UW Medicine Treatment Guidelines for SARS-CoV-2 Infection/COVID-19

Evidenced-based treatment for SARS-CoV-2 infection has evolved rapidly since the novel virus was identified in January 2020. Clinical trial data is emerging and national guidelines addressing treatment options and evaluating clinical data have been published by the National Institutes of Health and the Infectious Diseases Society of America. These guidelines are frequently updated, and the UW Medicine Treatment Guidelines closely follows the national guidance. The UW Medicine Treatment Guidelines will address institution specific practices, including availability of clinical trials within UW Medicine.

On October 22, 2020, IV Remdesivir (Veklury) was **granted FDA-approva**l for treatment of SARS-CoV-2 infection among hospitalized adults and children aged 12 and older. The FDA also grants Emergency use authorizations (EUAs) to make available medical countermeasures to prevent, protect against, treat or diagnose diseases related to emerging infectious diseases when there are no adequate, approved or available alternatives(1). Several EUAs have been granted for treatment of COVID-19, as detailed in the document.

Our best opportunity to understand how to treat COVID-19 is to study stepwise interventions and compare findings to the current best available standard. When available, clinical trials are recommended.

Clinical Trials Available at UW Medicine

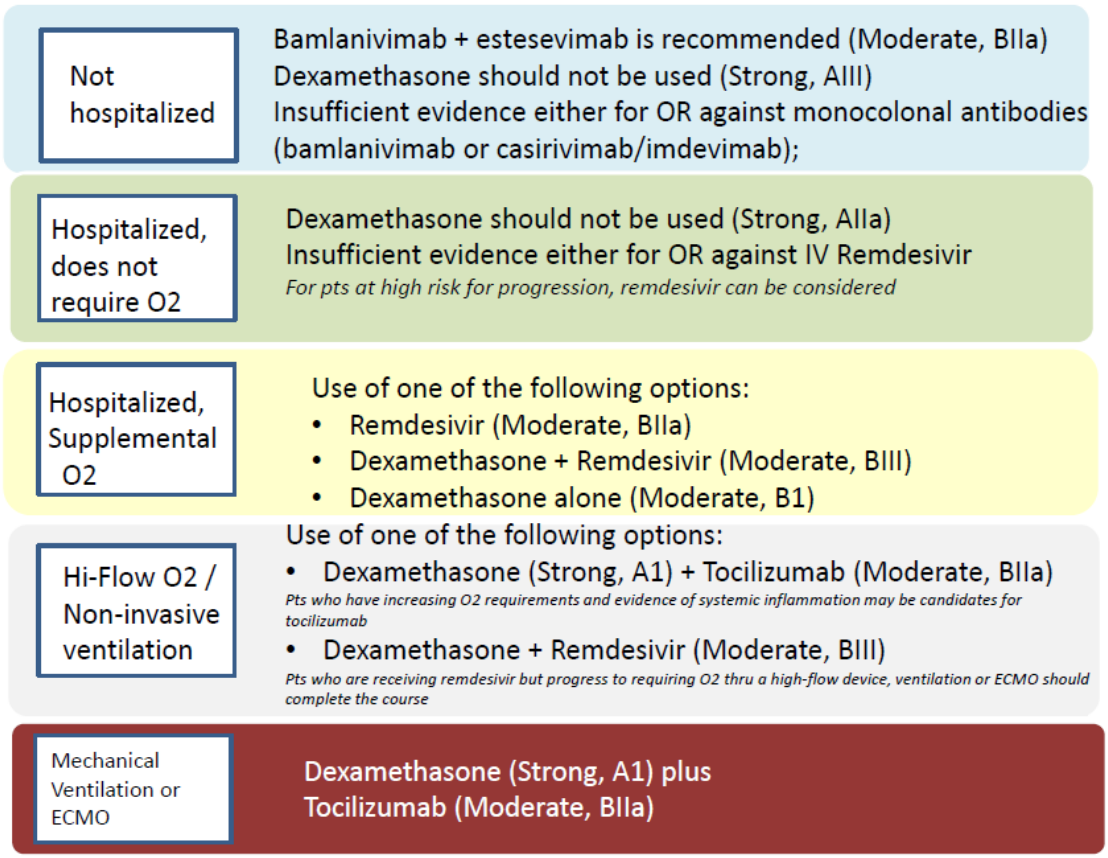
For available clinical trials, visit the ITHS website:
https://www.iths.org/iths-covid-19-research-resources/current-covid-19-research/

Inpatient Studies:
Convalescent Plasma: passitonhmc@uw.edu
Outpatient Studies

www.fredhutch.org/covidresearchcenter
www.riseabovecovid.org
http://stopcovidtrial.wustl.edu/

Please call the Infectious Diseases Consult team with questions about inpatient management of specific patients and refer to national published guidelines for recommendations.

Several therapies are currently being studied for treatment of COVID-19. These therapies are not currently recommended for use in patients, pending further data from clinical trials. Further information about these agents and the rationale for considering their use is available at NIH COVID-19 Guidelines (https://www.covid19treatmentguidelines.nih.gov/) and IDSA Guidelines (https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/)



Based on NIH Guidelines, 3/5/2021

*Tocilizumab (8mg/kg x 1) in combination with dexamethasone is recommended for hospitalized patients who meet the following criteria:

1. Recently hospitalized (within 3 days) admitted to the ICU, requiring mechanical ventilation, non-invasive ventilation, or high-flow nasal canula (Moderate, BIIa)
2. Recently hospitalized patients (within 3 days) admitted to acute care, with rapidly increasing oxygen needs who require NIV or HFNC with increased markers of inflammation, such as CRP>=75mg/L (Moderate, BIIa).

