UCHealth Covid-19 Pharmacotherapy Guidance, Last Updated 4-30-20

SARS-CoV-2 (COVID-19) positive or strongly suspected

General Considerations:

- Avoid corticosteroids unless indicated for separate comorbidity (e.g., septic shock, COPD, asthma, ARDS, etc.) - limited evidence exists for adjunctive corticosteroids and results mixed (see page 11)
- Consideration for VTE Prophylaxis (see page 2-3)
- Consider empiric antibiotics for CAP/HAP/VAP according to clinical evidence/suspicion and risk factors indicate need for antibacterial coverage—
    - Please d/c antibiotics if ongoing suspicion for bacterial infection low (negative cultures, low procalcitonin < 0.5, etc.)

Clinical Status?

Mild disease
- No hypoxia or radiographic evidence of pneumonia

Supportive Care Only
Anschutz Campus—Consider evaluation for PETAL Study inclusion (HCLQ vs. placebo)-see pages 4 & 8

Moderate Disease or Mild at high risk for complications/progression

- Moderate: hypoxia and/or radiographic evidence of pneumonia
- Risk factors: age ≥ 65 years, heart disease, lung disease, diabetes, transplant, immunocompromised state, obesity

Severe Disease
- Need for high-flow, NIV, or mechanical ventilation

Management Considerations*

No proposed antivirals have demonstrated efficacy for COVID-19

* Consideration for clinical trial enrollment first if available (page 4-10):
    - Earlier in symptom course (< 7 days) may respond to antivirals
    - Anschutz Campus only—Remdesivir moderate and severe COVID-19 clinical trials (see pages 4, 6-7)

Antibacterial therapy should be discontinued upon diagnosis of COVID-19 and absence of features consistent with bacterial pneumonia

Site-Specific Criteria for Treatment Decisions

Central Region: ID consult mandatory if considering therapy, ensure patient (or POA) are interested in investigational therapies before consulting.
South Colorado Region: Any experimental therapy used off label with the exception of hydroxychloroquine or tocilizumab should be discussed with infectious diseases, pulmonary/critical care, or pharmacy
Northern Colorado Region: Contact ID or pulmonology for guidance.

Other Therapy Options:

* Remdesivir - compassionate use if pregnant or < 18 years old (page 5)
* Other therapies not routinely recommended at present outside of a clinical trial. Pages 11-12 lists these agents as well as details about use and links to available studies if use is considered.

Evidence of hyperinflammatory response?
Host modifiers
(e.g. anti-IL6)

No proposed immune/host modulating therapies have demonstrated efficacy or safety for COVID-19

* Consider enrollment in sarilumab clinical trial, see pages 4-5 (Anschutz Campus only)
* Tocilizumab has been used off-label for this indication, see pages 12-13 for evidence, criteria, and considerations.

National Guidelines on COVID-19 Therapeutics

1. Infectious Diseases Society of America
2. National Institute of Health
3. Society of Critical Care Medicine

Updated 4-16-20

University of Colorado Hospital / University of Colorado Health Anticoagulation Subcommittee

ANTICOAGULATION RECOMMENDATIONS FOR HOSPITALIZED COVID-19 PATIENTS

I. GENERAL INFORMATION

- Patients infected with the COVID-19 virus are potentially at ***increased risk of venous thromboembolism*** due to hospitalization, immobilization/isolation, and likely the infection itself
- COVID-19 has been associated with a coagulopathic presentation that mimics DIC, which may be more pro-thrombotic than hemorrhagic
- Lab derangements may include elevated d-dimers, prolonged prothrombin time ratios, elevated fibrinogen, elevated ferritin and thrombocytopenia

