ZSFG Treatment Guidelines for Adult Inpatients with Confirmed COVID-19 (Version 11: Updated 2/1/2023)	
Invasive mechanical ventilation for COVID	• IV remdesivir (5 days; consider extension to up to 10 days). Administer in conjunction with dexamethasone and/or baricitinib/tocilizumab. Obtain LFTs q1-2 days and monitor for bradycardia. • Dexamethasone (unless corticosteroid contraindicated), target duration: 10 days • Consider tocilizumab if admitted to ICU <24 hours and no contraindication (e.g., bacterial infection present). Consider baricitinib an alternative. Do not combine baricitinib & tocilizumab. • Avoid therapeutic dose heparin anticoagulation if given solely for COVID-19 indication; can give prophylactic dose heparin anticoagulation unless contraindicated • ARDS management per critical care team to include low tidal volume ventilation, fluid conservation, possible prone positioning and/or paralytics.
High flow nasal cannula (HFNC) or non-invasive ventilation (NIV)	• IV remdesivir (target duration: 5 days; consider extending to 10 days if continued high level O2 support persisting on day 5 or clinically worsening). • Dexamethasone (unless corticosteroid contraindicated), target duration: 10 days (discontinue if discharge sooner than 10 days). Can consider baricitinib if steroid intolerant/contraindicated. • Consider adding baricitinib in addition to steroids on a case by case basis. Consider tocilizumab as an alternative to baricitinib if rapidly worsening and hospitalized x <3 days. Do not combine baricitinib and tocilizumab. • Avoid therapeutic dose heparin anticoagulation if given solely for COVID-19 indication; can give prophylactic dose heparin anticoagulation unless contraindicated.
Hospitalized, requiring oxygen by nasal canula (but not HFNC/NIV)	• IV remdesivir x 5 days (given RCT data on 5 days equivalent to 10). Consider extending to 10 days if not improving or persistent substantial O2 requirement by day 5. • Steroids *if* persistently hypoxic requiring ≥ 3-4L nasal canula O_2 **OR** if clinical trajectory suggests worsening severity (consider baricitinib if steroid intolerant/contraindicated). • Consider adding baricitinib in addition to steroids if clinically worsening • Start therapeutic dose heparin anticoagulation if meet criteria* and if no contraindications exist. Can give prophylactic dose heparin anticoagulation to patients who are not given therapeutic dose heparin.
Mild/moderate disease[1] (no hypoxia)	**Patients hospitalized for COVID-19 syndrome or for a COVID-19 induced decompensation of underlying medical illness:** • Consider remdesivir IV for three days if symptom onset within last 7 days and patient has risk factors for disease progression and/or is ≥65 years old. • Can consider other outpatient treatments (including Paxlovid, & molnupiravir) if hospital admission is not related to COVID-19, if patient meets EUA criteria for therapy, and if COVID-19 disease would have otherwise been handled as an outpatient. However, note: RDV is generally preferred for inpatients over other therapies due to fewer drug interactions, shorter treatment duration and more straightforward to obtain. • Start therapeutic dose heparin anticoagulation if meet criteria (see below) and if no contraindications exist. Can give prophylactic dose heparin anticoagulation for patients who are not given therapeutic dose heparin.

	Patients hospitalized for a non-COVID-19 related condition but who have mild COVID-19 that would otherwise have been treated as an outpatient: • See ZSFG guidelines for outpatient COVID-19 treatment recommendations (summarizes use of IV remdesivir and oral therapies) • For inpatients expected to have a longer length of stay (i.e., ≥2 days), remdesivir IV for three days is preferred over oral therapies. Can consider extending to 5 days in select patients. • For inpatients expected to discharge quickly (i.e. 1-2 day length of stay), Paxlovid or molnupiravir can be considered. Must be ordered through outpatient pharmacy. • Steroids, anti-inflammatory therapies, and anticoagulation are not recommended.
Pregnant woman with severe disease[1]	• IV remdesivir x 5 days • Adjunctive steroids if intubated or high flow oxygen with respiratory decompensation. Consultation with OB recommended – see table. • Prophylactic dose heparin anticoagulation recommended; therapeutic dosing not currently recommended.