Population	Corticosteroids	Remdesivir	Convalescent Plasma	Monoclonal antibodies	Other
Not hospitalized	No (Strong)	Insufficient evidence	Insufficient evidence	*Clinical Trials at ACTU (ACTIV-2) and FHCRC CCRC Bamlanivimab/etesevimab recommended (Moderate)*	Ivermectin – recommend against Colchicine – insufficient evidence
Hospitalized, no oxygen	No (Strong)	Insufficient evidence	Insufficient evidence	Insufficient evidence	
Hospitalized, with O2	Yes (Moderate) *	Yes (Moderate)	Insufficient evidence	Insufficient evidence	
Hospitalized, high-flow	Yes (Strong)*	Yes (Moderate)	Insufficient evidence	Insufficient evidence	Tocilizumab* (Moderate) (with corticosteroids) *with evidence of systemic inflammation
Hospitalized, MV or ECMO	Yes (Strong)	Consider if recently intubated (weak)	Insufficient evidence	Insufficient evidence	Tocilizumab (moderate) (with coticosteroids)

Please see NIH Guidelines for additional information

A = Strong; B = Moderate; C = optional; Ratings of Evidence:I= one or more randomized trials without major limitations; IIa:

other randomized trials or subgroup analyses of randomized trials IIb = Nonrandomized trials or observation cohort studies; III- Expert opinion

Recommended Agents and Available Clinical Trials

IV REMDESIVIR

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

Evidence Summary: *In-vitro* activity against MERS and SARS, has shown efficacy in animal models(2-4). Remdesivir inhibits SARS-CoV-2 *in vitro*(5).

The FDA approved IV Remdesivir based on evidence from three clinical trials(6-8).

Hospitalized patients with COVID-19 lower-respiratory tract disease who received remdesivir recovered faster than similar patients who received placebo in an NIH trial of 1062 people. The trial (known as the Adaptive COVID-19 Treatment Trial, or ACTT-1), sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, is the first randomized clinical trial launched in the United States to evaluate an experimental treatment for COVID-19(6). Adult patients hospitalized with lower respiratory tract disease were randomized to either IV remdesivir for 10 days or placebo. The primary endpoint was time to recovery, defined by either discharge from hospital or hospitalization for infection control purposes only.

In the final analysis, patients who received remdesivir (n =541) had a median recovery time of 10 days (95% CI, 9 to 11 days) compared to 15 days (95% CI 13-18 days) among those who received placebo (n =521) The Kaplan-Meier estimates of mortality were 11.4% with remdesivir and 15.2% with placebo by day 29 (HR, 0.73; 95% CI, 0.52 to 1.03). In the subgroup of 435 patients who required supplemental oxygen (but not high flow, non-invasive ventilation, invasive mechanical ventilation or ECMO), significantly improved time to recovery was demonstrated compared to placebo (recovery rate ratio 1.45 95% CI 1.18-1.79) In this group, remdesivir conferred a significant survival benefit (HR for death 0.30, 95% CI, 0.14 to 0.64). In patients who required high-flow oxygen or noninvasive ventilation at enrollment (n=193), there was no observed difference in time to recovery (recovery rate ratio 1.09 , 95% CI 0.76 to 1.57). Among patients who were on mechanical ventilation or ECMO at baseline (n = 285), there was no observed difference in time to recovery between remdesivir and placebo (recovery rate ratio 0.98; 95% CI 0.70-1.36).

Remdesivir was studied in a randomized, open-label of patients with moderate COVID-19 pneumonia, defined as the presence of pulmonary infiltrates but not requiring supplemental oxygen (room air O2 saturation>94%)(7). Participants received remdesivir (10 day course), remdesivir (5 day course) or standard therapy. The primary outcome was based on improvement in a 7-point ordinal scale on Day 11. The odds of a favorable clinical status was increased in the remdesivir 5-day group (OR=1.65, p=0.02) but not in the 10-day group (p=0.18). Nausea, hypokalemia and headache were more frequent in the remdesivir treated patients. The IDSA guidelines recommend against the use of remdesivir in this patient population given a very low certainty of evidence(9). NIH Guidance does not recommend for or against IV remdesivir in this patient population due to insufficient data, but recognizes that in certain situations, such as in patients with high-risk of clinical progression, clinicians may choose to use remdesivir among hospitalized patients with moderate COVID-19. The NIH guidelines no longer recommend IV Remdesivir in patients with advanced disease (ie ECMO or mechincally ventilated) because of lack of benefit, although it can be considered for those who were recently intubated (weak recommendation)(10).

The SOLIDARITY trial was a World Health Organisation-sponsored open-label, randomized trial comparing different investigational interventions plus standard of care to standard of care alone in hospitalized patients. Remdesivir was studied in one of arm of the study(11). The SOLIDARITY trial did not find a statistically significant difference in mortality between the remdesivir arm and the standard of care arm. The World Health Organisation does not recommend remdesivir for treatment of COVID-19(12).

Duration:

The optimal duration of IV remdesivir was evaluated in 397 patients hospitalized with COVID-19(8). Patients were randomized to to either receive 5 or 10 days of IV remdesivir; there was no placebo group in this study. The groups had similar demographics but not baseline diseases characteristics. A greater proportion of patients in the 10 day group were in the two most severe disease groups. Most of the patients were receiving noninvasive ventilation or high-flow oxygen or receiving low-flow supplemental oxygen at baseline. The primary endpoint was clinical status on day 14, assessed by a 7-point ordinal scale. After adjustment for baseline clinical status, patients in the 10-day group had a distribution in clinical status at day 14 that was similar to patients in the 5-day group (P=0.14). Few patients were mechanically ventilated in this study so the optimal duration for this population requires further study.

