Algorithm for Management of ADULT Patients with COVID-19 at MultiCare Health System

There is no FDA-approved treatment for COVID-19. All recommendations below are based on in vitro data, non-robust trials, and expert opinion. As there is no robust data to date, medications listed below should only be considered for patients with confirmed infection, or those at high risk for poor outcomes awaiting confirmation. Clinical judgement should always be used to weigh the cost/benefit for individual cases.

This guideline will be continually updated as more evidence is published.

Outpatients

Treatment:

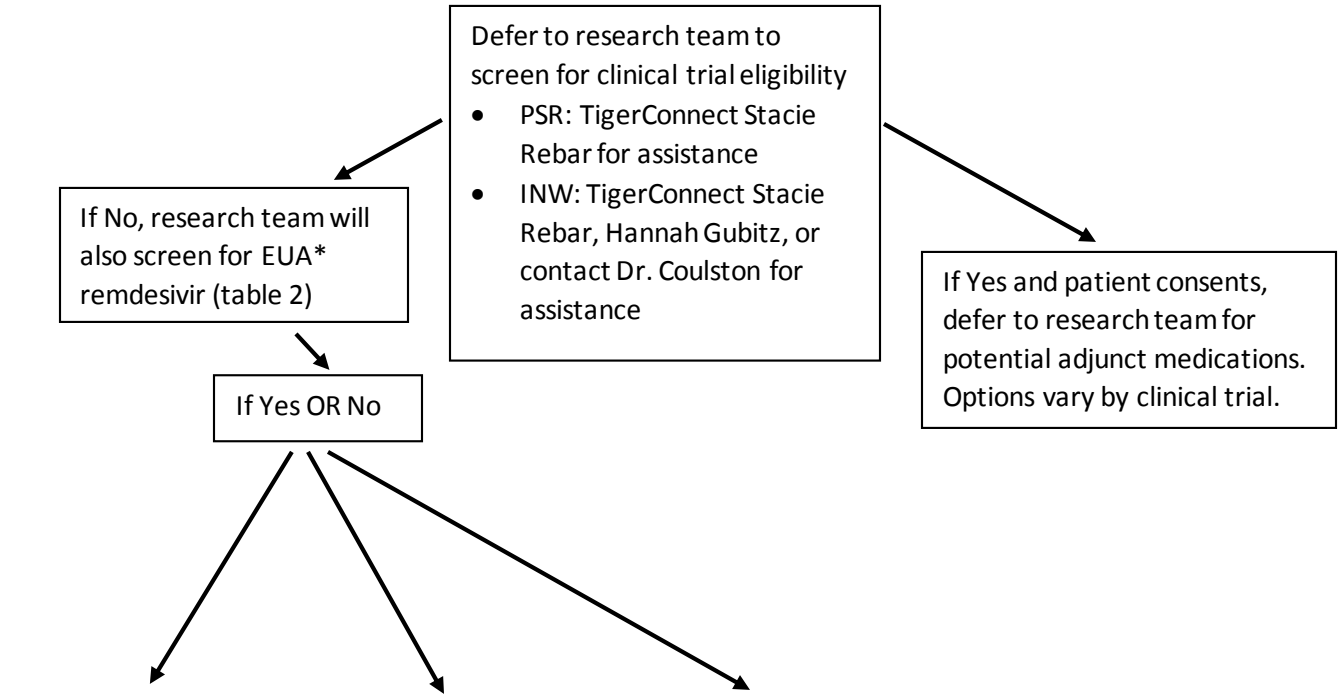
- Supportive care
- Physical activity should be encouraged as tolerated to reduce the risks of DVT/PE

Remain in self-isolation until ALL of the following have been met:

- At least 10 days since symptoms first started (or from date of positive test if patient has been asymptomatic for the duration)
- At least 72 hours have passed since last fever without the use of fever-reducing medications
- Improvement in respiratory symptoms

Inpatients

***EUA: Emergency Use Authorization**



URTI/LRTI without O2 Requirement	LRTI with O2 requirement	LRTI requiring mechanical ventilation
Supportive care	SpO2 ≤ 94% on Room Air • Consider corticosteroids (Table 3) Rapidly worsening O2 needs requiring >6L/min • Consider the following: **Convalescent plasma** • **Obtain ID and pulmonary consult** • Consider **tocilzumab** (Table 3)	Consider: • Corticosteroids (Table 3) • **Convalescent plasma** If not already considered, for cytokine storm: • **Obtain ID consult** • Consider **tocilizumab**. (Table 3)