II. RECOMMENDATIONS FOR SUBCUTANEOUS VTE PROPHYLAXIS

Floor Patients	**D-dimer <1500* AND** **TEG (MA) ≤ 70&** (Only if available, see info below)	**D-dimer > 1500* OR** **TEG (MA) > 70&** (Only if available, see info below)
Weight <100 kg	Enoxaparin 40 mg QD	Enoxaparin 30 mg BID
Weight 100-150 kg	Enoxaparin 30 mg BID	Enoxaparin 40 mg BID
Weight > 150 kg	Enoxaparin 40 mg BID	Enoxaparin 0.5 mg/kg BID
AKI (GFR<30 ml/min)#	UFH 5000 U TID	UFH 7500 U TID

ICU Patients	**D-dimer <1500* AND** **TEG (MA) ≤ 70&** (Only if available, see info below)	**D-dimer 1500* OR** **TEG (MA) > 70&** (Only if available, see info below)
Weight <100 kg	Enoxaparin 40 mg QD	Enoxaparin 40 mg BID
Weight 100-150 kg	Enoxaparin 40 mg BID	Enoxaparin 0.5 mg/kg BID
Weight > 150 kg	Enoxaparin 60 mg BID	Enoxaparin 0.5 mg/kg BID
AKI (GFR<30 ml/min)#	UFH 5000 U TID	UFH 7500 U TID

* Based on scarce available mortality data and preliminary data from anti-Xa activity levels in UCH pts

& This guideline does not endorse performing Thromboelastography (TEG) to be routinely done in COVID-19 patients, particularly those on the floor, but use of results may be considered if it is performed. Available in data from other populations indicate hypercoagulability is present in patients with TEG MA values above 70, although no outcomes data in COVD-19 to date. In addition, no clear data to date to incorporate other markers of inflammation like fibrinogen or ferritin at this time to drive anticoagulation choices, but these have been noted to be elevated in severely sick COVID-19 patients

Considerations for patients with AKI:

- Patients on renal replacement therapy (HD, CRRT) may require more aggressive anticoagulation therapy in order to prevent clotting of the filter. Renal service should be consulted for final recommendation

- Estimated GFR should not be used alone to assess renal function as patients with AKI may still have estimated GFR > 30 ml/min.

III. ADDITIONAL CONSIDERATIONS FOR PR0PHYLACTIC OR THERAPEUTIC ANTICOAGULATION IN COVID-19 PATIENTS.

a. COVID-19 patients with a ***history of thromboembolic disease and/or on chronic anticoagulation prior to admit*** should continue home anticoagulation regimen if clinically appropriate, or transition to alternative agent (most cases IV UFH) for therapeutic anticoagulation.

b. COVID-19 patients who develop ***new arterial of venous thromboembolic events*** should be treated with therapeutic anticoagulation (UFH, LMWH) as standard of practice would dictate

c. ***For high clinical suspicion of new thromboembolic events***, consider empiric therapeutic anticoagulation using heparin gtt and order a truncated, lower extremity DVT protocol (POCUS) as a confirmatory test.
   i. Initiation of therapeutic anticoagulation without confirmed or high clinical suspicion of DVT/PE, is controversial and is ***not*** recommended by ***national/international guidelines (see below)***
   ii. In the setting of extremely high D-dimers (e.g. >3000 ng/ml), persistent clotting of lines and/or worsening clinical course, therapeutic anticoagulation may be considered and a multidisciplinary discussion with critical care attending, anti-thrombosis services and others (path, heme) is recommended

d. Primary teams are recommended to consult the inpatient anticoagulation service (metro) or pharmacy (North and South) ***to assist with dose optimization*** (AKI, drug-drug interactions, extremes of body weight, other) ***or therapeutic selection*** (appropriate heparin order set, use of alternative anticoagulants such as DOACS or injectable DTIs). Issues include
   i. For Enoxaparin: measure anti-Xa level 4 hours after 3rd dose. Goal = 0.3-0.5. Increase dose as needed guided by anti-Xa level. Consider using TEG.