The NIH guidance recommends a five day duration for all populations but can be extended up to 10 days if no substanial clinical improvement is seen at Day 5. Of note, this differs slightly from the FDA prescribing information for remdesivir, which recommends a 10 day course of therapy for patients receiving ECMO or mechanical ventilation. The UW Medicine Guidelines are consistent with NIH guidance, which recommends starting with a 5 day course of therapy. **If patients are clinically stable and eligible for discharge, IV Remdesivir should be stopped. Patients do not need to stay for the full 5 day course.**

Precautions(13):

- Hypersensitivity including infusion related and anaphylactic reactions. Hypersensitivity reactions have been observed during and following the administration of Remdesivir.
- Increased risk of transaminase elevation. Perform baseline hepatic laboratory testing in all patients prior to starting therapy. Consider discontinuing IV Remdesivir if ALT levels increase to > 10 ULN. Discontinue therapy if ALT elevation is accompanied by signs or symptoms of liver inflammation.
- IV Remdesivir is not recommended for patients with a GFR ≤30 ml/min due to the vehicle found in (SBECD) the intravenous formulation.Due to the short course and experience with this vehicle in other FDA approved products (i.e. Voriconazole), this will not be an exclusion criteria for therapy at UW Medicine.
- Contraindicated in patients with known hypersensitivity to Remdesivir
- Reduced antiviral activity when co-administered with chloroquine or hydroxychloroquine.

Dosing:
200 mg IV x 1 on Day 1, followed by 100 mg IV daily

Duration:

- A 5 day course of Remdesivir will be prescribed to all hospitalized patients. The course can be continued up to 10 days if patient does not demonstrate substantial improvement by day 5. Patients who otherwise meet criteria for discharge before day 5, patient should be discharged without continuing therapy.
- FDA prescribing information for remdesivir recommends a 10 day course of therapy for patients receiving ECMO or mechanical ventilation. The UW Medicine Guidelines are consistent with NIH guidance, which no longer recommends IV Remdesivir in patients with advanced disease (ie ECMO or mechincally ventilated).
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Suggested Monitoring:

- Daily CBC, Chemistries, and Liver enzymes
- If ALT > 10 x ULN, stop medication.
- Patient education materials can be found here: https://www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_patient_pi.pdf

Use in Pregnancy: All the remdesivir trials listed above excluded pregnant and breastfeeding individuals including the ACTT-1 trial. Remdesivir should not be withheld from pregnant patients if it is otherwise indicated(10). Pregnant women were included in the Ebola Virus Disease trial which included r(14)OBJ. 6.1% (17/277) of women enrolled were pregnant at the time of Ebola diagnosis: of whom 6/77 (7.8%) were randomized to remdesivir. In the severe adverse event (SAE) supplemental material there were no maternal, pregnancy or neonatal related SAE noted in the remdesivir group. Among 86 pregnant women who received compassionate use remdesivir for treatment of severe COVID-19, (15)OBJ. Although 16% of the population experienced SAEs, most of these were due to pregnancy and underlying disease. There was one death due to underlying disease and no deaths attributed to Remdesivir.

Toxicities and Drug Metabolism: Elevated transaminases, reversible kidney injury, and hypotension during infusion.

Compassionate Use: https://rdvcu.gilead.com/ **Requests are ONLY for children less than 12 years of age with confirmed COVID-19 and severe manifestations of disease.**

Dexamethasone:

Based on preliminary analysis of the data from the RECOVERY trial, both IDSA and NIH issued the following recommendations for use of corticosteroids among these patient populations:

Patient population	NIH	IDSA
No supplemental oxygen	Recommends **against** the use of dexamethasone (A1)	Recommends **against** the use of glucocorticoids (conditional recommendation, low certainty of evidence)
Supplemental oxygen but not mechanically ventilated	Dexamethasone is recommended 6mg IV/PO for **up to** 10 days (B1)	Dexamethasone is recommended at 6mg IV/PO daily (or until discharge if earlier) (conditional recommendations, moderate certainty of evidence)
Require delivery of oxygen through a high-flow device or non-invasive ventilation or Mechanically ventilated	Dexamethasone recommended 6mg IV/PO daily for **up to** 10 days (A1)	Dexamethasone is recommended at 6mg IV/PO daily (or until discharge if earlier) (conditional recommendations, moderate certainty of evidence)

A1**:** Strong recommendation for the statement with one or more randomized trials with clinical outcomes and/or validated laboratory endpoints B1: Moderate recommendation for the statement with one or more randomized trials with clinical outcomes and/or validated laboratory endpoints

The RECOVERY (Randomized Evaluation of COVid-19 thERapY) trial enrolled over 11,500 inpatients with COVID-19 infection from over 176 hospitals in the UK. Participants are randomized to standard of care, low-dose dexamethasone, hydroxychloroquine, Lopinavir-ritonavir, or azithromycin. Simultaneously, participants are randomized to standard of care vs. convalescent plasma. Patients who decompensate clinically may also be randomized to placebo vs. tocilizumab.

