

Seattle Children's Hospital Interim Treatment Guidelines for SARS-CoV-2 Infection/COVID-19

(Adapted from UW Medicine Treatment Guidelines)

Last Updated: April 19, 2020

The Seattle Children's Hospital COVID-19 Clinical Treatment Guidelines aim to consolidate up-to-date evidence, best practice, and multidisciplinary expert consensus regarding the treatment of inpatients with COVID-19. The goal is to ensure a shared mental model to be utilized by clinical teams at the point of care to facilitate high quality medical care. This guideline may need to be adapted for each specific patient based on practitioners' professional judgement, patient-specific risks, and/or the availability of resources at Seattle Children's Hospital.

There are no FDA-approved or clinically proven therapies for treatment of SARS-CoV-2. The Infectious Diseases team should be consulted for all patients in whom treatment is being considered. Immunology and Rheumatology should be consulted in addition if there is concern for cytokine storm or poor prognostic markers. Clinical trial data is rapidly emerging from other parts of the world, and these guidelines will be updated frequently to reflect the most recent evidence.

These guidelines reflect what is known about therapies that have *in vitro* activity against coronaviruses, have been used to treat other coronaviruses, such as SARS or MERS, or may theoretically target of the underlying pathophysiology of severe acute respiratory syndrome (ARDS) due to SARS-CoV-2.

Our best opportunity to understand how to treat COVID-19 is to study stepwise interventions and compare findings to the current best available standard. Although there are interventions available, at this time, these are not evidence based and should not be considered effective. Some of the interventions are FDA-approved for other indications and have known toxicity profiles.

Some medications are in limited supply and use of these medications for off-label indications will affect patients who need the medications for indicated conditions. Therefore, off-label medications should be reserved for those who are at highest risk for complications as outlined below. Furthermore, patients and families should recognize that there is a potential RISK of these medications without known benefit. The decision to treat patients should involve shared decision making.

Please call the ID, Immunology, and Rheumatology teams with questions about inpatient management of specific patients.

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Treatment Guidelines

Disease Category	Clinical presentation	Management – standard risk	Management – high risk*
Mild/outpatient	<ul style="list-style-type: none"> • May include fever, sore throat, cough, and/or myalgias. • No dyspnea or supplemental oxygen requirement. 	Supportive care	Supportive care
Moderate	<ul style="list-style-type: none"> • May include fever, dyspnea, and/or chest imaging consistent with COVID-19 pneumonia. • <u>New or increased supplemental oxygen requirement.</u> 	Supportive care	Consider investigational agents (see algorithm).
Severe	<ul style="list-style-type: none"> • May include fever, dyspnea, and/or chest imaging consistent with COVID-19 pneumonia. • <u>New or increased requirement for invasive or non-invasive mechanical ventilation, sepsis, or multi-organ failure</u> 	Consider investigational agents (see algorithm).	Consider investigational agents (see algorithm).