e. When TEG monitoring available: Use Kaolin / heparinase

IV. AVAILABLE GUIDANCE ON ANTICOAGULATION IS AVAILABLE THROUGHT HE FOLLOWING ORGANIZATIONS:

a. International Society of Thrombosis and Haemostasis
b. American Society of Hematology
c. Anticoagulation Forum
d. American College of Cardiology

Remdesivir: Compassionate Use

Inclusion Criteria:

- Hospitalized with confirmed SARS-CoV2 by polymerase chain reaction (PCR) or known contact of confirmed case with syndrome consistent with coronavirus disease (COVID-19) with PCR pending
- Pregnant or < 18 years of age
- Adequate renal function with estimated glomerular filtration rate (eGRF) ≥ 30 ml/min by local laboratory measure
- Alanine aminotransferase (ALT) ≤ 5 x upper limit of normal (ULN) by local laboratory measure

Ongoing Trials at UCH (Anschutz Campus) for Patients with COVID-19

	Hydroxychloroquine	Remdesivir GS-5773 Resumed 4-21-20	Remdesivir GS-5774	Sarilumab	Convalescent Plasma
Max latency from first ever PCR+ to enrollment (days)	10 (but <48 hours from admission)	4	4	14	No limit
Probability of getting the study drug (%)	50 (1:1)	100	100	400mg vs Placebo	100
Languages supported	English, Spanish, Arabic, Dutch, Italian, Vietnamese, Portuguese, French, Russian, German, Somali, Greek, Haitian Creole, Chinese (Mandarin/ Traditional), Hebrew	English, Spanish	English, Spanish	English, Spanish	English
Age	≥ 18	≥ 18	≥ 18	≥ 18	≥ 18
Inclusion criteria	**One** or more the following symptoms: cough, fever (>37.5 C / 99.5F), shortness of breath, sore throat	**Hypoxia** (≤94% on RA, or on supplemental oxygen) **Pneumonia** (on imaging)	**No Hypoxia** (>94% on RA at screening) **Pneumonia** (on imaging)	**Pneumonia** (on imaging or exam) **NIPPV, HFNC, or mechanical ventilation**	**Moderate, Severe, or Life threatening** Moderate = ≥ 1 of the following: Dyspnea, Respiratory rate >30/min, Blood oxygen saturation <93% on RA
Exclusion criteria (the list is not comprehensive)	last ECG (within 72 hours) with QTc > 500ms OR Known diagnosis of long QT syndrome Seizure disorder Tx with amiodarone; cimetidine; dofetilide; phenobarbital; phenytoin; sotalol Inability to receive enteral medications	AST or ALT >5xULN Creatinine clearance <50ml/min using Cockcroft-Gault Multi-organ failure Enrollment into other COVID-19 trial Treatment with anti-viral medications for COVID-19	AST or ALT >5xULN Creatinine clearance <50ml/min using Cockcroft-Gault Mechanical ventilation Enrollment into other COVID-19 trial Treatment with anti-viral medications for COVID-19	ANC <2000 ALT/AST >5xULN Platelets <50 Suspected or active bacterial or fungal infection	None
Permitted co-interventions					
Anti-viral	✔	✘	✘	✔	✔
Anti-inflammatory	✔	✔	✔	✔	✔
Participation in another clinical trial	✔	✘	✘	✔* Only if open label	✔

Sarilumab (IL-6 receptor blocker) – sponsored by Regeneron (Trial ID – 6R88-COV-2040)

Rationale/mechanism: COVID-19 patients have been found to have significant immune activation and cytokine release leading to end-organ injury. Sarilumab is a monoclonal antibody directed against membrane bound and soluble IL-6 receptors. IL-6 receptor blockade may moderate the end-organ effects of immune activation

Trial design and treatment protocol: An Adaptive Phase 2/3, Randomized, Double-Blind, Placebo-Controlled Study Assessing Efficacy and Safety of Sarilumab for Hospitalized Patients with COVID-19. Participants are randomized in a 2:2:1 ratio to multiple doses (as needed) of Sarilumab 400 mg IV, 200 mg IV, or placebo (thus the probability of patient getting placebo is 20%). Patient will receive repeat doses at 24 hours after the initial administration if the patient meets one of the following criteria: remains febrile, fails to improve gas exchange (as measured by ventilator settings or O2 requirements), is hemodynamically unstable, or exhibits objective evidence of clinical worsening. Patient may also receive repeat weekly doses if they continue to require any supplemental oxygen above baseline.