A total of 2104 patients were randomized to dexamethasone 6 mg daily for 10 days and compared to 4321 patients who received standard care(16). Among those with standard care, 28-day mortality was 41% among those requiring mechanical ventilation, 25% among those who received oxygen alone, and 13% among those not requiring respiratory intervention. Dexamethasone significantly reduced deaths as among patients receiving ventilation (Rate Ratio (RR) =0.65, 95% CI=0.48-0.88) and among those receiving oxygen only (RR=0.80, 95% CI-0.67-0.96). No benefit was seen among persons who did not require oxygen therapy (RR=1.22, 95% CI=0.86-1.75). Patients with longer duration of symptoms had a greater mortality benefit. Dexamethasone was associated with a reduction in 28-day mortality in patients with symptoms for more than 7 days (RR: 0.69, 95% CI: 0.63 -0.94)(16).

A meta-analysis of 7 randomized trials using steroids to treat COVID-19 disease among critically ill patients showed a mortality benefit to use of steroids (summary OR=0.66, 95% CI=0.53-0.82, p<0.001).(17) Although dexamethasone was the only therapy that was significantly associated with decreased mortality, hydrocortisone and methylprednisolone were underpowered but showed trends toward favorable outcomes as well. When possible, dexamethasone should be used.

Considerations:

Before initiating dexamethasone, clinicians should evaluate the patient's medical history and assess the potential and benefits including co-pathogens such as influenza(10). Patient may experience hyperglycemia, neurological side effects, adrenal suppression and may be at risk increased bacterial infections. **Presence of co-infections should be evaluated. In severe viral pneumonia caused by influenza, corticosteroid therapy appears to result in worse clinical outcomes, including secondary bacterial infection and death**(18).

Strongyloidiasis is caused by a nematode (roundworm) infection. *Strongyloides* infection is predominantly acquired through contact with soil contaminated with free-living larvae, which penetrate the skin and migrate to the intestine, where they lay eggs. Although a majority of individuals with strongyloidiasis are asymptomatic, a severe disease manifestation is hyperinfection syndrome. The most common precipitator severe disease is use of a corticosteroid agent, which appears to be independent of dose or duration of treatment. Based on the available data, the benefit of dexamethasone outweighs the risk of possible *Strongyloides* hyperinfection, an uncommon complication. However, due to the high mortality associated with this syndrome and the availability of inexpensive and effective therapy, ivermectin could be used as a preventive strategy for at-risk patients. **No serology or laboratory confirmation is needed prior to treatment(19)**.

A. Birth or residence or long-term travel (> 6 months) in(20):
    a. Southeast Asia, Oceania, Sub-Saharan Africa, South America, Caribbean: Treat with ivermectin
    b. Mediterranean countries, Middle East, North Africa, Indian sub-continent, Asia: Treat with ivermectin only if exposure to rural or beach areas with skin contact to soil or sand. Otherwise, the risk is low and do not treat with ivermectin.
    c. Australia, North America (including Mexico) or Western Europe: low-risk, do not pre-emptively treat
B. Treatment: Ivermectin 200 µg/kg/day (round to the nearest 3mg tablet) po once daily x 2 doses on day 1 and 2

Corticosteroids may increase the risk of reactivation of latent infections (such as hepatitis B, herpes viruses, strongyloides or tuberculosis). PJP prophylaxis is not needed for short-term treatment with dexamethasone(21). If patients are on additional immunosuppression, PJP prophylaxis may be considered.

Of note, the dose equivalencies for dexamethasone 6 mg daily are prednisone 40 mg, methylprednisolone 32 mg, and hydrocortisone 160 mg.

Duration:

The duration of the dexamethasone studied was 6mg IV/PO for up to 10 days. If patients are otherwise ready for discharge before they have completed the 10 day course, dexamethasone may be discontinued. The median number of days of therapy was 6 days in the RECOVERY trial, therefore it is not recommended to continue dexamethasone therapy beyond hospitalization.

Pregnancy:

Very few pediatric or pregnant patients with COVID-19 were included in the RECOVERY trial; therefore, the safety and efficacy of using dexamethasone in these patients are unknown. Contact Maternal Fetal Medicine for evaluation of pregnant individuals. If gestational age 23-36 weeks, consider increasing dexamethasone dose to 6mg q12 hours x4 doses to promote fetal lung maturity.

Monoclonal Antibodies

Patient population EUA	IDSA(22)	NIH(10)
NON Hospitalized patients with COVID-19	Among ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease, the IDSA guideline panel suggests bamlanivimab/etesevimab rather than no bamlanivimab/etesevimab. (Conditional recommendation, low certainty of evidence) Recommend against the routine use of bamlanivimab in ambulatory patients with COVID-19 No comment on casirivimab plus imdevimab	There are insufficient data to recommend either for or against the use of monoclonal antibodies (bamlanivimab or casirivimab plus imdevimab) for the treatment of COVID-19. **bamlanivimab plus etesevimab recommended** for the treatment of outpatients with mild to moderate COVID-19 who are at high risk of clinical progression as defined by the EUA criteria **(BIIa)**.
Hospitalized patients	**Not eligible, see text**	**Not eligible, see text**

Clinical Trials:

There are two sites with clinical trials of monoclonal antibodies in outpatients with COVID-19 available at UW Medicine.

ACTU in the ACTIV-2 study: https://www.riseabovecovid.org/en/activ-2-study

Fred Hutch Cancer Research Center: https://www.fredhutch.org/en/research/covid-19-clinical-research-center/ccrc-current-studies.html

On November 3rd, the FDA issued an emergency use authorization(EUA) for an investigational monoclonal antibody therapy bamlanivimab for the treatment of mild-to-moderate COVID-19 in high-risk adult and pediatric patients(23). On November 21st, the FDA issued an EUA to casirivimab plus imdevimab combination available for treatment on nonhospitalized patients with mild to moderate COVID-19 disease. The approvals were based on interim analyses of two outpatient phase 2 trials. Both the bamlanivimab and casirivimab and imdevimab data have been published(24, 25). Information is also available on the FDA fact sheet(26).

