFH in COVID – 19 patients when indicated
- Follow Product labeling for dose adjustments for renal/liver dysfunction and drug-drug interactions

<u>Prophylaxis dosing</u>

- Standard dosing: Enoxaparin 40mg SubQ Q24 hours or UFH 5000 units SubQ Q8 hours

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- Obese dosing (≥ 120kg or BMI ≥ 40): Enoxaparin 40mg SubQ Q12 hours or UFH 7500 units SubQ Q8 hours
- Low body weight (<50kg): enoxaparin 30mg SubQ Q24 hours or UFH 5000 units SubQ Q12 hours

Intermediate-dose Prophylaxis dosing:

- Currently not recommended see information below

Treatment dosing

- Enoxaparin 1 mg/kg SubQ Q12 hours
- Heparin drip

Anticoagulation on Discharge for thromboprophylaxis:

- Rivaroxaban 10mg once daily orally for 31 to 39 days (including hospitalization and post discharge)
- Enoxaparin 40 mg SubQ once daily

Anticoagulation Studies:

- MPT: A large National Institutes of Health (NIH) multiplatform, adaptive-design trial (mpRCT) that incorporated three global studies/networks (REMAP-CAP, ATTACC, and ACTIV-4A) was designed to determine if full dose therapeutic anticoagulation can reduce mortality or need for organ support in critically ill or moderately ill patients.
  - **In noncritically ill patients** therapeutic heparin showed an increase in organ support-free days but no difference in mortality or length of hospitalization compared to prophylactic heparin**. Despite these findings there has not been a consensus for guideline recommendation changes.**
  - In critically ill patients therapeutic dose anticoagulation did not result in a greater probability of survival to hospital discharge, but increase in major bleeding.
- INSPIRATION trial: evaluated the effects of intermediate dose (enoxaparin 1mg/kg daily) vs standard prophylactic anticoagulation (enoxaparin 40mg daily) among patients admitted to the ICU. It did not result in a significant difference in the primary outcome of composite of thrombosis, treatment with ECMO, or mortality within 30 days.
- RAPID trial: Moderately ill hospitalized patients with elevated D-dimer and hypoxemia were treated with therapeutic or prophylactic heparin. The primary outcome was a composite of death, invasive mechanical ventilation, non-invasive mechanical ventilation or ICU admission. Therapeutic heparin did not significantly reduce the primary outcome but decreased the odds of death at 28 days
- HEP-COVID trial: enrolled patients who required supplemental oxygen and had a D-dimer >4 times ULN or a sepsis-induced coagulopathy score of ≥4. The occurrence of the primary outcome of VTE, arterial thromboembolism, or all-cause death at Day 30 was significantly lower in the therapeutic LMWH arm than in the prophylactic LMWH arm, but there was no difference in mortality at Day 30 between the arms
- ACTION trial: evaluated therapeutic anticoagulation (rivaroxaban 20 or 15 mg daily or enoxaparin 1mg/kg twice daily or IV unfractionated heparin followed by rivaroxaban for 30 days) vs prophylactic anticoagulation in hospitalized patients with elevated D-dimer. Therapeutic dosing did not improve clinical outcomes and increased bleeding compared with prophylactic anticoagulation. The efficacy of inpatient versus post-discharge anticoagulation cannot be determined because outcomes were only reported at 30 days after discharge
- MICHELLE trial: Rivaroxaban versus no anticoagulation for post discharge thromboprophylaxis after hospitalization for COVID-19. Showed a significant reduction in post-discharge thrombotic events (including screen-detected deep-vein thrombosis and PE at day 35) and death after 35 days of treatment with rivaroxaban 10 mg per day compared to placebo in a population of patients selected for increased VTE risk based on the IMPROVE-DD score. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02392-8/fulltext
- Luis Ortega-paz et al. meta-analysis pooled the results of 7 RCT evaluating the effect of therapeutic dose versus prophylactic dose anticoagulation in hospitalized patients. Therapeutic and intermediate dose anticoagulation data were combined and termed the escalated dose group which was compared to standard prophylactic dose; this approach differs from that of the mpRCT in which those treated with intermediate dose anticoagulation were combined with standard prophylactic dose anticoagulation. The results found no difference in mortality for escalated dose versus standard dose anticoagulation in all hospitalized patients. Major bleeding was increased in the

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escalated dose group .In subgroup analyses, there was also no difference in mortality for those treated in the ICU or for non-ICU hospitalized patients. A difference was found favoring escalated dose anticoagulation for the prevention of VTE, but not for MI or stroke.

