UVMMC COVID-19 ADULT INPATIENT Therapeutic Algorithm

The treatment algorithm presented here is based on a review of currently available literature and the NIH and IDSA treatment guidelines.
It will be updated to reflect new data as it becomes available.

Patient with COVID-19

No need for supplemental O_2

Supportive care

For patients who are at high risk of disease progression, the use of remdesivir or monoclonal antibodies[1] may be appropriate.

Needs supplemental O_2

- Remdesivir[1]: for patients who require minimal supplemental O_2
- Remdesivir[1] + Dexamethasone[2,3]: for patients who require increasing amounts of supplemental O_2

Needs O_2 via high-flow device or noninvasive ventilation

Dexamethasone[2]
OR
Dexamethasone[2,3] + Remdesivir[1]

For patients hospitalized < 72 hours with rapidly increasing oxygen needs and systemic inflammation add baricitinib[4] to one of the two options above.

Requires invasive mechanical ventilation or ECMO

Dexamethasone[2]

For patients admitted to the ICU for <24 hours add tocilizumab[5]

If tocilizumab is unavailable, substitute baricitinib. See table 4.

For patients who initially received remdesivir and progressed to requiring invasive mechanical ventilation or ECMO, remdesivir should be continued.

1. Remdesivir: 200mg IV x1, then 100mg IV daily for 4 days. Treatment can be extended to 10 days if there is no response by day 5. See tables 1 and 2 for information about remdesivir, including criteria for use and monitoring. See outpatient treatment algorithm for information about monoclonal antibodies & call ID attending for assistance if needed.
   - **Call ID for approval between the hours of 8am – 10pm. If started between 10pm – 8am, please notify ID the next morning**.
2. Dexamethasone 6mg daily x10 days or until hospital discharge, whichever is shorter. Oral therapy is preferred over IV therapy when possible. See table 3.
3. Baricitinib can be substituted for dexamethasone for patients who have a contraindication to corticosteroids. See tables 4 and 5.
4. See tables 4 and 5.
5. Tocilizumab 8mg/kg IV x1 (max dose 800mg). See Table 3.

The NIH recommends against the combination of baricitinib + tocillizumab except in a clinical trial.

Table 1. Remdesivir Drug Information

Remdesivir was approved by the FDA for treatment of SARS-COV-2 infection in patients ≥ 12 years of age and weigh at least 40-kg on October 22, 2020. Remdesivir is a nucleotide analog with antiviral activity. It is infused as an adenosine nucleotide prodrug, then metabolized to its pharmacologically active form of nucleoside triphosphate metabolite. It acts as an analog of adenosine triphosphate (ATP) to compete with the natural ATP substrate for incorporation into nascent RNA chains by the SARS-CoV-2 RNA-dependent RNA polymerase, resulting in delayed chain termination during replication of viral RNA.

Dosing	Notes
200 mg IV on day 1, then 100 mg IV daily for up to 4 days or hospital discharge, whichever is shorter. Therapy can be extended up to 10 days if no substantial clinical improvement is seen at day 5.	Remdesivir is a controlled antimicrobial. Infectious Diseases prior approval is required between the hours of 8am – 10pm with the exceptions of the ICUs and Emergency Department. Remdesivir was approved for the treatment of hospitalized patients ≥age 12 (weighing at least 40-kg) with COVID-19 on October 22, 2020. This decision was based on the following studies: • ACCT-1 clinical trial, conducted by National Institute of Allergy and Infectious Diseases, a randomized, double-blind, placebo-controlled trial comparing 541 patients who received remdesivir to 521 patients who received placebo + standard of care. The median time to recovery was 10 days in the remdesivir group compared to 15 days in the placebo group, which was statistically significant. • JAMA published a randomized, open-label multi-center clinical trial of hospitalized adults with moderate COVID-19. The study concludes that patients who received 5 days of remdesivir had a statistically significant difference in clinical status (favorable) compared to standard of care or 10 days of remdesivir at 11 days of care. • NEJM published a randomized, open-label multi-center clinical trial of adults comparing 5 days of remdesivir to 10 days of remdesivir at day 14. Researchers found that the odds of a patient's COVID-19 symptoms improving were the same in both groups and there were no statistically significant differences in recovery rates or mortality rates between the two groups. Notably, there is no placebo group in this study. Since the FDA approved remdesivir, the WHO has removed remdesivir from their treatment recommendations based on the WHO Solidarity trial, which found that remdesivir did not reduce mortality, initiation of ventilation, or hospital stay. **Remdesivir should not be co-administered with strong inducers of CYP450, such as rifampin. Check for drug-drug interactions prior to prescribing. Concomitant use of hydroxychloroquine, chloroquine, and remdesivir is not recommended.** **There have been reports of infusion-related reactions and anaphylaxis with symptoms including changes in blood pressure and heart rate, hypoxia, fever, shortness of breath, wheezing, swelling, rash, nausea, sweating, and shivering.**