The NIH guidance has recommended that this should not be considered the standard of care for outpatients and has stated that more data is required to determine the optimal patient population for use of this therapy. IDSA made a statement, urging for clinical trials to "continue and for close ongoing data monitoring and reporting on patients receiving bamlanivimab under the EUA so that we can determine its safety and efficacy."(27)

Mechanism of Action:

Bamlanivimab is a recombinant neutralizing human IgG1κ monoclonal antibody (mAb) to the spike protein of SARS-CoV-2, and is unmodified in the Fc region. Bamlanivimab binds to spike protein and blocks spike protein attachment to the human ACE2 receptor(28).

Casirivimab and imdevimab are two recombinant human mAbs, which are unmodified in the Fc region. Casirivimab and imdevimab bind to non-overlapping epitopes of the spike protein receptor binding domain (RBD) of SARS-CoV-2. Casirivimab, imdevimab and the casirivimab + imdevimab combination blocked RBD binding to the human ACE2 receptor(29).

Evidence summary:

BLAZE-1 is a randomized dose-finding phase 2/3 trial at 49 US centers including ambulatory patients who tested positive for SARS-CoV-2 infection and had 1 or more mild to moderate symptoms. Patients who received bamlanivimab monotherapy or placebo were enrolled first (June 17-August 21, 2020) =with a combination therapy arm (bamlanivimab and etesevimab) added August 22-September 3.(24)

Patients were randomized to receive a single infusion of bamlanivimab (700 mg [n = 101], 2800 mg [n = 107], or 7000 mg [n = 101]), the combination treatment (2800 mg of bamlanivimab and 2800 mg of etesevimab [n = 112]), or placebo (n = 156). The primary end point was change in SARS-CoV-2 log viral load at day 11. Prespecified secondary outcome measures were evaluated with comparisons between each treatment group and placebo, particularly the proportion of patients with a COVID-19–related hospitalization, an emergency department [ED] visit, or death at day 29).

Among non-hospitalized patients with mild to moderate COVID-19 illness, treatment with bamlanivimab and etesevimab, compared with placebo, was associated with a statistically significant reduction in SARS-CoV-2 viral load at day 11; no significant difference in viral load reduction was observed for any doses of bamlanivimab monotherapy. The proportion of patients with COVID-19–related hospitalizations or ED visits was 5.8% (9 events) for placebo, 1.0% (1 event) for 700 mg, 1.9% (2 events) for 2800 mg, 2.0% (2 events) for 7000 mg, and 0.9% (1 event) for combination treatment. Immediate hypersensitivity reactions were reported in 9 patients (6 bamlanivimab, 2 combination treatment, and 1 placebo). No deaths occurred during the study treatment.

The Emergency Use Authorization for bamlanivimab is based on an interim analysis from thisphase two randomized, double-blind, placebo-controlled clinical trial in 465 non-hospitalized adults with mild to moderate COVID-19 symptoms(30). Etesevimab is not available by EUA (Emergency Use Authorization). (30)

On February 23rd, the NIH issued an update on the monoclonal antibody therapy. The NIH panel recommend the use of bamlanivimab and etesevimab for the treatment of mild-moderate COVID-19 who are at high risk of clinical progression as defined by the EUA criteria.

The interim analysis of the phase 1-3 clinical trials evaluating casirivimab and imdevimab in symptomatic, non-hospitalized patients with COVID-19 was published recently(25). Patients were randomized (1:1:1) to receive placebo, low-dose (2.4g) or high-dose (8.0g) mAbs. To be eligible for the study patients had to be > 18 years of age, non-hospitalized with a SARS-COV2 result < 72 hours and symptom onset no more than 7 days before randomization. All patients were tested for anti-SARS-COV2 antibodies (AB), specifically IgA anti-S1 domain of spike protein, IgG anti-S1 domain of spike protein, and IgG nucleocapsid protein prior to randomization.

The pre-specified virologic endpoint was defined as time-weighted average change in viral load from baseline thru day 7. The pre-specified clinical endpoint was the percentage of patients with at least one COVID-19

medically attended visit (telemedicine, in-person, urgent care, emergency department visits and hospitalization) thru day 29.

The time-weighted average change in viral load from baseline (day 1) through day 7 day 1 to day 7 was −0.56 log_{10} copies/ml (95% [CI], −1.02 to −0.11) in those who were AB negative; −0.41 log_{10}copies per milliliter (95% CI, −0.71 to −0.10) for all patients. The percentage of patients with at least one COVID-19–related medically attended visit (telemedicine, ED or hospitalization) through day 29 was 6% in placebo and 3% in REGN group. Stratifying the groups by baseline antibody group, 15% in the AB neg and 6% REGN group (95% CI -29 to 11) had a medically attended visit. Time to alleviation of symptoms did not correlate with therapy. The percent of patients with hypersensitivity, infusion-related, or other adverse reactions were similar between groups.

The ACTIV-3 clinical trial is the only study evaluating bamlanivimab (and Remdesivir) in hospitalized patients with COVID-19. On October 26th, the data safety board stopped the trial because it is unlikely to help hospitalized COVID-19 patients recover(31). An independent data monitoring committee examining the use of REGN-CoV in hospitalized patients requiring high-flow oxygen or mechanical ventilation, due to a potential safety signal and an unfavorable risk/benefit profile(32). Other cohorts continue to enroll. Regeneron also has ongoing trials examining the use of its product in outpatients with COVID-19; current data is only available is via press release.