Inclusion criteria:

Hospitalized adult patients (18+ years of age) with laboratory confirmed COVID-19 by PCR/NAAT (up to 14 days prior to enrollment from first/initial positive result)

Evidence of pneumonia – by chest radiograph, chest CT, or auscultation (rales, crackles)

Oxygenation by high flow NC, non-rebreather, Mechanical Ventilation, OR ICU admission

Exclusion criteria:

Not expected to survive >48 hours (in the opinion of the investigator)

Labs: ANC <2000, ALT/AST >5xULN, and platelet count <50,000

Treatment with IL6 inhibitor or Janus kinase inhibitor (JAKi) in the past 30 days

Current simultaneous treatment with leflunomide and methotrexate

Active TB or history of incompletely treated TB. Suspected or known extrapulmonary TB

Active or suspected bacterial or fungal infection

Participation in a double-blind clinical trial (participation in open-label study of hydroxychloroquine, Remdesivir, or any other COVID-19 treatment is permitted).

Adverse reactions: neutropenia, transaminitis, hypersensitivity reaction, hypercholesterolemia, colitis
Notes: The drug is not dialyzable, so patients can continue their HD or CRRT

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Remdesivir – sponsored by Gilead. Trial ID – **GS-5773** **(Resumed 4-21-20) - SEVERE Arm**

Rationale/Mechanism: nucleotide analogue with activity against coronaviruses (SARS, MERS, SARS2) in vitro and in animal studies.

Trial design: Open-label, single arm, non-randomized trial. All patients receive the study drug (intravenous infusion) for up to 10 days.

Inclusion criteria:

Hospitalized adults 18+ years of age with confirmed COVID-19 with PCR/NAAT (within 4 days of first/initial ever positive PCR result from Randomization)

Radiographic evidence of pneumonia

Oxygen saturation ≤94% on room air or requiring oxygen supplementation

Exclusion criteria:

Participation in any clinical trial involving treatment of COVID-19

Receipt of any pharmacologic therapy (with known or possible direct antiviral activity) for COVID-19 for up to 24 hours prior to study drug dosing. (Anti-inflammatory therapy is allowed)

Multi-organ failure

On ECMO for 5 or more days

AST/ALT >5xULN

Creatinine clearance <50ml/min using Cockcroft-Gault formula

Pregnant or breastfeeding

Dosing: 200mg IV day 1, and 100mg IV daily up to 10 days (less if patient gets discharged earlier)

Adverse reactions: nausea, vomiting, transaminase elevation

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Remdesivir – sponsored by Gilead. Trial ID – **GS-5774—Moderate arm**

Rationale/Mechanism: nucleotide analogue with activity against coronaviruses (SARS, MERS, SARS2) in vitro and in animal studies.

Trial design: Open-label, three arm, randomized trial. Patients are randomized to the following treatment groups – 5-day course, 10-day course and no treatment (1:1:1). Treatment will stop if patient is discharged earlier than the completion of assigned therapy duration.