[1]***Mild Disease:*** No radiographic abnormality, no hypoxia
Moderate disease: Radiographic abnormality, O2 sat > 94% RA
Severe Disease: radiographic abnormality, O2 ≤ 94% on room air or needing supplemental O2/intubation or Pa02/Fi02 ≤ 300mmHg

Criteria for therapeutic anticoagulation: Patient meets ALL of the following criteria: (1) admitted with COVID-19 symptoms, (2) is within first 3 days of admission, (3) elevated d-dimer OR requiring oxygen by nasal cannula, (4) have no contraindications to anticoagulation, and (5) are not on dual anti-platelet therapy. Should not be given to patients on HFNC or in the ICU for a COVID-19 indication.

Overview of COVID-19 Specific Therapeutics

Remdesivir has shown efficacy in improving time to recovery and a trend towards mortality improvement and thus should be used for hospitalized patients requiring oxygen with COVID-19, including those in the ICU. A shorter course of 3 days of remdesivir can be considered for hospitalized patients not on oxygen who are within 7 days of symptom onset and who are at higher risk for disease progression, either by age≥65 or by having risk factors for disease progression.

Dexamethasone has been shown to improve mortality in intubated patients and should be used for all intubated patients unless there are contraindications for steroids. We recommend dexamethasone for most patients on HFNC, and dexamethasone can be considered for patients using at least 3-4L oxygen and/or have worsening clinical status.

Other anti-inflammatories such as JAK inhibitors and IL-6 inhibitors, and anticoagulants have been shown to benefit specific hospitalized populations as outlined below.

Consultation for COVID-19 Care for Hospitalized Patients:

- **COVID-19 hospital-wide rounds** are held daily on weekdays at 8:30am and welcome all teams caring for COVID-19 patients to call in and discuss diagnostics, therapeutics, or discharge logistics. For information on the daily hospital-wide Zoom call, please contact Vivek Jain, MD (Division of HIV, ID & Global Medicine, SFGH) at vivek.jain@ucsf.edu.
- At other times during weekdays, and on nights and weekends, please contact the Infectious Diseases Consult Team (pager 415-443-BUGS) for guidance regarding COVID-19 diagnostics and treatments.
- For infection control related questions including isolation and de-isolation of patients, please either join the weekday morning hospital zoom call or page infection control (weekdays 8am-5pm) at pager 415-443-1566.

COVID-19 Therapeutics

1. Remdesivir

A. Remdesivir is FDA approved. ***Remdesivir package insert here***.

B. Data support the use of 3 days of remdesivir in outpatients with symptomatic COVID-19 to reduce the risk of COVID-19 related hospitalization and death in those <7 days after symptom onset who are either age ≥65 or have ≥1 risk factors for COVID-19 disease progression. This use of remdesivir is reasonable for non-hypoxic inpatients who qualify (see above). Hypoxic inpatients are typically treated with 5 days of remdesivir, with consideration of extension to 10 days for those in the ICU or who are not clinically improving.

C. For patients on HFNC or who are mechanically ventilated, remdesivir should be given in conjunction with dexamethasone and/or either baricitinib or tocilizumab.

D. Patients who are ready for discharge should not remain hospitalized solely to complete remdesivir administration. There currently is not an oral formulation of remdesivir.

E. Remdesivir should not be started if AST > 10x ULN. Transaminases should be monitored during remdesivir administration at least every other day. There are limited data on using remdesivir in ESRD. The drug's vehicle contains cyclodextrin, which can accumulate in renal failure; however, remdesivir is likely to be safe given short duration of therapy, if benefits are judged to outweigh risks which is typically the case for most inpatients with COVID.

2. Anti-inflammatory therapies

Dexamethasone: Corticosteroids improve mortality among intubated COVID patients and, to a lesser degree, among persons requiring supplemental oxygen. The strongest signal for benefit has been with dexamethasone but there are data to support the benefit of hydrocortisone as well. Corticosteroids should be considered in all intubated patients with COVID-19 unless there are significant contraindications. Dexamethasone for non-intubated patients can be considered for those with a substantial oxygen requirement and worsening respiratory status, as above. Dexamethasone is not recommended in presence of typical steroid contraindications (uncontrolled systemic co-infection such as fungal infections, uncontrolled hyperglycemia, active GI bleeding, substantial delirium, etc.). There is no contraindication to giving dexamethasone + RDV together.