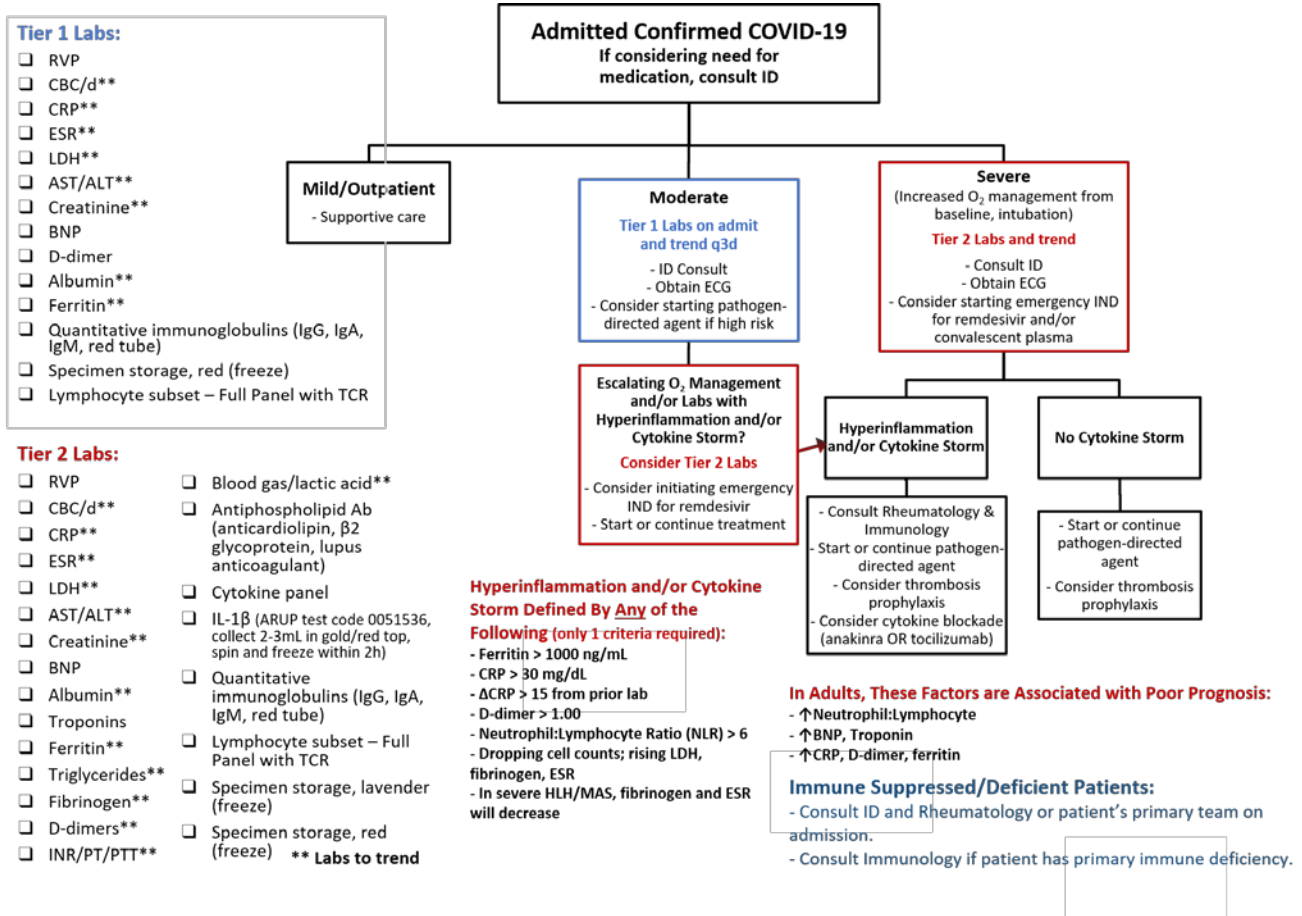
- If considering use of investigational agent consult ID
- If considering use of cytokine blockade, consult Rheumatology, Immunology, and ID

* **High risk** patients include those with underlying heart or lung disease, hypertension, diabetes, obesity (BMI ≥30), cancer, hematopoietic cell transplant (HSCT), solid organ transplant (SOT), immunosuppressed/immunodeficient patients, or age ≥20 years old (for which, use UW guidelines)

- Medications concerning for immunosuppression include but are not limited to: chronic steroids, tacrolimus, cyclosporine, cyclophosphamide, azathioprine, mycophenolate mofetil, methotrexate, JAK inhibitors, TNFα inhibitors, rituximab

Adapted from PIDs Guidance

Treatment and Laboratory Algorithm



Medications to Consider

Medications to Consider

PATHOGEN-DIRECTED

Medication	Dosing	Special Considerations
Remdesivir	Per emergency IND (eIND)	- Requires eIND - Review inclusion & exclusion criteria
Hydroxychloroquine (HCQ)*	13mg/kg (max 800mg) PO then 6.5mg/kg (max 400 mg) PO at 6, 24, and 48 hours after initial dose (duration could be extended for up to 5 days on a case-by-case basis)	Obtain baseline EKG given risk of QT prolongation; contraindicated in WPW and QTc >500ms
Convalescent plasma	Contact blood bank	<18 years: eIND via FDA 18+: expanded access protocol pending (eIND in meantime)

*Recommend monitoring QT interval with prolonging agents (i.e., azithromycin, cyclosporine, tacrolimus)

• Azithromycin not routinely recommended in conjunction with HCQ for COVID-19 therapy; do **NOT** recommend discontinuing if on chronic therapy

**Steroids should only be considered in the context of ARDS. Routine use of steroids not advised.

Do **NOT** recommend discontinuing ACE/ARB therapy if patient on chronic therapy but do not recommend initiating for the treatment of COVID-19.

