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

Revision DATE	1/11/2021
CREATED BY	COVID Clinical Advisory Committee
Description	A guideline detailing the current medical treatment of COVID-19 for both inpatients and outpatients at MultiCare Health System
Is this a new policy or a change to an existing policy?	Update to an existing policy
If this is a change, please highlight the significant changes.	• EUA Baricitinib (Table 3)

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:

Remdesivir, currently the only FDA approved treatment for COVID-19, received approval on October 22, 2020 for the treatment of COVID-19 in hospitalized patients 12 years and older and > 40 kg.[36] All other recommendations below are based on in vitro data, non-robust trials, and/or expert opinion.

Evidence to support the routine use of remdesivir is conflicting
There is a lack of consensus among the IDSA, WHO, and NIH guidelines on whether remdesivir should be used in the management of COVID-19, given the varying results of existing clinical trial data, the largest being ACTT-1 and SOLIDARITY.[46]

The **ACTT-1** trial randomized 541 patients to remdesivir for 10 days vs. placebo. It enrolled patients from the US and Europe early in the pandemic through the end of April. The remdesivir group had a significantly improved median time to recovery (TTR) of 10 days vs 15 days for placebo. Patients requiring oxygen derived the most benefit. There was no difference in TTR for patients requiring high-flow oxygen or mechanical ventilation. There was a trend toward reduced mortality, however the study was not powered to assess this. The was no change in the outcome when adjusted for use of other medications, however all 'standard of care' measures were not detailed, including anticoagulation strategies between the two groups. The shorter TTR led the data and safety monitoring board to recommend deviating from the protocol and unblinding the data to study team members at the end of April. The team subsequently decided to offer remdesivir to the 169 placebo patients who had not yet completed the 29-day follow-up visit.[41]

In contrast, the **SOLIDARITY** trial sponsored by WHO was an open-label, randomized trial that enrolled 11,266 patients to receive one of several study drugs, 2,750 of whom received remdesivir for 10 days compared to usual care alone. By day 28, remdesivir did not significantly decrease mortality, need for mechanical ventilation, or hospitalization. Proponents of the trial advocate for its large sample size and "real world"

model, however there were important limitations. The trial was conducted early in the pandemic across 30 countries, primarily in Asia, Africa and Latin America, with many sites using crisis standards of care during surges where resources were limited, and no detailed data provided on what these standards looked like. There was also no data provided on time from symptom onset to receipt of remdesivir.

At this time, there is not sufficient high-quality evidence to confidently recommend for or against the use of remdesivir in patients hospitalized due to COVID-19 who are hypoxemic requiring oxygen.

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
- Monoclonal antibody Emergency Use Authorizations – COMING SOON

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

Defer to research team to screen for clinical trial eligibility

- PSR: TelmedIQ Stacie Rebar for assistance
- INW: TigerConnect Stacie Rebar, Hannah Gubitz, or contact Dr. Coulston for assistance

If Yes and patient consents, defer to research team for potential adjunct medications. Options vary by clinical trial.

If Yes OR No

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
	• **Corticosteroids** (Table 2)
	• **Remdesivir**
	• **Baricitinib**
	
	Rapidly worsening O2 needs requiring >6L/min
	• Consider the following:
	  ○ **Convalescent plasma**
	  ○ **pulmonary consult**
	
	DVT prophylaxis recommended if no contraindications
	• Enoxaparin 1st line
	• Heparin subcutaneous 2nd line
		Consider:
		• Corticosteroids (Table 2)
		• **Convalescent plasma**
		• **Remdesivir**
		• **Baricitinib**
		
		If not already considered, for cytokine storm:
		• Consider **tocilizumab**. (Table 2)
		
		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 > 1 mcg/mL (1,000 ng/mL)
Pre-existing pulmonary disease	Heart rate > 125 bpm	CPK > 2 x ULN
Chronic kidney disease	SpO2 < 94% on room air	CRP > 10 mg/dL (100 mg/L)
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 > 500 ng/mL
History of transplant or other immunosuppression		
All patients with HIV (regardless of CD4 count)		
Healthcare personnel with significant aerosolizing exposure		
Sickle Cell		

Table 2: 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 • Psychiatric effects (i.e. agitation, anxiety, insomnia, euphoria, restlessness)	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 **Duration is up to 10 days or at hospital discharge, whichever comes first. It is NOT recommended to continue steroids after discharge (assuming the patient has been weaned from O2)** **Consider a longer course of therapy if no improvement or worsening oxygenation at 10 days. Abrupt discontinuation of steroids in these patients may lead to clinical deterioration.** ***Steroids are not recommended for COVID-19 in those not requiring oxygen or who improve rapidly****, as this sub-group of*