Table 1: Risk Factors for Severe COVID-19 Disease		
Epidemiological	**Vital Signs**	**Labs**
Age > 55	Respiratory rate > 24	D-dimer > 1000 ng/mL
Pre-existing pulmonary disease	Heart rate > 125 bpm	CPK > 2 x ULN
Chronic kidney disease	SpO2 < 90% on room air	CRP > 100
Diabetes with A1c > 7.6%		LDH > 245 units/L
History of hypertension		Elevated troponin
History of cardiovascular disease		Admission absolute lymphocyte count < 0.8
Use of biologics for immune suppression		Ferritin > 300 ug/L
History of transplant or other immunosuppression		
All patients with HIV (regardless of CD4 count)		
Healthcare personnel with significant aerosolizing exposure		

Table 2: EUA Remdesivir Screening Criteria PSR: TigerConnect Stacie Rebar or her cell (253.209.8972), available 24 hours INW: TigerConnect Stacie Rebar, Hannah Gubitz, or contact Dr. Coulston	
Inclusions	**Exclusions**
Age > or =18 years	CrCl < 30 mL/min
COVID-19 test positive < or = 4 days	ALT > 5 x ULN; ALT >3 and total bilirubin > 2 x ULN
SpO2 < or = 94%	Will likely die within the next 24 hr.
	Improving and likely will be discharged within 72 hr.
	Access to the drug through another means (trials, compassionate use, etc.)
	Intubated > 5 days (unless delay accessing drug)
	Hospitalized for > 10 days
Other Considerations	
- Prioritizing patients requiring oxygen but not yet requiring mechanical ventilation - For those requiring mech vent, favoring the least number of days on either - Using a second 5 day course if no improvement or worsening or need for persistent mech vent after first 5 day course	
Eligibility/Approval	
- Research (MIRI) will assess eligibility into existing clinical trials, and if patient fails or declines, will look at IE for Remdesivir EUA; Dr. Malhotra will sign off - Look for note from Research team	
Dosing	
200 mg IV on day 1, followed by 100 mg IV daily x 4 more days. If not improving after 5 days of therapy, consider 5 more days.	

Table 3: Potential Treatment Options			
Drug	**Dose**	**Side Effects**	**Notes**
Corticosteroids [2,3,27-33]	• Dexamethasone 6 mg IV OR PO daily • Prednisone 40 mg PO daily • Methylprednisolone 0.5-1 mg/kg/day IM	• Hyperglycemia Dexamethasone is not recommended for use in Pregnancy	Preliminary data suggests low-dose corticosteroids may improve outcomes when started in hypoxemic patients requiring oxygen therapy. It is unclear whether patients with mild hypoxemia benefit from steroids compared to those with moderate-severe hypoxemia. Optimal timing of initiation, dose and duration are not yet clear, therefore steroid initiation should be judged on a case-by-case basis. **Criteria for Steroid Initiation** • Confirmed COVID-19 infection • Hypoxemia (SpO2 </=94% on room air) requiring oxygen support and/or mechanical ventilation **Stop steroids once patient is weaned from oxygen (or back to their pre-hospital baseline) OR at 10 days.** *Steroids are not recommended for COVID-19 in those not requiring oxygen*
COVID Convalescent Plasma	1 Unit, minimum of 200mL	Potential for transfusion-related side effects (consistent with any conventional plasma infusion)	Convalescent plasma therapy is allowed concomitantly with Remdesivir
Remdesivir[8]	200 mg IV on day 1, followed by 100 mg IV for 5-10 days	• Transient elevations in LFT's • Reversible AKI (animal studies)	Full adverse effect profile unknown. Drug interaction profile unknown • May decrease efficacy of hormonal contraception. EUA: See Table 2 for criteria
Tocilizumab[10]	8 mg/kg IV up to max of 800 mg once. • If adequate or no response, repeat dosing not recommended	• Can cause long-lasting neutropenia with potential increased risk for secondary infection	May be difficult to obtain drug Inclusions 1. Positive COVID-19 2. Diagnosis codes U07.1 (COVID Virus Identified) and R65.11

	• If partial response, may repeat up to 3 total doses as deemed appropriate by provide		(Cytokine Release Syndrome) are present on the chart 3. Completion of patient financial screening and Genentech Foundation Enrollment Form submitted (see attached workflow pdf) 4. All of the below: a. Abnormal chest imaging consistent with COVID-19 b. Persistent fever with temperature >/=38C c. Rapidly worsening gas exchange requiring > 6L/min (if not vented) OR Pa02/FIO2<200 (if vented) d. Absence of systemic bacterial or fungal co-infection 5. Lab parameters (at least one): a. Ferritin > 300 ug/L with doubling within 24 hrs b. Ferritin > 600 ug/L at presentation AND LDH >250 U/L c. Elevated D-dimer (>1 mg/L) Exclusions 6. AST/ALT > 5x ULN 7. ANC < 500 8. Plt <50K 9. Sepsis or infection from non-COVID pathogens 10. Anti-rejection immunosuppressive therapy
Selinexor	20 mg orally on day 1, 3, and 5 of each week, up to a total of 28 days	• Myelosuppression • Hyponatremia • Nausea/Vomiting • Diarrhea • Weight loss	• Thrombocytopenia, neutropenia, anemia may require dose adjustments or interruptions in therapy. Contact trial coordinators for details

Table 4: Changes in Therapy NOT Recommended	
Angiotensin/RAS Blocking Agents (ACEi/ARBs)[11]	• Based on multiple cardiology and nephrology societies' review, it is not recommended to routinely discontinue ACEi/ARB therapy to decrease risk for more severe COVID-19 disease.