HOST-DIRECTED

Medication	Dosing	Special Consideration
Methylprednisolone **	Wt >60 kg: 60mg QD; <u>OR</u> Wt <60kg: 2mg/kg QD	Consult ID and Rheumatology
Anakinra	4mg/kg IV QD (can increase frequency) Max dose 100mg	Consult ID, Rheumatology, & Immunology prior to giving
Tocilizumab	8mg/kg IV x 1 Max dose 800mg	Consult ID, Rheumatology, & Immunology prior to giving

ADJUNCTIVE THERAPY

Medication	Dosing	Special Considerations
Stress Dose Hydrocortisone	See formulary dosing	For patients on chronic glucocorticoids, if febrile or requiring O ₂ , low blood pressure, unexplained vomiting
Thrombosis prophylaxis with enoxaparin or heparin	See formulary for prophylactic dosing	Consult pharmacy. Strongly consider thrombosis prophylaxis in all COVID-19 positive patients.

POTENTIAL THERAPY INFORMATION

Post exposure prophylaxis (PEP) of COVID-19 is not currently recommended. Several trials of post exposure prophylaxis are currently underway or are planned.

CLINICAL TRIAL AND COMPASSIONATE USE AGENTS

REMDESIVIR

Mechanism of Action: Nucleotide analogue, initially developed for treatment of Ebola. Works by inhibiting RNA-dependent RNA polymerase.

Dosing: Dosing determined by manufacturer at time of emergency IND.

Evidence Summary: *In-vitro* activity against MERS and SARS, and has shown efficacy in animal models. (Gordon et al 2020, de Wit et al 2020, Sheahan et al 2017)²⁻⁴. It has been shown to inhibit SARS-CoV-2 *in vitro* (Wang et al, 2020)⁵.

There are reports of its use in patients with SARS-CoV2 in China, but there is no published data yet.

Remdesivir was used in a single patient with COVID-19 infection in Washington State; administration was associated with clinical improvement (Holshue et al 2020)⁶.

Clinical Trials Underway: NCT04349410, NCT04314817, NCT04315948, NCT04321616, NCT04323761, NCT04280705, NCT04292899, NCT04292730, NCT04302766. NCT04280705 is a randomized placebo-controlled clinical trial being conducted at UW Medicine (>18 years). No clinical trials available for treatment at Seattle Children's Hospital.

Compassionate Use: <https://rdvcu.gilead.com/>. The requesting physician and pharmacist must complete all relevant paperwork to qualify a patient for this program. Per Gilead website as of 3/22/2020, they are unable to accept new individual compassionate use requests, **UNLESS the requests are for pregnant women and children less than 18 years of age with confirmed COVID-19 and severe manifestations of disease.**

1. Key Inclusion criteria: Hospitalization, confirmed SARS-CoV-2 by PCR, moderate to severe disease presentation as determined by the principal investigator
2. Key Exclusion criteria: Evidence of multi-organ failure, pressor requirement to maintain blood pressure, ALT levels > 5x ULN, Cr clearance <30 mL/min or dialysis or continuous veno-venous hemofiltration, use of other experimental antiviral agents for COVID-19. Pregnancy not currently an exclusion criteria.

Toxicities and Drug Metabolism:

- Elevated transaminases
- Reversible kidney injury
- Hypotension during infusion
- AVOID acetaminophen use through day 15

CONVALESCENT PLASMA

Mechanism of Action: Polyclonal IgG against SARS-CoV-2.



Dosing: Dosing determined at time of emergency IND.

Evidence Summary: Passive immunotherapy is under development locally and nationally as a therapy for COVID-19. A recent very small case series indicates safety and clinical improvement¹⁸. Convalescent plasma infusion (CPI) generated at UW Medicine/Bloodworks Northwest is expected to be available soon and prior to pooled immune globulin products. CPI has been studied in 80 persons for SARS-CoV-1 during the previous outbreak¹⁹ and was generally safe, as well as for MERS, influenza, and viral hemorrhagic fevers. CPI is considered FDA approved (<https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma>), reducing regulatory burden. Experience from SARS-CoV indicated that early treatment was associated with a higher proportion of patients with good outcomes.