Inclusion criteria:

Hospitalized adults 18+ years of age with confirmed COVID-19 with PCR/NAAT (within 4 days of first/initial ever positive PCR result from Randomization)

Oxygen saturation >94% on room air at screening

Radiographic evidence of pulmonary infiltrates

Exclusion criteria:

Participation in any clinical trial involving treatment of COVID-19

Receipt of any pharmacologic therapy (with known or possible direct antiviral activity) for COVID-19 for up to 24 hours prior to study drug dosing. (Anti-inflammatory therapy is allowed)

Mechanical ventilation at screening

AST or ALT >5xULN

Creatinine clearance <50ml/min using Cockcroft-Gault formula

Pregnant or breastfeeding

Dosing: 200mg IV day 1, and 100mg IV daily up to 5 or 10 days, whichever assigned. Treatment will stop if any elevations in ALT > 5 xULN; or ALT > 3 xULN and total bilirubin > 2 xULN, confirmed by immediate repeat testing OR Creatinine Clearance < 30 mL/min OR Any SAE or ≥ Grade 3 AE suspected to be related to RDV

Adverse reactions: nausea, vomiting, transaminase elevation

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Hydroxychloroquine – ORCHID Trial, run by PETAL Network, sponsored by NHBLI

Rationale/Mechanism: Low endosomal pH plays a role in allowing viral replication inside the target cell. Endosomal acidification inhibitors such as Chloroquine and Hydroxychloroquine, may have a potential role in treatment.

Trial design: randomized, double-blind, placebo-controlled phase 3 trial. 1:1 randomization to hydroxychloroquine or placebo (50% chance of receiving the study drug)

Inclusion criteria:

Hospitalized adults 18+ years of age with confirmed SARS-CoV-2 PCR positive within last 10 days

One or more the following symptoms: cough, fever (>37.5 C / 99.5F), shortness of breath, sore throat

Exclusion criteria:

Pregnancy or breastfeeding

Prisoner

>10 days since symptom onset

>48 hours since hospital arrival

last ECG (within 72 hours) with QTc > 500ms

Known diagnosis of long QT syndrome

Seizure disorder

Porphyria cutanea tarda

Receipt in the 12 hours prior to enrollment, or planned administration during the 5-day study period that treating clinicians feel cannot be substituted for another medication, of any of the following: amiodarone; cimetidine; dofetilide; phenobarbital; phenytoin; sotalol

Receipt of >1 dose of hydroxychloroquine or chloroquine in the 10 days prior to enrollment

Inability to receive enteral medications

Dosing: Hydroxychloroquine 400mg twice daily for 2 doses, and 200mg twice daily for 8 doses

Monitoring: ECG or Telemetry to follow up on QTc 24 to 48 hours of study drug initiation

Adverse reactions: QTc prolongation

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Convalescent Plasma

INCLUSION CRITERIA

1. Age ≥ 18 years

2. Laboratory confirmed diagnosis of infection with SARS-CoV-2

3. Admitted to an acute care facility for the treatment of COVID-19 complications

4. Moderate to Severe or life threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease

5. Informed consent provided by the patient or healthcare proxy

Moderate COVID-19 is defined by one or more of the following:

- Dyspnea
- Respiratory frequency >30/min
- Blood oxygen saturation <93%

Severe COVID-19 is defined by one or more of the following:

Moderate criteria plus one of the following:

- Radiologic evidence of > 50% pulmonary involvement
- Requirement for supplementary oxygen therapy to maintain blood oxygen saturation >90%

Life-threatening COVID-19 is defined as one or more of the following:

- Respiratory failure requiring mechanical ventilation or non-invasive non-rebreather oxygen support
- Prone positioning to support oxygenation
- Multiple organ dysfunction or failure

Scoring System for allocation of Plasma:

Score	0	1	2	3
PaO2/FiO2	>400 mmHg	200-400 mmHg or O2 > 5L/min	100-200 mmHg or mechanical ventilation	Prone ventilation, ECMO
Cardiovascular (Hypotension)	MAP > 70 mmHg	MAP < or = 70mmHg	On norepi < or= 1 mcg/kg/min	Norepi > 0.1 mcg/kg/min or more than 1 pressor
Renal (S. Creat)	<1.2	1.2-2.0	2.0-4.0	> 4.0 or on dialysis
Age	>75	60-75	40-60	<40
Days since admission	>7	5-7	3-5	< 3
Pregnancy status	No or N/A			Yes
Immunocompromised state- immunosuppressive medications, transplant recipient	No	Immuno-suppressive medications including chemotherapy		Functioning organ transplant