Table 3. Miscellaneous Medication Information

Medication	Available Information
Fluvoxamine	• Not recommended at this time based on insufficient evidence • TOGETHER trial: While fluvoxamine treatment significantly reduced the primary composite outcome (i.e., retention in the emergency department for >6 hours or admission to a tertiary hospital), the difference in hospitalizations between arms was not significant. • STOP COVID trial: reduced clinical deterioration at Day 15. Clinical deterioration was defined as shortness of breath plus oxygen saturation (SpO_2) <92% or hospitalization plus SpO_2 <92%. This was a small study with limited cases of clinical deterioration and a short follow-up period. 24% of participants stopped responding to surveys prior to Day 15. • STOP COVID 2 trial: stopped for futility by a data safety monitoring board after lower than expected case rates and treatment effect were observed
Vaccine Induced Immune Thrombotic Thrombocytopenia	Please note possible cerebral venous thrombosis association and need for specific treatment and testing similar to HIT. Pleas e see link for detailed recommendations. https://emergency.cdc.gov/han/2021/han00442.asp https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia
Inhaled corticosteroids	NIH COVID-19 treatment guidelines: There is insufficient evidence for the Panel to recommend either for or against the use of inhaled budesonide for the treatment of COVID-19 Inhaled budesonide was studied in two open-label trials in outpatients with mild symptoms of COVID-19 Results of these trials suggest that in adult outpatients with mild COVID-19, initiation of inhaled budesonide may reduce the need for urgent care or emergency department assessment or hospitalization and reduce time to recovery. The findings from these trials should be interpreted with caution given the open-label design of the studies, incomplete data, and other limitations. Additional trials of inhaled corticosteroids are ongoing
Hydroxychloroquine (HCQ)	• Based on the most recent data available, use outside of a clinical trial is not recommended. **Therefore, inpatient treatment is NOT recommended at CMH at this time.** • Co-administration of Remdesivir and chloroquine phosphate or hydroxychloroquine sulfate is not recommended as it may result in reduced antiviral activity of Remdesivir
Azithromycin	• Current data does not support use for the treatment of COVID-19. May be used for treatment of suspected Bacterial Infection.
Angiotensin-Converting Enzyme Inhibitors (ACEI) and Angiotensin II Receptor Blockers (ARBs)	• Concerns have been raised about the use of ACEI and ARBs in COVID-19 Patients. This is based upon the fact that SARS-CoV-2 bind to their target cells through angiotensin converting enzyme 2 (ACE2) and the hypothesis that because ACE2 is increased in patients treated with ACE inhibiters and ARBs this might facilitate infection with COVID-19 • There is proposed hypothetical benefit of ARBs as having a protective effect in COVID 19 patients • American Heart Association (AHA), American College of Cardiology (ACC), Heart Failure Society of America, and European Society of Cardiology all recommend to continue use of ACEI and ARBs in patients currently prescribed them • IDSA guidelines recommend against their use in treatment of COVID-19 • ACEI and ARBs need only be discontinued in the inpatient setting if clinically indicated per usual practice

Non-steroidal anti-inflammatory drugs (NSAIDS)	• Concerns have been raised about the use of NSAIDS in COVID-19 Patients. This is based upon the fact that SARS-CoV-2 bind to their target cells through angiotensin converting enzyme 2 (ACE2) and the hypothesis that because ACE2 is increased by Ibuprofen this might facilitate infection with COVID-19. • Currently there is no scientific evidence to support this.
Nebulized medications	• SARS-CoV-2 is an easily transmitted virus spread through respiratory droplets because of this the use of nebulized medications has the potential to increase viral transmission • Risk of aerosolization is minimized with specialized devices including bacterial/viral filters and one-way valve for nebulizer administration, which should be utilized when nebulizer treatments are needed. If device not available, use appropriate personal protective equipment (PPE) and limit those present in the room per AGP policy. • Alternatively, may use Metered dose inhalers when clinically appropriate.
Statins	• At this time there is no evidence to support the addition of statin therapy in the treatment of COVID-19 patients
Ascorbic acid; Zinc; Famotidine	• Current data is insufficient to show efficacy in the treatment of COVID-19 patients
Ivermectin	• The following study found that Treatment with ivermectin did not result in a lower incidence of medical admission to a hospital due to progression of Covid-19 or of prolonged emergency department observation among outpatients with an early diagnosis of Covid-19. • https://www.nejm.org/doi/full/10.1056/NEJMoa2115869 • IDSA guidelines recommend against their use for the treatment of COVID-19.
Convalescent Plasma	• No longer recommended by NIH guidelines or IDSA. Has not shown to have benefit

Table 4. Dose Adjustments for Patients with Abnormal Laboratory Values on Baricitinib [a, b]

Laboratory Analyte	Laboratory Analyte Value	Recommendation
eGFR	≥60 mL/min/1.73 m²	• Adults and pediatric patients 9 years of age and older: 4 mg once daily • Pediatric patients 2 years to less than 9 years of age: 2 mg once daily
	30 to <60 mL/min/1.73 m²	• Adults and pediatric patients 9 years of age and older: 2 mg once daily • Pediatric patients 2 years to less than 9 years of age: 1 mg once daily
	15 to <30 mL/min/1.73 m²	• Adults and pediatric patients 9 years of age and older: 1 mg once daily • Pediatric patients 2 years to less than 9 years of age: Not recommended
	<15 mL/min/1.73 m²	Not recommended
Absolute Lymphocyte Count (ALC)	≥200 cells/µL	Maintain dose
	<200 cells/µL	Consider interruption until ALC is ≥200 cells/µL
Absolute Neutrophil Count (ANC)	≥500 cells/µL	Maintain dose
	<500 cells/µL	Consider interruption until ANC is ≥500 cells/µL
Aminotransferases	If increases in ALT or AST are observed and drug-induced liver injury (DILI) is suspected	Interrupt baricitinib until the diagnosis of DILI is excluded

[a] Abbreviations: ALC = absolute lymphocyte count, ALT = alanine transaminase, ANC = absolute neutrophil count, AST = aspartate transaminase, DILI = drug induced liver injury, eGFR = estimated glomerular filtration rate.

[b] If a laboratory abnormality is likely due to the underlying disease state, consider the risks and benefits of continuing baricitinib at the same or a reduced dose.

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