- <18 years of age: obtain emergency IND via FDA
- 18+ years of age: an expanded access protocol is pending; in the meantime, obtain emergency IND via FDA

Clinical Trials Underway: NCT04345679, NCT04346446, NCT04343261, NCT04338360, NCT04345991, NCT04347681, NCT04344535, NCT04333355, NCT04343755, NCT04348656, NCT04342182, NCT04345523, NCT04344015, NCT04340050, NCT04346589, NCT04332380, NCT04332835, NCT04327349, NCT04345289, NCT04292340, NCT04323800, NCT04348877, NCT04333251

To Obtain a Single Patient Emergency IND

- For requests between 8am EST and 8pm EST (Mon-Sun), the requesting physician may contact FDA by completing Form FDA 3926 (<https://www.fda.gov/media/98616/download>) and submitting the form by email to CBER_eIND_Covid-19@FDA.HHS.gov. For eIND requests submitted via email during this time frame, FDA will respond within 4 hours.
 - The completed form should include a brief clinical history of the patient, including: diagnosis, current therapy, and rationale for requesting the proposed investigational treatment in order to meet the expanded access use requirements in 21 CFR 312.305 and 312.310.
 - The form should include information regarding where the COVID-19 convalescent plasma will be obtained.
 - Providers should complete the form to the extent possible, and FDA will work with the provider if additional information is required. Providers are strongly encouraged to fill out the form electronically whenever possible.
 - FDA will review the request and, upon authorization, send the requesting physician a confirmatory email that includes the emergency IND number.
- For requests between 8am EST and 8pm EST where the provider is unable to complete and submit Form FDA 3926 due to extenuating circumstances, the provider can contact FDA's Office of Emergency Operations at 1-866-300-4374  to seek verbal authorization.
- For requests that are **overnight** between 8pm EST and 8am EST, the provider should contact FDA's Office of Emergency Operations at 1-866-300-4374  to seek verbal authorization.

- If verbal authorization is given, the requestor must agree to submit an expanded access application (e.g., Form FDA 3926) within 15 working days of FDA's authorization of the use. (21 CFR 312.310(d)(2)).

Patient Eligibility

To facilitate requests for eINDs for use of COVID-19 convalescent plasma to treat patients, health care providers seeking an emergency IND may want to consider the eligibility criteria used for the [National Expanded Access Treatment Protocol](#)[External Link Disclaimer](#). These criteria include:

- Laboratory confirmed COVID-19
- Severe or immediately life-threatening COVID-19, for example,
 - Severe disease is defined as one or more of the following:
 - shortness of breath (dyspnea),
 - respiratory frequency ≥ 30 /min,
 - blood oxygen saturation $\leq 93\%$,
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300 ,
 - lung infiltrates $> 50\%$ within 24 to 48 hours
 - Life-threatening disease is defined as one or more of the following:
 - respiratory failure,
 - septic shock,
 - multiple organ dysfunction or failure
 - Informed consent provided by the patient or healthcare proxy.

Contraindications:

- History of transfusion reactions
- Overt volume overload will be contraindications
- Renal failure

EMPIRIC THERAPIES

HYDROXYCHLOROQUINE (PLAQUENIL)/CHLOROQUINE

Mechanism of action: Heme polymerase inhibitor; increases the pH of the phagolysosome, which interrupts virus/cell fusion, as well as interferes with the glycosylation of cellular receptors of SARS-CoV (Colson et al 2020).⁷

Evidence Summary: Hydroxychloroquine has been shown to inhibit replication of SARS-CoV-2 *in vitro* (Wang et al 2020)⁵. Chloroquine has been shown to inhibit many viruses *in vitro*. However, it has not been shown to be an effective antiviral *in vivo* in limited trials. In an animal model of Chikungunya virus infection, chloroquine delayed the immune response, resulting in lack of viral clearance (Reviewed in Touret & deLamballerie 2020)⁸. In a recently published open-label, non-randomized study, of 20 patients with COVID-19 who received hydroxychloroquine 200 mg three times daily, 14 (70 %) had clearance of virus from the nasopharynx at day 6, compared to 2 (12.5%) of 16 who did not receive hydroxychloroquine (p= 0.001) (Gautret et al 2020 in press).

Clinical Trials underway: As of 4/19/2020, 104 trials were reported on <https://clinicaltrials.gov/ct2/home>. No clinical trials available for treatment at UW Medicine and Seattle Children's Hospital.