Table 2. Prescribing and Monitoring of Remdesivir

Criteria of Use

Remdesivir is a controlled antimicrobial. Infectious Diseases prior approval is required between the hours of 8am – 10pm with the exceptions of the ICUs and Emergency Department.

Current criteria for consideration of use:
Positive COVID-19 PCR test
Symptom onset ≤ 10 days
Need for supplemental O_2 or increase O_2 need from baseline
AST & ALT ≤ 5x upper limit of normal
Adults > 40 kg
The use of IV medication is appropriate

Monitoring

Daily laboratory monitoring:
Creatinine and creatinine clearance
AST, ALT
CBC
Electrolytes

Use when CrCl <30ml/min:
Caution is advised if administering remdesivir to patients with a CrCl <30ml/min, who receive renal replacement therapy, or have a decline in renal function while receiving remdesivir. Patients with a CrCL <30ml/min were excluded from the initial remdesivir trials and therefore there is a lack of safety data. There is a theoretical risk of nephrotoxicity from a solubilizing factor (sulfobutylether-β-cyclodextrin (SBECD), not the drug itself. The lyophilized powder formulation of remdesivir has 3g of SBECD, which is well below the maximum recommended safety threshold dose of 250mg/kg per day. SBECD is readily dialyzable. There is emerging literature to suggest safe administration of remdesivir to patients with CrCl <30ml/min due to the short duration of treatment[1,2].

Risk of Infusion related reaction
Infusion-related reactions have been observed during, and/or been temporally associated with, administration of remdesivir. Signs and symptoms may include hypotension, nausea, vomiting, diaphoresis, and shivering. If signs and symptoms of a clinically significant infusion reaction occur, immediately discontinue administration of remdesivir and initiate appropriate treatment. The use of remdesivir is contraindicated in patients with known hypersensitive to remdesivir.

Hepatotoxicity
Discontinue remdesivir if ALT ≥ 5x upper limit of normal. Remdesivir may be restarted when ALT ≤ 5x upper limit of normal. Discontinue remdesivir if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR.

1. Adamsick ML, Gandhi RG, *et al*. Remdesivir in Patient with Acute or Chronic Kidney Disease and COVID-19. *JASN* 31:134-1386, 2020.
2. Thakare S, Gandhi C, *et al*. Safety of Remdesivir in Patients with Acute Kidney Injury or CKD. *Kidney Int Rep* (2021) 6, 206-210.

Table 3. Anti-inflammatory Agents – Dexamethasone and Tocilizumab

Medication	Dosing	Notes	Criteria for consideration of use
Dexamethasone	6mg po or IV daily x for up to 10 days, or until hospital discharge, whichever is shorter	The UK Recovery Trial found that patients with COVID-19 and required supplemental O2, who received dexamethasone 6mg daily x 5-10 days had reduced 28 day mortality compared to those patients who did not need supplemental oxygen therapy. This study prompted the IDSA and NIH to include dexamethasone in their treatment recommendations. Oral dexamethasone is the preferred agent for patients not intubated nor receiving positive pressure ventilation. Dexamethasone 6mg = methylprednisolone 32mg = prednisone 40mg.	Indication for prescribing: Positive COVID-19 PCR test Need for supplemental O2
Tocilizumab Tocilizumab is an interleukin-6 (IL-6) receptor inhibitor, binding to soluble and membrane-bound IL-6 receptors.	8mg/kg IV (max dose 800mg) IV x 1	**On June 24, 2021 the FDA issued an EUA for ACTEMR (tocilizumab) for the treatment of COVID-19 in hospitalized adults and pediatric patients (>2 years of age) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation. ACTEMRA is not FDA-approved for this use.** Results from randomized clinical trials regarding the efficacy of tocilizumab in the treatment of patients with COVID-19 have been conflicting. The largest trial (RECOVERY) showed that patients receiving tocilizumab (and usually with corticosteroids) were more likely to be discharged from the hospital within 28 days, had a decrease in 28 day mortality in patients, and reduced progression to needing invasive mechanical ventilation. The NIH COVID-19 Guidelines recommend the use of tocilizumab in combination with dexamethasone in certain hospitalized patients who are exhibiting rapid respiratory decompensation due to COVID-19. Inhibition of IL-6 may lead to increased metabolism of drugs that are CYP450 substrates. Caution should be exercised who co-administering tocilizumab with CYP3A4 substrate drugs where decrease in effectiveness is undesirable.	Inclusion criteria: Positive COVID-19 PCR test Worsening respiratory decline (escalating supplementary oxygen needs to high flow nasal cannula or noninvasive ventilation within 72 hours of admission or within 24 hours of ICU admission). Onset of symptoms < 10 days and hospitalization < 72 hours Exclusion criteria: **Any concurrent active infection** Significant immunosuppression Recent receipt of biologic immunomodulating drugs ALT > 10x ULN GI perforation ANC <1000 cells/uL Platelet <50,000 cells/uL Active hepatic disease or hepatic impairment Tocilizumab has been shown to be safe in pregnancy.

