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

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

Clinical Symptoms: Range from uncomplicated asymptomatic infection to URI, to pneumonia, to ARDS and shock, with several risk factors for severe disease identified (Table 1).

Supportive care: Appropriate treatment of concomitant pneumonia, respiratory failure, ARDS, sepsis, septic shock. DVT chemoprophylaxis is recommended in all patients without contraindications, with preference given to agents needing less frequent administration to limit staff exposure.

Pharmacologic Treatment: The only FDA-approved treatment for COVID-19 currently is remdesivir, which was approved for emergency use in May 2020.[35] This agent has been granted emergency use authorization for treatment of adults and children hospitalized with suspected or laboratory confirmed severe disease with COVID-19. Severe disease is defined as patients with low blood oxygen levels or need for supplemental oxygen support. All other recommendations below are based on in vitro data, non-robust trials, and/or expert opinion.

Limited evidence supporting routine use of corticosteroids: Prior studies assessing outcomes in patients receiving systemic corticosteroids for infections due to closely related viruses (SARS-CoV and MERS-CoV) found a lack of effectiveness and possible harm.[20,21] Recently, however, more evidence has been emerging that dexamethasone is efficacious in the management of COVID.[26-34] Accordingly, the Infectious Disease Society of America updated its guidelines on 6/25/2020 to include the use of glucocorticoids in hospitalized patients with hypoxemia requiring supplemental oxygen.[33] Corticosteroids are also warranted for other medical indications (i.e., ARDS, asthma exacerbation).

Recommend against routine use of azithromycin: Preliminary data evaluating the combination of hydroxychloroquine and azithromycin for treatment of COVID-19 were recently published.[6] The authors of this study conclude that combination therapy led to greater viral load reduction compared to monotherapy with hydroxychloroquine. However, more patients receiving hydroxychloroquine monotherapy had higher baseline viral burden (estimated by cycle threshold values). When limiting the analysis to those with comparable baseline cycle threshold values, combination therapy with hydroxychloroquine and azithromycin led to a similar proportion of negative testing by day 6 compared to hydroxychloroquine monotherapy. Furthermore, the study does not report the clinical outcomes of these patients, and it is unknown if reductions in viral load correlate with improvements in clinical outcomes. Thus, based on this limited (only 6 patients in combination group) and weak evidence, we recommend against the routine use of azithromycin for the treatment of COVID-19 at this time.

Outpatients

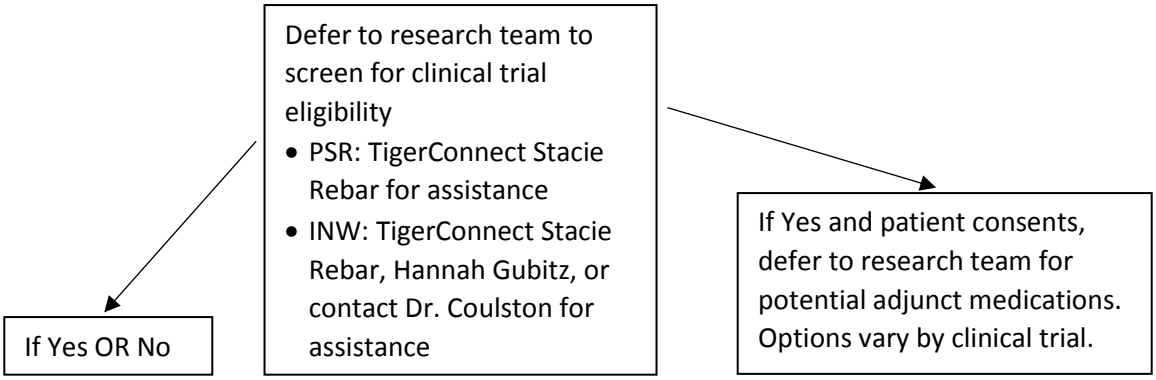
Treatment:

- 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



URTI/LRTI without O2 Requirement	LRTI with O2 requirement	LRTI requiring mechanical ventilation
Supportive care DVT prophylaxis recommended if no contraindications • Enoxaparin 1st line • Heparin subcutaneous 2nd line	SpO2 ≤ 94% on Room Air • Consider corticosteroids (Table 3) • Remdesivir (Table 2) Rapidly worsening O2 needs requiring >6L/min • Consider the following: **Convalescent plasma** • **Obtain ID and pulmonary consult** • Consider **tocilzumab** (Table 3) DVT prophylaxis recommended if no contraindications • Enoxaparin 1st line • Heparin subcutaneous 2nd line	Consider: • Corticosteroids (Table 3) • **Convalescent plasma** If not already considered, for <u>cytokine storm</u>: • **Obtain ID consult** • Consider **tocilizumab**. (Table 3) DVT prophylaxis recommended if no contraindications • Enoxaparin 1st line • Heparin subcutaneous 2nd line

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		
Sickle Cell		

Table 2: EUA Remdesivir Screening Criteria	
Inclusions	**Exclusions**
• Age > or =18 years • COVID-19 test positive • SpO2 < or = 94% on room air	• Intubated • Duration of symptoms > or = 10 days • CrCl < 30 mL/min • ALT > 300 (5 x ULN); AST > 160 (3 x ULN) and total bilirubin > 2.8 (2 x ULN) • Oxygenation improving / at baseline • Patient received any duration of remdesivir in the past six months
Dosing	
200 mg IV on day 1, followed by 100 mg IV daily x 4 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 IV	• 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 Contacts: • INW: Hannah Gubitz cell: 206.930.4102 • PSR: Stacie Rebar cell: 253.209.8972
Remdesivir[8]	200 mg IV on day 1, followed by 100 mg IV for 5 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 • If partial response, may repeat up to 3 total doses as deemed appropriate by provide	• 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 (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

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