Toxicities and Drug Metabolism

- Nausea and diarrhea, both mild
- QTc prolongation
- May increase levels of cyclosporine
- Retinopathy with prolonged use (>5 years), not in the acute setting
- Anuric patient steady state levels are ~30% higher than patients w/ normal renal function
- The estimated half-life is 40 days

Administration

- For Wt >60kg: 800mg PO followed by 400 mg PO in 6 hours, 24 hours and 48 hours after initial dose (duration could be extended for up to 5 days on a case-by-case basis)
- For Wt <60kg: 13mg/kg PO followed by 6.5 mg/kg PO in 6 hours, 24 hours and 48 hours after initial dose (duration could be extended for up to 5 days on a case-by-case basis)
- If hydroxychloroquine is unavailable, Chloroquine phosphate 500 mg PO q12h for 10 days (adult dosing; equivalent to 300mg chloroquine base)
- We do not recommend routine co-administration with azithromycin
- **Cardiac monitoring guidance**
 - **General Principles**
 - **Given the growing evidence of myocarditis and arrhythmias with COVID, HCQ should be used with caution in this group of patients. HCQ is a known QT prolonging drug.**
 - **Discontinue all other QT prolonging agents* (continue azithromycin if chronic therapy)**
 - Normal QRS < 120 msec
 - **What is optimal? - QTc increase is <50 msec from baseline AND absolute QTc <500 msec (550msec if QRS >120 msec)**
 - **What is NOT optimal? - QTc increase is >50 msec from baseline OR absolute QTc > 500 msec (550msec if QRS >120 msec) → Consider CARDIOLOGY CONSULT**
 - **EKG/Tele monitoring recommendations**

- EKG#1/QTc#1 – at Baseline
- EKG performed daily thereafter while on QT prolonging agent(s) until steady state
- Obtain pre-discharge EKG
- If the patient is on a QT prolonging drug* that is considered critical for their medical/psychiatric care - then either: 1) HCQ should not be used or, 2) Discussion with Cardiology about the risk and benefits of the drug
- If patient's QTc increases beyond 50 msec after the second dose, reduce dose, but monitor subsequent QTcs closely on telemetry (while making sure that Telemetry QTc matches with EKG QTcs +/- 20msec)
- Any questions - please Consult Cardiology
- A complete list of QT-prolonging drugs is available on <https://crediblemeds.org/>

Rationale for use: Hydroxychloroquine is an inexpensive and generally safe drug for short term use, with few drug-drug interactions. While it is **unknown** if it is effective to treat COVID-19, there is a favorable risk:benefit and cost ratio. Multiple trials are ongoing, and this recommendation will be updated when further data is available. See text below regarding the use of hydroxychloroquine with azithromycin.

COMBINATION OF AZITHROMYCIN AND HYDROXYCHLOROQUINE

The combination of **AZITHROMYCIN and HYDROXYCHLOROQUINE** has not been rigorously studied; it is unknown if it provides additional benefit. The combination may cause significant cardiac toxicity and is not recommended.

Evidence Summary: In a small study (n = 36 patients) in France, hospitalized patients were given hydroxychloroquine (HCQ, n=20) for confirmed COVID-19 infection compared to controls (n=16)¹⁰. Providers gave azithromycin in addition to the hydroxychloroquine based on clinical judgement to prevent bacterial superinfection with daily EKG. Primary endpoint was virologic clearance on day 6. At day 6, 70% of HCQ-treated patients compared to 12.5% of control patients were virologically cured (p=0.001). At day 6, 100% of patients (n=6) treated with combination of HCQ and azithromycin were virologically cured compared with 57% of HCQ-treated patients and 12.5% of control patients (p<0.001). These preliminary results suggest a synergistic effect of combination of HCQ and azithromycin but virologic cure is only a surrogate marker, the true clinical benefit is not yet established, and the potential additive risk of QTc prolongation should be carefully considered.

In another observational study published by the same investigators in France, 80 patients with confirmed COVID-19 infections received the combination of hydroxychloroquine 200mg TID x10 days and azithromycin 500mg x1, then 250mg daily x 4d. The median age was 53 years old with 41% with URI symptoms and 44% with LRI symptoms, the time between onset of symptoms to hospitalization was about 5 days¹⁷. Baseline EKG were performed, and if QTc>500msec, medication was either not started or discontinued. The primary outcomes were clinical course requiring oxygen therapy or transfer to ICU, contagiousness as assessed by PCR or viral culture, and hospital length of stay. Approximately 15% of patients require oxygen therapy and 4% of patients were transferred to the ICU, and about 81% of patients were either discharged home or transferred to step down units with an average length of stay of 5 days. Viral load tested by PCR (C_T>34) were negative in 93% of patients at day 8, and viral culture were negative in 98% of patients at day 5. The authors concluded that clearing viral carriage may decrease risk of transmission. The limitation of the study is the lack of a control group, and lack of follow up EKG monitoring after initiation of therapy. The clinical benefits of combination hydroxychloroquine/azithromycin remain unclear. This combination is NOT recommended.