Chloroquine[4,8,24, 26]	• While early small trials may have showed activity of the drug against SARS-CoV-2, recent data indicates a high number of cardiac complications that have resulted in deaths.
Darunavir/cobicistat[12]	• No in vitro or clinical data yet exist to support this use, though a clinical trial has been registered in China.
Hydroxychloroquine[25]	• Limited evidence of effectiveness of hydroxychloroquine in treatment of Covid-19 patients, and a recent study showed an association of increased overall mortality was identified in patients treated with hydroxychloroquine alone, highlighting importance of waiting for results of prospective, randomized, controlled studies before widespread use.
Immune globulin (IVIG)	• There is little rationale for this use 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.
Interferons[13-14]	• Typically used in combination with ribavirin, interferons have been studied for patients with other coronaviruses, with mixed results. Their adverse effect profiles are also generally unfavorable.
Nitazoxanide[15-16]	• Some in vitro studies have demonstrated potency against SARS-CoV-2, though clinical use against other coronaviruses has not demonstrated benefit. Poorly tolerated formulation; safety profile is relatively benign.
Non-Steroidal Anti-inflammatory Drugs (NSAIDs)[22]	• No evidence exists to support its use in mitigating the inflammatory response associated with COVID-19. There are reports of NSAID use preceding clinical deterioration in some patients with severe COVID-19 disease, however data is very limited. APAP preferred first line, however NSAIDs could be considered second line.
Oseltamivir	• Coronaviruses do not utilize neuraminidase for the budding stage of reproduction and therefore no activity is expected. • If influenza is unknown or positive, oseltamivir should be started. Stop if flu A/B PCR negative AND low suspicion.
Ribavirin (oral)[17-19]	• Typically used in combination with an interferon, ribavirin has been studied for patients with other coronaviruses, with mixed results. Additionally, its adverse effect profile can be significant (anemia), particularly at the dosages for which it has been tested for MERS (~800-3600mg/day).
Lopinavir-ritonavir	• Recent study showing lack of benefit in severe cases. • Side effects can be moderate/severe are often treatment limiting • In vitro studies suggesting activity, but clinical reports inconclusive to negative. • Limited supply, many drug interactions