EUA authorized populations for both products:

- **Mild to moderate COVID-19 in adults and pediatric patients > 12 years old (> 40kg)**

AND

- **Are at high risk for progressing to severe COVID-19**

High risk is defined as patients who meet at least one of the following criteria:

- Have a body mass index (BMI) ≥35
- Have chronic kidney disease, diabetes or
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment or
- Are ≥65 years of age

OR

- Are ≥55 years of age AND have
- cardiovascular disease, OR
- hypertension, OR
- chronic obstructive pulmonary disease/other chronic respiratory disease.

OR

- Are 12 – 17 years of age AND have
- BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm, OR
- sickle cell disease, OR
- congenital or acquired heart disease, OR
- neurodevelopmental disorders, for example, cerebral palsy, OR
- a medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), OR

- asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.

Exclusion criteria:

- Patients who are hospitalized due to COVID-19, OR
- Patients who require oxygen therapy due to COVID-19, OR
- Patients who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.

Dose:

- Bamlanivimab Single IV infusion 700mg plus Etesevimab 1400mg administered over 21 to 60 minutes
- Casirivimab/imdevimab: 1,200 mg of casirivimab/1,200 mg of imdevimab administered together as an intravenous infusion over at least 60 minutes via pump or gravit
- Should be given as soon as possible after positive results and within 10 days on symptom onset.

Safety and Monitoring:

- There is a potential for serious hypersensitivity reaction, including anaphylaxis, with administration of bamlanivimab and/or casirivimab and imdevimab. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive therapy.
- Infusion-related reactions have been observed with administration of bamlanivimab.
    - Signs and symptoms of infusion related reactions may include:
    - Fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, dizziness.
    - If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care.
- Clinical monitor patient during administration and observe patients for at least one hour after infusion is complete
- Cannot receive vaccine within 90 days of infusion

Use in Pregnancy:

There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes(28). Bamlanivimab and/or Casirivimab and imdevimab should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus. Nonclinical reproductive toxicity studies have not been performed with bamlanivimab. In a tissue cross reactivity study with bamlanivimab using human fetal tissues, no binding of clinical concern was detected. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, bamlanivimab has the potential to be transferred from the mother to the developing fetus. It is unknown whether the potential transfer of bamlanivimab provides any treatment benefit or risk to the developing fetus.

UW Medicine process: Currently, the drug is only available by state allocation(33). Two monoclonal antibody therapies (bamlanivumab and casirivimab/imdevimab) have been given Emergency Use Authorization by the FDA for high-risk patients with positive results of SARS-CoV-2 virologic testing who do not require hospitalization

for COVID-19. These therapies should NOT be considered standard of care for treatment of mild to moderate COVID-19 in outpatients per NIH guidelines and the IDSA guidelines. These panels recommend against routine use, although acknowledge it may be reasonable in certain patients after discussion of risks and benefits. These therapies could be considered on a case-by-case basis in high-risk patients who have undergone a shared decision making process with their providers, discussing the unclear certainty of benefit and the low risk of side effects. This discussion should include information regarding participation in clinical trials if appropriate.

The NIH recently recommended bamlanivimab plus estesvimab for high risk individuals therefore can be considered as noted above .

Banlanivimab (soon in combination with estesvimab) therapy is available on a first-come, first-serve basis at Valley Medicine Emergency Department.

SARS CoV-2 Convalescent Plasma

Patient population	IDSA	NIH
Hospitalized patients with COVID-19	Recommend COVID-19 convalescent plasma only in the context of a clinical trial.	There are insufficient data to recommend either for or against the use of the following blood-derived products for the treatment of COVID-19

On August 23, 2020, FDA issued an EUA for COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19(34). The NIH Guidelines do not recommend for or against CP for treatment of COVID-19, citing a lack of evidence(35). The IDSA Guidelines recommend COVID-19 convalescent plasma only in the context of a clinical trial(36). When available, patients should be offered enrollment into randomized controlled trials. At this time, there is an **ongoing randomized clinical trial at UW Medicine (passitonhmc@uw.edu)**. If desired, CP is available at UW Medicine through transfusion services. CP can be ordered using the COVID-19 Convalescent Plasma orderset in ORCA.

Mechanism of Action:

The most likely mechanism is viral neutralization by providing or boosting anti-SARS CoV-2 neutralizing antibodies to the recipient. Other possible specific antibody-dependent mechanisms include antibody-dependent phagocytosis or enhancement of cytotoxic lymphocyte responses(37). Antibody-independent (e.g. coagulation factors, albumin) or non-specific immunologic effects are also possible.

Evidence Summary:

Convalescent plasma (CP) has been administered since the late 19th century for a variety of infectious and non-infectious entities, most notably influenza (1918, 2009 H1N1 and 2007 H5N1), SARS CoV-1(38, 39) and MERS CoV(40, 41) infections. An exploratory meta-analysis of these earlier studies suggested that convalescent plasma offered recipients with respiratory viral infections a mortality benefit (OR 0.25, 95% CI 0.14-0.45), which was largely seen when plasma was administered early after symptom onset (<10-14 days) and prior to seroconversion. However, these studies largely lacked control groups and had high risk of bias.

Initial experience with convalescent plasma in SARS CoV-2 infection includes case series with or without propensity-matched "control" patients, and a few small RCTs. The RCT have not included non-convalescent control plasma.(42) A randomized clinical trial of convalescent plasma in addition to standard treatment among 103 patients hospitalized with severe laboratory-confirmed COVID-19 suggested clinical improvement at 28 days among the convalescent plasma group (Hazard Ratio=1.4, p=0.26)(43). However, the study was stopped early due to inability to recruit cases and therefore was underpowered to detect a significant difference(43).