ANAKINRA

Mechanism of action: Anakinra is a recombinant IL-1 receptor antagonist (IL-1Ra) that is FDA-approved for treatment of rheumatoid arthritis (RA) and Cryopyrin-Associated Periodic Syndromes (CAPS). It is also frequently used off-label for secondary hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS), cytokine release syndrome (CRS), systemic juvenile idiopathic arthritis (SJIA), gout, and recurrent pericarditis.

IL-1 is pleiotropic cytokine primarily produced by activated macrophages. It functions to activate the vascular endothelium and lymphocytes leading to a local inflammatory response and tissue damage and also acts on the liver to drive the acute phase response as well as production of IL-6. The body naturally produces IL-1Ra, which is a plasma protein that binds to the IL-1 receptor and inhibits signaling by both IL-1 α and IL-1 β .

Evidence Summary: Anakinra has not been rigorously studied for COVID-19. It has however been effectively used to treat secondary HLH/MAS in both pediatric and adult patients in numerous studies including in cases of HLH secondary to infection^{11,12}. In a retrospective study of 44 pediatric patients with secondary HLH treated with anakinra, earlier initiation of anakinra (within 5 days of hospitalization) was linked with decreased mortality specifically in patients with non-malignancy associated HLH/MAS¹³.

Anakinra has a wide safety profile as it was initially developed for use in patients with sepsis. While it did not prove effective in this large randomized phase III placebo-controlled trial, survival was modestly improved; therefore it is widely considered to be safe for use in the setting of infection. In a subgroup analysis of the original trial, patients with hepatobiliary dysfunction (elevated LFTs and bilirubin) and evidence of DIC (prolonged PT/PTT and thrombocytopenia) had increased 28-day survival when treated with anakinra, suggesting that patients with features of HLH/MAS pathophysiology may benefit from treatment with anakinra (Shakoory et al. 2016)¹⁴. Since it is used to treat patients with neonatal-onset multisystem inflammatory disease (NOMID), it is known to be safe for use in infants as well as children and adults.

Ongoing Clinical Trials: NCT02735707, NCT04339712, NCT04330638, NCT04324021. A multicenter clinical trial in the United States is being designed to test the use of anakinra in adults with COVID-19.

No clinical trials available at UW Medicine and Seattle Children's Hospital at this time.

Adverse events

- LFT abnormalities
- Local injection site reactions

Administration:

- Anakinra 4mg/kg IV q24h (can increase frequency and/or dose; max dose 100mg)

Rationale for use: A profound inflammatory response resulting in ARDS, circulatory collapse, and multiorgan failure appears to be an important component of the critical illness associated with COVID-19. A proportion of critically ill patients will exhibit shock and cardiac dysfunction, presumably due to cytokine storm resulting from the host response to viral infection. Increased IL-1 β levels have been found in patients with SARS; less data have been reported to date in COVID-19.

Recommendations:

Treatment: Until more data are available, the routine use of anakinra in patients with severe or life-

threatening –COVID-19 is not recommended. However, the use of anakinra may be considered, in consultation with ID, Immunology, and Rheumatology in conjunction with the patient’s primary team in patients with severe disease and clinical deterioration, including the following conditions:

- Ferritin > 1000 ng/mL
- CRP > 30 mg/dL
- ΔCRP > 15 from prior lab
- D-dimer > 1.00
- Dropping cell counts, fibrinogen, ESR, rising LDH
- Acute cardiomyopathy or myocarditis or elevated BNP

TOCILIZUMAB

Mechanism of Action: Tocilizumab is a recombinant humanized monoclonal antibody against IL-6 receptor that is FDA-approved for the treatment of rheumatoid arthritis, systemic juvenile idiopathic arthritis, and polyarticular juvenile idiopathic arthritis. More recently, it has been used for the treatment of severe/life-threatening cytokine release syndrome after CAR-T cell therapy. An increased risk for developing serious infections is reported in individuals receiving chronic therapy with tocilizumab, primarily in individuals being treated with concomitant immunosuppressants, such as methotrexate or corticosteroids.

Evidence summary: Tocilizumab has not been rigorously studied for COVID-19. There are limited data from uncontrolled studies about the potential benefit of tocilizumab in patients with COVID-19. There are ongoing randomized, controlled clinical trials of tocilizumab in China and Italy and a phase III clinical trial in the U.S. is in progress.