References

1. COVID-19 Antiviral and Pharmacotherapy Recommendations. University of Nebraska. Revised 3/17/2020

2. Massachusetts General Hospital COVID-19 Treatment Guidance. Massachusetts General Hospital. Revised 7/1/2020
3. UW Medicine Interim Treatment Guidelines for SARS-CoV-2 Infection/COVID-19. University of Washington. Revised 6/20/2020
4. Multicenter collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia. Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia *Chinese Journal of Tuberculosis and Respiratory Diseases* 43, no. 0. https://www.ncbi.nlm.nih.gov/pubmed/32075365.
5. Yao X, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020 Mar 9. https://www.ncbi.nlm.nih.gov/pubmed/32150618.
6. Cortegiana, et al. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. J Crit Care. 2020 Mar 10. https://www.sciencedirect.com/science/article/pii/S0883944120303907.
7. Hydroxychloroquine clinical trial (NCT04261517). https://clinicaltrials.gov/ct2/show/NCT04261517?cond=covid-19&draw=8.
8. Wang M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Research. 2020 30;269-71. https://www.nature.com/articles/s41422-020-0282-0.
9. Gautret et al. (2020) Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International Journal of Antimicrobial Agents – In Press 17 March 2020 – DOI : 10.1016/j.ijantimicag.2020.105949. https://www.mediterranee-infection.com/wp-content/uploads/2020/03/Hydroxychloroquine_final_DOI_IJAA.pdf
10. Xiaoling X, et al. Effective treatment of Severe COVID-19 Patients with Tocilizumab. [Pre-print – not peer reviewed]. http://chinaxiv.org/abs/202003.00026.
11. NephJC (nephrology online journal club) detailed review with links to society statements. Accessed 2020 Mar 16. http://www.nephjc.com/news/covidace2.
12. Darunavir/cobicistat clinical trial (NCT04252274). https://clinicaltrials.gov/ct2/show/NCT04252274.
13. Arabi YM, et al. Ribavirin and Interferon Therapy for Critically Ill Patients With Middle East Respiratory Syndrome: A Multicenter Observational Study. Clin Infect Dis. 2019 Jun 25. https://www.ncbi.nlm.nih.gov/pubmed/31925415.
14. Mo Y, Fisher D. A review of treatment modalities for Middle East Respiratory Syndrome. J Antimicrob Chemother. 2016 Dec;71(12):3340-3350. https://www.ncbi.nlm.nih.gov/pubmed/27585965.
15. Wang M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Research. 2020 30;269-71. https://www.nature.com/articles/s41422-020-0282-0. Revision Date: 3/17/2020
16. Gamino-Arroyo AE, et al. Efficacy and Safety of Nitazoxanide in Addition to Standard of Care for the Treatment of Severe Acute Respiratory Illness. Clin Infect Dis. 2019 Dec 69;11:1903-11. https://academic.oup.com/cid/article/69/11/1903/5308603.
17. Gross AE, Bryson ML. Oral Ribavirin for the Treatment of Noninfluenza Respiratory Viral Infections: A Systematic Review. Ann Pharmacother. 2015 Oct;49(10):1125-35. https://www.ncbi.nlm.nih.gov/pubmed/26228937.
18. Arabi YM, et al. Ribavirin and Interferon Therapy for Critically Ill Patients With Middle East Respiratory Syndrome: A Multicenter Observational Study. Clin Infect Dis. 2019 Jun 25. https://www.ncbi.nlm.nih.gov/pubmed/31925415.
19. Mo Y, Fisher D. A review of treatment modalities for Middle East Respiratory Syndrome. J Antimicrob Chemother. 2016 Dec;71(12):3340-3350. https://www.ncbi.nlm.nih.gov/pubmed/27585965.
20. WHO. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. Accessed 2020 Mar 12. https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected.
21. CDC. Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19). Accessed 2020 Mar 12. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html.
22. Godoy, Maria. "Concerned About Taking Ibuprofen For Coronavirus Symptoms? Here's What Experts Say." NPR, 19 Mar. 2020, www.npr.org/sections/health-shots/2020/03/18/818026613/advice-from-france-to-avoid-ibuprofen-for-covid-19-leaves-experts-baffled.
23. Cao B, Wang Y, Wen D, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2001282. https://www.nejm.org/doi/full/10.1056/NEJMoa2001282?query=featured_home
24. Borba M, Val F, et al. Chloroquine diphosphate in two different dosage as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: Preliminary safety results of a randomized, double-blinded, phase IIb clinical trial (CloroCovid-19 Study). Accessed 2020 Apr 16. https://www.medrxiv.org/content/10.1101/2020.04.07.20056424v2
25. Magagnoli J, Narendran, S, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. BMJ 2020 Apr 16. https://www.medrxiv.org/content/10.1101/2020.04.16.20065920v1
26. Borba, MGS, et al. Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: Preliminary safety results of a randomized, double-blinded, phase IIb clinical trial (CloroCovid-19 Study). BMJ 2020 April 7. https://www.medrxiv.org/content/10.1101/2020.04.07.20056424v2
27. Horby P, et al. Effect of Dexamethason Horby P, Lim W, Emberson J, RECOVERY collaborative group et al. Effect of dexamethasone in hospitalized patients with COVID-19: Preliminary Report. Accessed 2020 June 30. https://www.medrxiv.org/content/10.1101/2020.06.22.20137273v1
28. Salton F, et al. Prolonged low-dose methylprednisolone in patients with severe COVID-19 pneumonia. Accessed 2020 June 29. https://www.medrxiv.org/content/10.1101/2020.06.17.20134031v2

29. Corral-Gudino, L et al. GLUCOCOVID: A controlled trial of methylprednisolone in adults hospitalized with COVID-19 pneumonia. Accessed 2020 June 30. https://www.medrxiv.org/content/10.1101/2020.06.17.20133579v1
30. Fadel R, Morrison AR, Vahia A, et al. Early Short Course Corticosteroids in Hospitalized Patients with COVID-19 [published online ahead of print, 2020 May 19]. *Clin Infect Dis*. 2020
31. The National Institutes of Health COVID-19 Treatment Guidelines Panel Provides Recommendations for Dexamethasone in Patients with COVID-19. Accessed 2020 June 30. https://www.covid19treatmentguidelines.nih.gov/dexamethasone/
32. Bhimraj A et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Accessed 2020 Jun 30. http://www.idsociety.org/COVID19guidelines
33. Villar J, et al. Rationale for Prolonged Corticosteroid Treatment in the Acute Respiratory Distress Syndrome Caused by Coronavirus Disease 2019. *Crit Care Explor*. 2020;2(4):e0111. Published 2020 Apr 29.