Priority for convalescent plasma to be given to patient with highest score

Convalescent Plasma

Process for allocation/administration:

1. Inpatient ID team to be consulted to decide if appropriate candidate for allocation of convalescent plasma.
2. ID Team can send Epic chat message/call Lakshmi or David Beckham to help with consent/orders for convalescent plasma between 8am-3pm daily including weekends.
3. Patients will be enrolled under the FDA expanded access protocol and will also be included in a multi-institutional prospective, cohort study.
4. 1-2 units per patient to be allocated based on weight.
5. There is limited ability to consent and prepare convalescent plasma/day, so attached screening system could be used as a guide to refer patients. Higher score may indicate sicker patients, patients at higher risk for progression to serious disease and those who may benefit most.
6. Neutralizing antibody titer is not being checked in donor plasma at this time. ABO matched plasma is given whenever possible.
7. Premedication can be administered by primary team if needed.
8. Inclusion in convalescent plasma trial may exclude patients from other clinical trials for example: remdesivir clinical trial- please consult with your local clinical trials coordinator. Patients will be eligible for sarilumab trial.

Forms to be signed for each eIND transfusion:

- Transfusion consent
- Additional COVID19 transfusion consent
- CCP eIND consent.

Consult ID if you believe your patient is good candidate for convalescent plasma.

Author: Lakshmi Chauhan, updated 5/1/2020

Evidence Summary for Potential COVID-19 Therapies

Last Revised 3/28/20

Therapy	Mechanism	Evidence	Comments/Recommendation
Remdesivir	Nucleoside analog: inhibits viral RNA polymerase	In Vitro—low EC_{50} value = 0.77 µM Clinical trials for COVID-19—ongoing	Investigational antiviral, access via clinical trial or expanded access program only. Compassionate use still supported for pregnant patients and pediatrics (< 18yr)
Hydroxychloroquine (HCLQ)/Chloroquine (CLQ)	Anti-inflammatory and inhibition of viral entry	In Vitro—HCLQ EC_{50} = 0.72 µM & CLQ EC_{50} = 5.47 µM Clinical: • Tang et a.l. Open-label, randomized, controlled trial • Mehevas M et al. retrospective cohort • Chen et al. Randomized, open label study of HCLQ 200mg PO BID x 5 days for COVID-19 (n=31) vs. standard of care alone (n=31) in mild disease. • Gautret et al. non-randomized, prospective study of HCLQ vs. supportive care among cohort of mostly mild disease. No clinical outcomes reported. Poor quality study. • Gautret et al. 80 patients, non-comparative • Gao et al. editorial, reports unpublished, positive results from Chinese trials	Unclear role, evidence published to date is mixed and study designs are not highest quality. Current use outside of a clinical trial should be weighed against risk for adverse events and unclear benefit for COVID-19 infection. • Proposed dose: 400mg BID x 2 doses, then 200mg PO BID x 8 doses (total duration = 5 days) • Monitoring: QTc (avoid concurrent QTc prolonging meds, avoid use if baseline or subsequent QTc > 500 msec or > 520-540 if QRS > 120 msec), LFTs, hemoglobin (anemia), vision (retinopathy—rare) • Pregnancy category C
HIV Protease Inhibitors: Lopinavir/ritonavir (LPV/r) Darunavir/cobicistat (DRV/c) Atazanavir (ATV)	Inhibition of viral protease	♦ LPV/r: in vitro activity extrapolated from SARS-CoV-1 and MERS-CoV. • Chu-2004 and Chan-2003 retrospective SARS-CoV-1 • NEJM prospective study of LPV/r vs. supportive care for SARS-CoV-2. No differences identified. ♦ DRV/c— Janssen, found no relevant in vitro activity ♦ ATV—no in vitro studies, but reports that models show high affinity for docking	Role unclear for us in COVID-19. NEJM study vs. supportive care showed no benefit, though small and most started on therapy later in illness. Presently unclear role, and might be an alternative if other options unavailable due to supply or contraindications/intolerance. • Significant drug interactions • Monitor: QTc, liver impairment, cytopenias
Ribavirin (RBV)	Nucleoside analog: inhibits viral RNA polymerase	In vitro EC_{50} = 109.5 µM No clinical evidence for SARS-CoV-2, some combination with LPV/r or IFN evidence from SARS-CoV-1	Not recommended as monotherapy, might consider in combination with LPV/r, but unclear role. Use with caution given safety (anemia, teratogenicity). Enteral route preferred.
Nitazoxanide (NTZ)	Unclear, potentially interaction with host regulated pathways	In vitro only, EC_{50} = 2.12 µM Evidence in flu with shorter symptom length	Insufficient evidence for routine use, might be considered if other therapies unavailable. Well-tolerated, $$$, suggested dose 1,000mg P O BID
ACE-I / ARB	Anti-hypertensives	Theoretical increased viral entry through animal models showing RAAS inhibition leads to ACE-2 upregulation. **No evidence to date of a strong association.** Kassiri et al. ACE2 knockout mice have adverse ventrilcular remodeling Oudit et al. ACE-2 downregulation associated with myocardial dysfunction during SARS-CoV-1 Zhang P, et al. Retrospective analysis of ACEi/ARB use	**ACC, AHA, and others recommend continuation of these meds in setting of COVID-19 infection, as abrupt discontinuation can worsen underlying conditions that have proven mortality benefit.** Insufficient evidence to avoid/discontinue ACE-I or ARBs when compelling indications for their use exists. Insufficient evidence to recommend use of these agents for treatment of COVID-19.