A 1:1 randomized RCT of CP plus standard of care of hospitalized COVID-19 patients found no differences in 60-day mortality, length of stay, or day 15 severity(44). While patients were treated early (median 10 days of symptoms), most had endogenous antibody when treated. Donor CP with the highest available neutralizing titer was used. In small subgroups, the increase in patient antibody levels at day 7 after treatment was similar between CP-treated and control patients. The study was stopped early by the DSMB due to the presence of endogenous antibody in most recipients and lack of efficacy during interim analysis.

An RCT assigned patients with severe COVID-19 in a 2:1 ratio to receive CP or placebo(45). The primary outcome was clinical status 30 days post intervention. Among 333 patients enrolled, 228 received CP, at a median titer of 1:3200 SARS-CoV-2 antibodies. There was no significant difference in the groups at day 30 with similar distribution of clinical outcomes according to ordinal scale (OR=0.83, 95% CI=0.52-1.35). The mortality in the groups was also similar (CP=10.96, placebo=11.43). Adverse events were similar in the 2 groups.

Recently Joyner et al. reported outcome data on 35,322 US recipients treated with CP during April, May, and June 2020(46). Inclusion criteria were liberal for patients with or at risk for severe COVID-19. Analyses were clustered by duration of symptoms prior to receipt, calendar interval reflecting evolving standards of care, and level of CP anti-SARS-CoV-2 antibody by ELISA, available on ~9% of the CP units. Overall, 27% of patients were ventilated at time of CP. During the 3 month study, CP recipients trended to less ill and a shorter duration of illness prior to CP receipt. The primary endpoints were 7 and 30 day crude mortality. There were no propensity-matched controls. Mortality rates were lower for persons treated within 3 days of symptoms vs. later in each of the 3 months, for persons in each age strata, and for persons on or off the ventilator at time of treatment. Mortality rates were lower in persons treated with high titer CP. Combined analyses of days of symptoms and CP titer showed that early and high titer treatment were each associated with lower mortality. For example, adjusted 30 day mortality was 30% in persons treated at 4 or more days of illness with lower titer CP, versus 20% in persons treated within 3 days with high titer CP. Subgroup analyses of CP titer vs. outcome in patient groups varying by ventilator status, severe risk factors, and time of treatment generally did not, however, reach significance. A retrospective study of 3082 patients in this cohort showed a decreased risk of death among patients who had not received mechanical ventilation prior to receipt of CP and among those who received high-titer CP as compared to low-titer plasma (RR=0.66, 95% CI=0.48-0.91)(47).

A double-blind, placebo controlled trial of high titer CP conducted in Argentina among adult outpatients age >75 years or 65-74 with at least one comorbidity and with COVID-19 showed a decreased risk of severe respiratory disease among those who received CP (16% vs 31%, RR=0.52, 95% CI=0.29-0.94)(48). This study was stopped early due to lack of cases in the region.

Adverse events and cautions:

- CP appears to be safe in a review of 20,000 doses(49). Mortality occurred in 63 (0.3%) of persons within 4 hours of CP. Of these, 13 were considered possibly or probably related to CPI.

  -Risk of transfusion reactions including TRALI, TACO, severe allergic reactions, and blood-borne pathogen infection.

- Contraindicated in IgA deficiency or in patients with a history of transfusion reaction; caution in volume overload.

- Theoretical risk of worsening clinical course due to antibody-dependent enhancement, which has been described for MERS-CoV, or possibly through non-specific immune activation should be considered.

Administration:

1 unit IV once

Pregnancy: In a small case series of four critically ill patients in China who received convalescent plasma and recovered from COVID-19, one of the patients was pregnant(50).

Baricitinib

On November 19th, the FDA authorized baracitinib, in combination with remdesivir, for the treatment of hospitalized COVID-19 adult and pediatric patients requiring supplemental oxygen, invasive mechanical ventilation, or ECMO under an emergency use authorization(51), based on results from the ACTT-2 trial(52).

Mechanism

Baricitinib is an oral Janus kinase (JAK) inhibitor that is selective for JAK1 and JAK2. It is FDA approved for treatment of rheumatoid arthritis. Baricitinib inhibits intracellular signaling pathways induced in severe COVID-19 (IL-2, IL-6, IL—10, IFN-γ) and has antiviral activity, preventing SARS-CoV-2 entry into lung cells because of its affinity for adaptor-associated kinase-1 (AAK1)(53).

Evidence Summary

The data supporting this EUA for baricitinib combined with remdesivir are based on a randomized, double-blind, placebo-controlled clinical trial (ACTT-2), which was conducted by the National Institute of Allergy and Infectious Diseases (NIAID(52)). This clinical trial evaluated whether baricitinib 4mg daily for up to 14 days + remdesivir (200 mg IV x 1, followed by 100 mg IV daily for up to 10 days) decreased recovery time from COVID-19 among hospitalized patients. The trial followed patients for 29 days and included 1,033 patients with moderate or severe COVID-19; 515 patients received baricitinib plus remdesivir, and 518 patients received placebo plus remdesivir. The median time to recovery from COVID-19 was seven days for baricitinib plus remdesivir and eight days for placebo plus remdesivir (RR=1.16, 95% CI=1.01-1.32, p=0.03). Patients who were receiving high-flow oxygen or noninvasive ventilation at enrollment had the most pronounced effect, with a recovery time of 10 days with baricitinib plus remdesivir and 18 days with placebo plus remdesivir (RR=1.51, 95% CI=1.10-2.08). Serious adverse events were lower in the baricitinib plus remdesivir group.