Baricitinib: is an oral JAK inhibitor with anti-inflammatory and potential anti-viral properties. JAK inhibitors have been shown to reduce time to clinical recovery in hospitalized COVID-19 patients, reduce progression to respiratory failure, and improve mortality in some studies, with the most pronounced benefit in those on high flow nasal cannula oxygen support. Baricitinib has not been beneficial in those not on oxygen. Baricitinib is FDA approved for COVID-19 treatment and is a consideration for patients who are on HFNC/NIV in addition to steroids or for those cannot tolerate dexamethasone or who have contraindications to steroids. There are also data to support baricitinib in addition to dexamethasone in mechanically ventilated patients. ***Baricitinib package insert here***

Tocilizumab: is an IL-6 inhibitor FDA-approved for COVID-19 treatment which has been shown to improve outcomes and reduce mortality in some hospitalized patients, with strongest evidence to support those newly requiring ICU level care (admission to ICU in past 24 hours and hospital admission in past 3 days) and those already on corticosteroids. Tocilizumab should not be given if serious concomitant infection or pre-existing immunocompromise, and should not be given at concomitantly with JAK inhibitors - if progression to ICU and Tocilizumab is to be given, baricitinib should be stopped. ***Tocilizumab package insert here.***

3. Anticoagulation

There are substantial data indicate COVID-19 promotes a hypercoagulable state and raises risks for thrombosis. The following guidance is recommended for thromboprophylaxis:

A. DVT prophylaxis is recommended in all hospitalized COVID-19 patients unless there is a contraindication.

B. ICU patients and those on HFNC should *not* receive therapeutic anticoagulation solely for a COVID-19 indication. Prophylactic-dose heparin anticoagulation is preferred.

C. Therapeutic-dose heparin anticoagulation is a consideration for the patients meeting the following criteria:

- Primary hospitalization for COVID-19 symptoms (respiratory OR GI)
- No contraindications to therapeutic anticoagulation (and are not already on DUAL-antiplatelet therapy)
- On nasal cannula oxygen therapy OR have an elevated D-dimer level

D. Not on HFNC, not in the ICU
E. Initiation within 72 hours of hospitalization
F. Target duration: 14 days; discontinue at discharge if sooner than 14 days
G. Dosing in table below

4. Oral COVID therapy for mild COVID-19 in inpatients hospitalized for other reasons

Oral COVID-19 therapies can be used during hospitalization when the inpatient hospitalization is definitively due to a non-COVID-19 cause and COVID-19 would have otherwise been handled on an outpatient basis. Note that IV remdesivir is preferred to oral therapies for inpatients as is an approved treatment for outpatients (3 days), has fewer drug-drug interactions than Paxlovid, and can be started promptly, as does not have to come through the outpatient pharmacy (as is the case for oral medications)

5. COVID antibody treatment

Currently, anti-SARS-CoV-2 antibody therapies are not available for inpatients or outpatients with COVID-19.

Medications/interventions to avoid

- Avoid other pharmaceutical treatments specifically to treat COVID-19 unless part of a clinical trial.

Clinical Trials

Clinical trials may be available and should be considered for all participants who qualify and are interested. The following contacts can provider more information about studies

- lucy.kornblith@ucsf.edu → anti-coagulation studies & COVID therapeutics for hospitalized COVID patients
- carolyn.hendrickson@ucsf.edu: → ICU based studies
- annie.luetkemeyer@ucsf.edu → COVID therapeutics for outpatients

Considerations for COVID-19 treatments

Remdesivir	
Dosing	200mg IV x 1, then 100mg IV q24h during hospitalization for 5 days. Consider extension for up to 10 days for intubated patients or those who are not improving or are worsening. 3 days is recommended for non-hypoxic symptomatic patients with symptom onset ≤ 7 days and ≥65 year of age or ≥1 or more risk factors for disease progression
Dose adjustment in renal dysfunction	Limited data for use with CrCl < 30 or dialysis – however, can be considered on case by case basis if benefits outweigh risks. No dose adjustment if given in renal disease
Pregnancy/Lactation	Pregnant women who are offered remdesivir should be enrolled in https://covidpr.pregistry.com. There are limited data on remdesivir in lactation. The consideration of continued breastfeeding while taking remdesivir should considered in a shared decision making context of risks and benefits.
Important drug interactions	Coadministration with strong CYP3A4 inhibitors is not recommended and coadministration with weak/moderate 3A4 inhibitors should be avoided if possible.
Adverse effects	Increased AST/ALT, reversible upon drug discontinuation, nausea/vomiting, rash, bradycardia. Rare allergic reaction.