***There are currently no FDA approved agents for the treatment of COVID-19, and limited evidence supports clinical benefit, weigh risks and benefits prior to initiation. Data is rapidly evolving with therapeutics for COVID-19 and recommendations are subject to change. Please refrain from printing this document.**

Evidence Summary for Potential COVID-19 Therapies

Last Revised 3/28/20

Therapy	Mechanism	Evidence	Comments/Recommendation
NSAID's	Anit-inflammatory, analgesic, anti-pyretic	Uncontrolled case report of 4 patients taking ibuprofen who had worsening infection and theoretical upregulation of ACE-2 receptors (target for viral entry). No strong evidence to avoid NSAIDs for fever/analgesia in COVID-19 patients.	EMA, FDA and WHO do not recommend to avoid NSAIDs due to concerns about worse outcomes in COVID-19. Use APAP or NSAID as indicated based on underlying comorbid conditions. Do not stop low-dose Aspirin for cardiovascular benefit.
Corticosteroids	Anti-inflammatory	Mixed—some instances of delayed viral clearance (indifference/ worse outcomes—extrapolated from SARS-CoV-1, MERS, influenza, RSV) to improved survival among those with ARDS.	Evidence weak regarding corticosteroid administration. Routine use recommended against by CDC and WHO. SCCM guidelines provided weak recommendations to consider in refractory shock and/or ARDS
Tocilizumab	IL-6 receptor antagonist Theoretical management of patients with hyperinflammatory response (aka cytokine release)	Case series (n=20), described rapid improvement in patients from oxygenation and inflammatory markers after 400mg dose. Only 2 patients were intubated at time.	Low quality evidence with improvement. Concerns with safety, particularly with worsening of infections (TB, fungal, other bacterial) due to immunosuppressive characteristics. Criteria for off-label prescribing for COVID-19 on page 11
Sarilumab	IL-6 antagonist	None, clinical trials underway	Similar considerations to tocilizumab
Baricitinib & other Jak-I's	Janus kinase (Jak) inhibitor AAK1 inhibition impacting viral entry and anti-inflammatory	Theoretical, no clinical evidence available presently.	Not recommended given limited evidence and theoretical mechanisms
IVIG	Neutralizing antibodies, immunomodulating effects	Cao et al. case report, n=3	Presence of neutralizing antibodies not expected, theoretical immunomodulating effects. Not routinely recommended. SCCM guidelines recommend against use.
Convalescent serum	Neutralizing SARS-CoV-2 specific IgG from recovered patients	Shen, et al. 2020—case report, n=5 patients.	FDA allowing EIND use.
Interferon	Direct viral effects and indirect stimulation of innate immune responses against viral infection	Mostly reports of combination use with ribavirin or LPV/r from China. INTEEREST trial—INF β1b had no effect on mortality in ARDS, but increased mortality in subgroup when combined with steroids	No direct comparison studies in SARS-CoV-2. Recommend against routine use. SCCM guidelines do not recommend.