The NIH COVID-19 Guidelines have stated 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 for hospitalized, non-intubated patients who require oxygen supplementation (moderate strength, BIIa)(54). Baricitinib should not be used alone. The impact of concomitant corticosteroid use is unknown. There is an ongoing clinical trial (ACTT-4) of dexamethasone+remdesivir vs baricitinib+remdesivir (not available at UW Medicine).

The IDSA has recommended that among hospitalized patients with severe COVID-19 who have a contraindication to corticosteriods, baracitinib may be considered with remdesivir(36).

TOCILIZUMAB

Patient population	**IDSA**	**NIH**
Hospitalized patients with COVID-19 **Note: Dose is 8 mg/kg(max dose is 800mg), not 400mg as stated in ORCA.**	Among hospitalized adults with progressive severe* or critical** COVID-19 who have elevated markers of systemic inflammation, the IDSA guideline panel suggests tocilizumab in addition to standard of care (i.e., steroids) rather than standard of care alone. (Conditional recommendation, Low certainty of evidence)(55)	Tocilizumab (8mg/kg) is recommended in combination with dexamethasone in patients who are exhibiting rapid respiratory decompensation due to COVID-19. These patients include: Recently hospitalized patients admitted to the ICU within the prior 24 hours, requiring mechanical ventilation, NIV, or HFNC -or- Recently hospitalized patients with rapidly increasing O2 needs who require NIV/HFNC and have increased markers of inflammation (BIIa, moderate)(56)

Mechanism of Action: Tocilizumab is a recombinant humanized monoclonal antibody against IL-6 receptor that is FDA-approved for the treatment of rheumatoid arthritis.

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 elevated in patients with severe COVID-19(57). The prognosis for critically ill patients with COVID-19 is poor, with mortality ranging from 50-67% in reported case series(58-60). There is institutional experience with the use of tocilizumab for CRS after CAR-T therapy, which is mediated by IL-6.

Evidence Summary:

Eight randomized control trials have evaluated patients with severe COVID-19 to treatment with tocilizumab (8 mg/kg) or placebo/usual care(61-68). Several trials allowed patients to be included when on mechanical ventilation at randomization, while other trials allowed patients to start therapy with lower severity of illness.

The RECOVERY trial included patients with clinical evidence of progressive COVID-19 defined as <92% oxygen saturation on room air or receiving oxygen and CRP >/= 75 mg/L. The primary outcome was mortality at 28 days; 82% of participants in both arms received dexamethasone. Among hospitalized patients, tocilizumab showed a trend toward reduced mortality at 28 days compared to no tocilizumab treatment (RR: 0.91; 95% CI: 0.79, 1.04)

The REMAP-CAP is an international trial that evaluated tocilizumab (8 mg/kg) or sarilumab (400mg) given within 24 hours of starting organ support or standard of care(63). The primary outcome was respiratory and cardiovascular organ support-free days on an ordinal scale combining in-hospital death and days free of organ

support to day 21. At that time, 353 patients had been assigned to tocilizumab, 48 to sarilumab, and 402 to control. The median number of organ support–free days was 10 (interquartile range, −1 to 16) in the tocilizumab group, 11 (interquartile range, 0 to 16) in the sarilumab group, and 0 (interquartile range, −1 to 15) in the control group. The median adjusted cumulative odds ratios were 1.64 (95% credible interval, 1.25 to 2.14) for tocilizumab and 1.76 (95% credible interval, 1.17 to 2.91) for sarilumab as compared with control.

NIH recommends Tocilizumab to be given within 3 days of hospitalization. The median days of hospitalization until randomization was 1.2 days (IQR 0.8–2.8 days) in REMAP-CAP and 2 days (IQR 1–5 days) in the RECOVERY trial.

Caution is advised in patients with:

- significant immunosuppression, particularly in those with a history of recent use of other biologic immunomodulating drugs
- Alanine transaminase >5 times the upper limit of normal
- High risk for gastrointestinal perforation
- uncontrolled, serious bacterial, fungal, or non-SARS-CoV-2 viral infection
- absolute neutrophil count <500 cells/µL; or platelet count <50,000 cells/µL
- Cases of severe and disseminated strongyloidiasis have been reported with the use of tocilizumab and corticosteroids in patients with COVID-19.
    - Prophylactic treatment with ivermectin should be considered for persons who are from areas where strongyloidiasis is endemic. See dexamethasone section.

Dosing:

- single intravenous dose of 8 mg/kg based on actual body weight, up to 800 mg
- vial size is 400mg and 200mg; round to the nearest vial size as needed.
- there are insufficient data to determine which patients will benefit from a second dose therefore it is not recommended despite being given during the RECOVERY and REMAP-CAP trials

UW Medicine Recommendations:

Tocilizumab in combination with dexamethasone is recommended for patients (admitted within 3 days) with increasing O2 needs due to COVID-19 in the ICU and/or with need for NIV or HFNC and elevated markers of inflammation on the acute care ward. At UWMC-ML and HMC, discussion with pulmonary critical care is recommended for patients that are not in the ICU; at UWMC-NW these patients should be discussed with infectious disease.

These guidelines were drafted by a working group, including Fred Buckner, Jeannie Chan, Guang-Shing Cheng, Shireesha Dhanireddy, Margaret Green, Robert Harrington, Josh Hill, Rupali Jain, Christine Johnston, H. Nina Kim, David Koelle, Manoj Menon, Sylvia LaCourse, Paul Pottinger, Alpana Waghmare, Anna Wald, Anne Woolfrey, and Mark Wurfel

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