In an open-label study in 21 patients in China with documented COVID-19 and severe oxygenation impairment, including RR≥30 breaths/min, SpO₂≤93% on room air, PaO₂/FiO₂≤300mmHg or need for mechanical ventilation, shock, or combined organ failure, tocilizumab reduced oxygen requirement, normalized the CRP, and increased the lymphocyte count to normal; 19 of the 21 patients were discharged (Xu 2020)¹⁵. Of note all patients were also treated with an antiviral (lopinavir) and methylprednisolone.

Ongoing Clinical Trials: ChiCTR2000029765, NCT04335123, NCT04346693, NCT04349410, NCT02735707, NCT04322773, NCT04330638, NCT04333914, NCT04339712, NCT04335305, NCT04332913, NCT04320615, NCT04346355, NCT04332094, NCT04331795, NCT04317092, NCT04310228, NCT04306705

No clinical trials available at UW Medicine and Seattle Children’s Hospital at this time.

Adverse events

- Serious bacterial and fungal infections as well as reactivation of TB
- LFT abnormalities
- Hyperlipidemia
- Neutropenia
- Local injection site reactions

Administration:

- Tocilizumab 8mg/kg x 1 (max dose 800mg)

Rationale for use: A profound inflammatory response resulting in ARDS, circulatory collapse, and multiorgan failure appears to be an important component of the critical illness associated with COVID-19. A proportion of critically ill patients will exhibit shock and cardiac dysfunction, presumably due to cytokine storm resulting from the host response to viral infection. IL-6 levels have been found to be elevated in patients with severe COVID-19.

Recommendations:

Treatment: -Until more data are available, the routine use of tocilizumab in patients with severe or life-threatening COVID-19 is not recommended. However, the use of anakinra may be considered, in consultation with ID, Immunology, and Rheumatology in conjunction with the patient's primary team in patients with severe disease and clinical deterioration, including the following conditions:

- Ferritin > 1000 ng/mL
- CRP > 30 mg/dL
- ΔCRP > 15 from prior lab
- D-dimer > 1.00
- Dropping cell counts, fibrinogen, ESR, rising LDH
- Acute cardiomyopathy or myocarditis or elevated BNP

CORTICOSTEROIDS

Data on the use of corticosteroids for novel coronavirus infections are quite variable with mixed results and little clarity on appropriate dosing or timing. In SARS-CoV, any steroid therapy was associated with increased need for ICU admission or mortality¹⁷, although lower mortality and shorter hospitalization was seen among critical cases¹⁸ and pulse steroids did appear to result in lower oxygen requirements and better radiographic outcomes compared to non-pulsed steroids¹⁹. In MERS-CoV, however, steroid therapy was evaluated both by dose and duration and no effect was seen on mortality; however, increased time to viral clearance was observed²⁰. One study of SARS-CoV-2 suggests, delayed use of steroids may increase risk of death in the ICU²¹. In another COVID-19 cohort, the use of methylprednisolone in patients who developed ARDS was associated with decreased risk of death²²; short courses of low-moderate dose steroids has also been recommended in critically ill patients²³.

Given these mixed data, and the potential for steroid therapy to worsen disease severity and lead to secondary infections, routine use of steroids is not recommended at this time. Use of steroids in patients with severe disease (requiring oxygen support or mechanical ventilation) could be considered as part of the supportive care regimen for patients with ARDS on a case-by-case basis.

Ongoing Clinical Trials: NCT04344288, NCT04345445, NCT04329650, NCT04327401, NCT04344730, NCT02735707

AGENTS NOT RECOMMENDED

Several agents have been reported for management of COVID-19. Given a combination of lack of efficacy, potential toxicity, and cost, the following agents are NOT RECOMMENDED for treatment of COVID-19.

ANTIBIOTICS

Hospitalized patients in China were frequently treated with antibiotics, although the true incidence bacterial co-infection has not been fully characterized. We do not recommend routine antibiotics for patients with COVID-19 unless there is another indication for antibiotics¹⁶.

LOPINAVIR/RITONAVIR (KALETRA)

Lopinavir/ritonavir is a fixed-dose combination antiretroviral for treatment of HIV infection. Both drugs are protease inhibitors; ritonavir slows lopinavir metabolism (boosts lopinavir). This medication is hypothesized to inhibit SARS-CoV-2-encoded protease; however, inhibitory lopinavir levels exceed achievable blood levels.