Table 4. Anti-inflammatory Agent - Baricitinib

Medication	Dosing	Notes	Criteria for consideration of use
Baricitinib Baricitinib inhibits Janus kinase (JAK) enzymes, which are involved in stimulating hematopoiesis and immune cell function through a complex signaling pathway. Its role in the treatment of COVID-19 is evolving. The current thought is early administration of baricitinib could stave off cytokine storm/hyperinflammatory syndrome and ARDS. Baricitinib may also have anti-viral properties by inhibiting AP2-associated protein kinase 1 and binding G-associated kinase, both though to be involved in receptor mediated endocytosis of SARS-CoV-2.	eGFR ≥ 60 mL/min/1.73m^2: 4mg po daily x 14 days while hospitalized, or until hospital discharge, whichever is shorter. eGFR 30 – 59 mL/min/1.73m^2: 2mg po daily x 14 days while hospitalized, or until hospital discharge, whichever is shorter. eGFR 15 – 29mL/min/1.73m^2: 1mg po daily, or until hospital discharge, whichever is shorter. eGFR ≤14 mL/min/1.73m^2: do not use	On November 19, 2020 the FDA issued an EUA for baricitinib, in combination with remdesivir, for the treatment of COVID-19. On July 28, 2021 the EUA changed such that baracitinib no longer needs to be given in combination with remdesivir. This is not the same as an FDA approval. The Adaptive COVID-19 Treatment Trial (ACTT-2) showed that baricitinib + remdesivir decreased median recovery time by 1 day compared to remdesivir alone. Additionally there was a decrease in death among patients treated with remdesivir + baricitinib (5.1%) vs. remdesivir alone (7.8%) at day 29. The IDSA and NIH recommend the use of baricitinb in combination with remdesivir in patients who cannot receive corticosteroids. The NIH recommends prescribing baricitinib for patients who are already receiving dexamethasone or dexamethasone + remdesivir who have rapidly increasing supplemental oxygen needs within 72 hours of hospitalization. **If the baricitinib tablets need to be crushed to facilitate enteral administration, please contact the pharmacy for guidance.	Inclusion criteria: Positive COVID-19 pcr test + need for supplemental O_2 Age > 2 years **Patient has contraindication to corticosteroids or patient hospitalized < 72 hours with rapidly increasing oxygen needs and systemic inflammation** Exclusion criteria: Acute kidney injury, eGFR <15 mL/min/1.73m2), or receiving dialysis Active infection with tuberculosis Absolute lymphocyte count <200 cells/mL Absolute neutrophil count <500 cells/mL Drug induced liver injury is suspected Baricitinib should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus. Baricitinib has not been studied in patients with severe hepatic impairment. It should only be used inpatients with severe hepatic impairment if the potential risk outweighs the potential risk. It is not known if dose adjustment is needed in patients with severe hepatic impairment. Baricitinib exposure increases when co-administered with strong OAT3 inhibitors (ex: probenecid). It should be dose reduced by half. Caution is advised if patients are already taking a JAKi or other biologic DMARD, anti-IL6 or anti-IL8 antibodies, or potent immunosuppressants, such as azathioprine and cyclosporine, have a malignancy and are receiving immunosuppressant therapy, have an Active or suspected bacterial, fungal, or viral infection other than SARS-CoV-2, or symptoms of or known diagnosis of thromboembolism, phlebitis, or hypercoagulable state.