Statin's	Pleiotropic, immunomodulating effects, cardioprotective	No published evidence, based on mechanism and extrapolation from other data	Not routinely recommended, consider adding/continuing if other compelling indication exists for statin.
Favipiravir	RNA polymerase inhibitor	In Vitro EC50 higher then remdesivir and CLQ/HCLQ Cai et al. 2020—open label, prospective comparison vs. LPV/r	Favipiravir is under investigation, but is not approved for use in the U.S., and no active study sites listed in U.S.
Zinc	Unclear, inhibits viral replication	No published studies, theoretical	Recommend against routine use
Vitamin C	Unclear, likely immunomodulating	No published evidence, ongoing high-dose IV study in China	Low quality evidence, recommend against routine use
Azithromycin	Antibacterial and proposed anti-inflammatory effects	No in vitro antiviral effects published • Gautret et al. n=6 patients on azithro and HCLQ • Gautret et al. 80 patients, non-comparative with combo	Low quality evidence. Combination not recommended outside concern for atypical pneumonia. Monitor QTc closely.

***There are currently no FDA approved agents for the treatment of COVID-19, and limited evidence supports clinical benefit, weigh risks and benefits prior to initiation. Data is rapidly evolving with therapeutics for COVID-19 and recommendations are subject to change. Please refrain from printing this document.**

Tocilizumab: System Criteria for Use

- Confirmed COVID-19 positive (No empiric use)
- Critical illness associated with COVID-19 evidenced by: Respiratory failure requiring mechanical ventilation *or* Shock *or* failure of other organs requiring ICU care
- Evidence of ≥2 laboratory abnormalities associated with hyperinflammatory response: D-Dimer > 1 mcg/mL, Serum ferritin > 600 mcg/L, Persistent fever > 38.3 °C, C-Reactive Protein > 100 mg/L or 10x ULN, Interleukin-6 ≥ 3x ULN
- Ordered/recommended by Infectious Diseases or Pulmonology Services
- Review and approval by secondary provider(s) not directly involved in the patients care
- ALT/AST < 5x ULN
- Platelet Count is ≥ 50,000/mm3
- Absolute Neutrophil Count (ANC) is ≥ 500/mm^3
- No presence of active or strongly suspected bacterial or fungal infection. Stability of these infections with appropriate antibiotics/antifungals and proceeding with tocilizumab should be carefully weighed by ordering/consulting infectious diseases and/or pulmonology physician.
- Consider avoiding use for significantly elevated procalcitonin levels (i.e > 2 ng/mL), as this may represent an active bacterial infection
- No history of untreated or inadequately treated TB, or latent TB infection
- Caution if high risk of GI perforation (primarily reported as a complication of diverticulitis)
- Not a candidate for Sarilumab Clinical Trial (Anschutz only)

Dosing: 400mg IV once (if < 50kg then 8mg/kg)

- Repeat dose x 1 after 12-24h may be considered