Evidence Summary: There is evidence of *in vitro* activity against SARS-CoV-2 and in a retrospective trial in patients with SARS, improved outcomes were noted when it was used as initial treatment compared to matched cohort (2.3% death vs 15.6%). However, there were no differences in outcomes when used as rescue therapy (Chan 2003)¹⁷. In a randomized, open-label study of lopinavir-ritonavir 400-100 mg BID x 14 days vs. placebo for treatment of COVID-19 were enrolled in China (ChiCTR2000029308)¹⁷. The primary endpoint was time to clinical improvement; secondary endpoints included 28-day mortality and detectable RNA levels during therapy. 199 patients with laboratory documented SARS-CoV-2 infection and evidence of impaired oxygenation ($SpO_2 \leq 94\%$ or $PaO_2 : FiO_2 < 300$ mmHg) were enrolled. There was no difference in primary or secondary outcomes. Based on these data, lopinavir-ritonavir is not recommended.

RIBAVIRIN ± INTERFERON (alpha-2a/b, β1)

During the SARS epidemic as well as the MERS-CoV epidemic, ribavirin was often used in clinical practice. However, there is no clear evidence of clinical benefit, and toxicities (both early and late) were common. Notably, ribavirin did not inhibit viral growth in one study at concentrations attainable in human serum¹⁸. The largest clinical study to date on the use of ribavirin plus interferon was a multicenter observational study of MERS-CoV patients, comparing 144 patients who received ribavirin with some form of interferon (IFN-2a, IFN-2b or IFN-1) with 205 who received neither¹⁷. In crude and multivariable analyses, ribavirin and IFN was associated with higher 90-day mortality compared with no treatment; with no difference in these groups noted after accounting for time-varying confounders. Given this and the significant toxicities related to ribavirin (with or without IFN), we do not recommend use at this time.

INTERFERONS

There is no clinical data on monotherapy with any of the interferon formulations for SARS-CoV, MERS-CoV or the current SARS-CoV-2 though *in vitro* data suggest that IFN might have inhibitory effects against SARS-CoV¹⁴. Additionally, a randomized controlled trial of IFN-beta-1a for treatment of ARDS did not show improvement in death or ventilator-free days¹⁷. There is insufficient evidence to support the use of interferons, alone or in combination with other agents, at this time. The pathophysiology of respiratory failure caused by COVID-19 appears to involve an aberrant immune response, which may be

exacerbated by interferon administration.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

No evidence exists to support its use in mitigating the inflammatory response associated with COVID-19. There have been concerns voiced regarding clinical worsening of COVID-19 in patients taking ibuprofen but these are unsubstantiated at this time. We do not recommend the addition of NSAIDs for treatment primarily due to lack of evidence for benefit. These drugs can also exacerbate acute kidney injury in the setting of serious illness. However, if a patient is taking an NSAID for chronic therapy, it may be continued.

Pregnancy (non-COVID-19 indications): Note that administration of NSAIDs (primarily indomethacin) are often considered in pregnancy to decrease preterm birth, or postpartum for pain management. NSAIDs should be avoided in pregnancy and postpartum for COVID-19+ women.

IMMUNE GLOBULIN (IVIG)

There is little rationale for this use in COVID-19 since available IVIG products are unlikely to contain specific antibodies to SARS-CoV-2, given lack of widespread immunity. IVIG has been suggested to have anti-inflammatory or immunomodulatory effects; however, given the lack of conclusive clinical data for treatment of novel coronaviruses and national shortage of IVIG products, routine use of IVIG is not recommended at this time.

Angiotensin-receptor blockers and Angiotensin converting enzyme blockers

SARS-CoV-2 uses the ACE2 receptor for cell entry in epithelial tissues and thus the course of the infection could be impacted by the use of these antihypertensive agents. Furthermore, ACE2 itself is protective against lung injury, thus reduced levels may exacerbate pulmonary complications²⁴. There is no consensus on whether these drugs would exacerbate or ameliorate COVID-19 disease. No clinical data currently exist to guide the initiation or cessation of these agents in patients with SARS-CoV-2 infection. The HFSA, ACC and AHA emphasize the lack of experimental or clinical data on these classes of drugs in COVID-19 and recommend that patients currently taking these medications for known beneficial indications (HF, HTN, or ischemic heart disease, for example) be advised to continue them. They advise against adding/removing beyond what would be done in standard practice and urge individualized treatment decisions based on the patient's clinical presentation and hemodynamics. Ongoing clinical trials, including of recombinant ACE2, are currently underway (NCT04287686).

These guidelines were adapted from UW Medicine guidelines (<https://covid-19.uwmedicine.org/>) were constructed and finalized by a multidisciplinary group at Seattle Children's Hospital.

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