Dexamethasone	
Dosing	6 mg IV /PO x 10 days
Dose adjustment in renal dysfunction	None needed
Pregnancy/Lactation	The American Society for Maternal-Fetal Medicine recommends dexamethasone for pregnant patients since the benefit of mortality reduction outweighs the risk of fetal steroid exposure for this short course of treatment. Can discuss steroid choice (dexamethasone, betamethasone, prednisolone, methylprednisolone, or hydrocortisone) with Maternal Fetal Medicine/OB.
Important drug interactions	Consider dose increase when given with strong CYP3A4 inducers (e.g., rifampin)
Adverse effects	Typical steroid risks include hyperglycemia, hypertension, delirium, GI bleeding, increased risk of infection or superinfection (including strongyloides hyperinfection), etc.

Baricitinib	
Dosing	4 mg PO daily for up to 14 days, while inpatient as an alternative, can be given dispersed in water orally or via OGT/NGT
Dose adjustment in renal dysfunction	eGFR 30 to <60 : 2 mg eGFR 15 to <30 : 1 mg
Monitoring	Consider holding dose if ALC < 200 or ANC < 500 Hold dosing if transaminase elevation (AST or ALT >10xULN) or drug-induced liver injury (DILII) suspected. Use has not been studied in severe hepatic impairment
Pregnancy/Lactation	Not studied in pregnant women with COVID-19 infection
Important drug interactions	Caution when dosed with strong OAT inhibitors, such as probenecid. Discontinue if tocilizumab started
Adverse effects	Do not use if TB suspected or untreated LTBI. May increase risk for serious infections and/or thrombosis with chronic use (NB: neither increased in ACTT-2 study)

Tocilizumab	
Dosing	8 mg/kg x 1 dose total (max dose 800 mg)
Dose adjustment in renal dysfunction	Dosing for CrCl <30 not defined
Monitoring	Follow AST/ALT, ANC, platelets after dosing. Monitor for evidence of infection
Pregnancy/Lactation	Not studied in pregnant women with COVID-19 infection
Important drug interactions	CYP2c19 inducer and CYP314 inducer (both minor)
Contraindications	Do not use if serious concomitant infection, immunocompromised (particularly if on immunomodulators), ANC <500, platelets < 50, ALT > 5x ULN.

Prophylactic Dose Anticoagulation (for duration of hospitalization)						
CrCl	**BMI**	**Enoxaparin**	**Dalteparin**	**Tinzaparin**	**Fondaparinux**	**Heparin**
≥30	<40	40 mg SC q24h	5000 units SC q24h	4500 units SC q24h	2.5 mg SC q24h	5000 units SC q8-12h
	≥40	40 mg SC q12h	5000 units SC q12h	9000 units SC q24h	NA	7500 units SC q8h
<30	<40	Heparin 5000 units SC q8-12h				
	≥40	Heparin 7500 units SC q8h				

Therapeutic Dose Anticoagulation (for maximum 14 days while hospitalized)					
CrCl	**BMI**	**Enoxaparin**	**Dalteparin**	**Tinzaparin**	**Heparin**
≥30	<40	1 mg/kg SC q12h OR 1.5 mg/kg SC q24h	200 units/kg SC q24h OR 100 units/kg SC q12h	175 units/kg SC q24h	IV bolus, with continuous infusion to titrate to anti-Xa 0.3-0.7 IU/mL or corresponding aPTT values*
	≥40	1 mg/kg SC q12h	100 units/kg SC q12h		
<30	<40	Heparin IV bolus, with continuous infusion to titrate to anti-Xa 0.3-0.7 IU/mL or corresponding aPTT values*			
	≥40				

* UFH anti-Xa titration is preferred over aPTT if available because achieving a therapeutic aPTT may be challenging in patients with a pro-inflammatory state such as COVID-19. Note: Fondaparinux not advised in this setting due to its long half life