			patients in the RECOVERY trial showed a trend towards harm, potentially due to inhibition of the immune response, reducing viral clearance, and increasing viral shedding.
COVID Convalescent Plasma (CCP)	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 See CCP EUA workflow document for criteria
Remdesivir[32,33, 41-45]	200 mg IV on day 1, followed by 100 mg IV for 5 days	• Transient elevations in LFT's • Reversible AKI (animal studies). Unclear if observed AKI in trials was due to remdesivir or the disease process • May decrease efficacy of hormonal contraception. • May increase PT/INR • Anemia NOTE • Full adverse effect profile unknown • Drug interaction profile unknown	**Inclusion Criteria:** Moderate-severe disease requiring O_2 ≥ 2 L/min **Exclusions:** ALT/AST > 10x ULN, or evidence of acute liver failure **Precautions:** CrCl < 30 mL/min is not an absolute contraindication to remdesivir. Patients with CrCl <30 ml/min were excluded from trials because remdesivir contains SBECD, used to improve its solubility, which is renally cleared and has been associated with AKI at high concentrations. The risk is thought to be low as the SBECD concentration in remdesivir is low and the duration of therapy is short. It is also cleared by HD and CRRT. Ultimately the decision to use should weigh the benefit vs. risk. Consider stopping if patient develops severe AKI after starting remdesivir. ALT/AST < 10x ULN: the risk of hepatotoxicity is not known, as patients with an ALT/AST > 5x ULN were excluded from trials.
Tocilizumab[10, 35-40]	8 mg/kg IV up to max of 800 mg once. •	• Can cause long-lasting neutropenia with potential increased risk for secondary infection	Inclusions 1. Positive COVID-19 2. Restricted to pulmonary/critical care 3. All of the following: a. Abnormal chest imaging consistent with COVID-19 b. Persistent fever with temperature >/=38C c. Rapidly worsening gas exchange

			with ARDS or evidence of progression to ARDS d. Absence of systemic bacterial or fungal co-infection 4. Lab parameters (at least one) a. Ferritin > 300 ug/L and doubling within 24 hrs b. Ferritin > 600 ug/L at presentation AND LDH >250 U/L a. Elevated D-dimer (>1 mg/L) 5. Exclusions a. AST/ALT > 5x ULN b. ANC < 500 c. Plt <50K d. Sepsis or systemic infection from non- COVID pathogens e. 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 3. Baricitinib Emergency Use Authorization Criteria

Background:

Baricitinib has been authorized for emergency use by FDA, in combination with remdesivir, for the treatment of suspected or confirmed COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or ECMO.

Baricitinib is a Janus-associated kinase (JAK)-inhibitor that blocks the activity of several cytokines interfering with the pathway that leads to inflammation. It may also have antiviral effects by inhibiting the factors viruses use to enter human cells and by suppressing type I interferon-driven viral receptor upregulation.

EUA was granted based on the ACTT-2 trial of hospitalized patients, 515 receiving baricitinib/remdesivir vs. 518 receiving remdesivir alone. The primary outcome was time to recovery (TTR) within 28 days. Remdesivir plus baricitinib improved the median TTR by one day in the overall cohort (7 vs 8 days; rate ratio 1.16; 95% CI, 1.01–1.32; *P* = 0.03). The subgroup of patients requiring high-flow oxygen or noninvasive ventilation at baseline had the largest improvement in TTR (10 days for the combination vs. 18 days for remdesivir alone; rate ratio 1.51; 95% CI, 1.10–2.08). Baricitinib also reduced the need for subsequent intubation (10% vs 15%). It was not possible to estimate the TTR within the first 28 days for patients who were on invasive mechanical ventilation at study entry as not enough patients had met the study definition of recovered. There was no significant difference in mortality by day 28 (OR 0.65; 95% CI, 0.39–1.09).

The NIH COVID-19 Guidelines state that there are insufficient data to recommend either for or against baricitinib in combination with remdesivir when corticosteroids can be used instead. However, if corticosteroids cannot be used, baricitinib could be used in combination with remdesivir. The impact of concomitant corticosteroid use is unknown.

Inclusions:

- Age > or = 2 years
- Suspected or confirmed COVID-19
- Requiring supplemental O_2 (new requirement or increase from baseline) or mechanical ventilation
- Prescribed in combination with remdesivir at treatment initiation (not required to continue remdesivir for the duration of baricitinib therapy)

Exclusions:

- Dialysis or acute kidney injury (Scr > 0.5 mg/dL above baseline or oliguric/anuric)
- ALT > 300 (5 x ULN); AST >160 (3 x ULN)
- Absolute neutrophil count (ANC) < 500 cells/µL
- Absolute lymphocyte counts (ALC) < 200 cells/µL
- Suspected serious bacterial, fungal, mycobacterial, or other viral infection
- Receiving other biologic treatments (i.e. TNF-inhibitors, Rituximab, JAK inhibitors, tocilizumab, anakinra)
- Immunocompromised patients and patients with a chronic medical condition that, in the judgement of the provider, predisposes the patient to an increased risk for serious infection

Dosing:

	Adults & Peds ≥ 9 years	**Peds 2 - 8 years**
eGFR > 60 mL/min	4 mg daily	2 mg daily
eGFR 30 – 60 mL/min	2 mg daily	1 mg daily
eGFR 15 – 30 mL/min	1 mg daily	Not recommended
eGFR < 15 or AKI	Not recommended	

Duration:

14 days of total treatment or until hospital discharge, whichever is first

Monitoring:

Adverse reactions: nausea (2.8%), infections (rarely)
Discontinue if ALT/AST rise > 5 x ULN
Consider interruption if ALC falls below 200 cells/µL. May resume when cell count rises > 200 cells/µL.
Consider interruption if ANC falls below 500 cells/µL. May resume when cell count rises > 500 cells/µL.
Reactions such as angioedema, urticaria, and rash that may reflect drug hypersensitivity have been observed in patients receiving baricitinib. Life-threatening hypersensitivity reactions potentially due to baricitinib must be reported to the FDA MedWatch program.

Drug interactions

Note: max dose 1 mg daily while taking probenecid

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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