Table 5. Prescribing and adverse event reporting of Tocilizumab

Prescribing details

Inclusion criteria:
Positive COVID-19 PCR test
Worsening respiratory decline (escalating supplementary oxygen needs to high flow nasal cannula or noninvasive ventilation within 72 hours of admission or within 24 hours of ICU admission).
Onset of symptoms < 10 days and hospitalization < 72 hours

Exclusion criteria:
Any concurrent active infection
Significant immunosuppression
Recent receipt of biologic immunomodulating drugs
ALT > 10x ULN
GI perforation
ANC <100 cells/uL
Platelet <50,000 cells/uL
Active hepatic disease or hepatic impairment

Prior to administration:
1. Results of CBC with differential, creatinine, AST, ALT are reviewed.
2. It must be communicated with the patient or caregiver:
   - FDA has authorized the emergency use of tocilizumab to treat suspected or laboratory-confirmed COVID-19 in hospitalized adults and pediatric patients 2 year or older requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation. This is not an FDA-approved use of tocilizumab.
   - The patient or parent/caregiver has the option to accept or refuse tocilizumab.
   - The significant known and potential risks and potential benefits of tocilizumab, and the extent to which such potential risks and benefits are unknown.
   - Information on available alternative treatments and the risks of benefits of those alternatives, including clinical trials.
3. The patient or caregiver has received a copy of the "Fact Sheet for Patients, Parents, and Caregivers."

Adverse Event Reporting

Adverse Events or death must be reported to FDA MedWatch within 7 days of event. www.fda.gov/medwatch/report.htm and copied to Gilead at Safety_fc@gilead.com. Submitted reports should include in the field name "Describe Event, Problem, or Product Use/Medication Error" the statement **"Tocilizumab treatment under Emergency Use Authorization (EUA)."**

Serious adverse events are defined in the EUA are:
- Death
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- A medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly

The prescribing healthcare provider and/or the provider's designee are/is to provide mandatory responses to request from FDA for information about adverse events and medication errors following receipt of tocilizumab.

Report adverse events or medication errors to Genentech at:
1-888-835-2555
In addition, please provide a copy of all FDA MedWatch forms to:
Genentech US Drug Safety
Fax: 1-650-238-6067 or 1-650-225-4630
Email: us_drug.safety@gene.com

Table 5. Prescribing and adverse event reporting of Baricitinib

Prescribing details

Inclusion criteria:
Positive COVID-19 PCR test
Age > 2 years
Need for supplemental O2, mechanical ventilation, or ECMO
Patient has a contraindication to corticosteroids

Exclusion criteria:
Acute kidney injury, eGFR <15 mL/min/1.73m2), or receiving dialysis
Active infection with tuberculosis
Absolute lymphocyte count <200 cells/mL
Absolute neutrophil count <500 cells/mL
Drug induced liver injury is suspected

Prior to administration:

1. Results of CBC with differential, creatinine, AST, ALT are reviewed.
2. It must be communicated with the patient or caregiver:
   - FDA has authorized the emergency use of baricitinib, in combination with remdesivir, to treat suspected or laboratory-confirmed COVID-19 in hospitalized adults and pediatric patients 2 year or older requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation. This is not an FDA-approved use of baricitinib.
   - The patient or parent/caregiver has the option to accept or refuse baricinitib.
   - The significant known and potential risks and potential benefits of baricitinib, and the extent to which such potential risks and benefits are unknown.
   - Information on available alternative treatments and the risks of benefits of those alternatives, including clinical trials.
3. The patient or caregiver has received a copy of the "Fact Sheet for Patients, Parents, and Caregivers."

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Adverse Events or death must be reported to FDA MedWatch within 7 days of event. www.fda.gov/medwatch/report.htm and copied to Gilead at Safety_fc@gilead.com. Submitted reports should include in the field name "Describe Event, Problem, or Product Use/Medication Error" the statement **"Baricitinib treatment under Emergency Use Authorization (EUA)."**

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- Congenital anomaly/birth defect
- A medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly

The prescribing healthcare provider and/or the provider's designee are/is to provide mandatory responses to request from FDA for information about adverse events and medication errors following receipt of baricitinib.

Report adverse events or medication errors to Lilly at:
1-855-LillyC19 (1-855-545-5921)
In addition, please provide a copy of all FDA MedWatch forms to:
Eli Lilly and Company, Global Patient Safety
Fax: 1-317-277-0853
Email: mailindata_gsmtindy@lilly.com