Stony Brook Medicine COVID-19 Treatment Guidelines

Summary Recommendations

			Treatment Recommendations
Post-exposure prophylaxis	No symptoms High risk contact with infected person[1]		COVID monoclonal antibodies in situation of a high risk contact with infected person[1] by a patient who is not fully vaccinated[2] or who has risk of poor vaccine uptake[3]
Mild	Oxygen saturation >94% on room air Chest X-ray without evidence for pneumonia	Symptoms ≤ 10 days	COVID monoclonal antibodies in patients with high risk factors[4]
Moderate	Oxygen saturation >94% on room air Chest X-ray with evidence for pneumonia	Symptoms ≤ 10 days	COVID monoclonal antibodies in patients with high risk factors[4]
Severe (Hospitalized)	Oxygen saturation ≤94% on room air Change in baseline oxygen requirement Chest X-ray with evidence for pneumonia	Using low flow oxygen (nasal cannula,	Remdesivir 200mg x1 then 100mg IV x 4days Dexamethasone 6mg IV/PO daily x 10 days
		Using high flow oxygen (high flow nasal cannula, noninvasive mechanical ventilation)	Dexamethasone 6mg IV/PO daily x 10 days Remdesivir 200mg x1 then 100mg IV x 4days Consideration for additional immune modulators (tocilizumab or baricitinib)
Critical (Hospitalized)	PaO_2/FiO_2 <100 Requiring mechanical ventilation Requiring ECMO		Methylprednisolone 1 mg /kg/day IV daily x 10 days[5] Consideration for tocilizumab within 24 hours of admission

1. High risk contact is defined as a person who spends a cumulative 15 minutes or more in contact with an infected person with SARS-CoV2. Note that persons infected with SARS-CoV2 can be contagious up to two days prior to symptom onset and typically during the first 10 days of symptoms.
2. Persons are considered to be fully vaccinated if they are two weeks out from their second dose of a mRNA vaccine (Pfizer or Moderna) or two weeks out from their first dose of a Johnson and Johnson vaccine
3. Persons not expected to mount an adequate immune response to complete SARS-CoV2 vaccination include those with immunocompromising conditions and those taking immunosuppressive medications
4. Persons with high risk factors for progression to severe COVID-19 are defined on page 2
5. Dexamethasone 6mg IV/PO can also be considered

Medication Dosages

Medication	Dose	Contraindications	Laboratory Monitoring	ID Approval Needed for Inpatients
Casirivimab-imdevimab (REGEN CoV)	600mg+600mg IV, infused over one hour	Hypoxemia (O2 sat <94%)	None	Yes
Remdesivir (Veklury)	200mg IV on day 1 100mg IV daily on days 2-4*	CrCl or eGFR <30 cc/mL ALT or AST >200 IU/L	Chem8 LFT	Yes
Dexamethasone	6mg IV or PO daily x 10 days*	Intolerance to corticosteroids		No
Baricitinib (Olumiant)	eGFR>60 4mg PO daily x 14 days eGFR 30-60 2mg PO daily x 14 days	Use of other immune modulator (including outpatient) CrCl or eGFR <30 cc/mL Uncontrolled bacterial or fungal infection ALT or AST >200 IU/L Neutropenia (<500 cells/uL)	Chem8 CBC LFT	Yes
Tocilizumab (Actemra)	8mg/kg IV x 1 (round to dose of 400, 600, or 800mg)	Use of other immune modulator (including outpatient) ALT or AST >200 IU/L Uncontrolled bacterial or fungal infection Neutropenia (<500 cells/uL) Leukopenia (<1000 cells/uL)	Chem8 LFT CBC	Yes

*Duration of therapy is as listed or until time of hospital discharge, whichever time is shorter

COVID-19 Monoclonal Antibodies (Casivirimab-imdevimab, REGEN-COV)

The administration of monoclonal antibodies targeting the spike protein of SARS-CoV2 has been demonstrated to decrease COVID-19 related hospitalizations and all-cause death in persons with mild-to-moderate disease (ARR 2.2%, RR 70%). Protective benefits have also been reported as postexposure prophylaxis amongst household contacts (72%).

At Stony Brook Medicine, casivirimab-imdevimab is the preferred monoclonal as *in vitro* data demonstrates efficacy against the prevalent variants (alpha, beta, gamma, and delta).

Currently, casivirimab-imdevimab has emergency use authorization for

(1) the treatment of persons with mild-to-moderate disease, symptoms for <= 10 days, and high risk factors for progression to severe COVID-19

(2) postexposure prophylaxis in persons who are not fully vaccinated against SARS-CoV2 or who are not expected to mount an adequate response to complete SARS-CoV2 vaccination.

The FDA defines patients with high risk factors for progression to severe COVID-19 as the following:

- Age ≥12 and Weight ≥40 kg with one of the following:
    - Age ≥65
    - Obesity or being overweight (BMI >25 kg/m^2), or if age 12-17, BMI ≥ 85th percentile for their age and gender based on CDC growth charts
    - Pregnancy
    - Chronic kidney disease
    - Diabetes mellitus
    - Immunocompromised disease or immunosuppressive treatment
    - Cardiovascular disease (including congenital heart disease)
    - Hypertension
    - Chronic lung disease (i.e. chronic obstructive pulmonary disease, moderate-to-severe asthma, cystic fibrosis)
    - Sickle cell disease
    - Neurodevelopmental disorder (i.e. cerebral palsy) or other conditions that confer medical complexity
    - Having a medical related technology dependence (i.e. tracheostomy)

The FDA EUA allows for the use of COVID monoclonal antibodies in persons who are not hospitalized and who do not require supplemental oxygen or an increase in baseline oxygen requirements.

Ideally, patients who qualify for a monoclonal antibody should be treated within 3-5 days of symptom onset. While this therapy is approved for up to 10 days of symptoms, the benefits wane with delayed treatment.

COVID monoclonal antibodies are *not* a substitute for vaccination.

Because of potential interference, SARS-CoV2 vaccination should be deferred for 90 days after receiving a COVID monoclonal antibody infusion.

Use of a COVID monoclonal antibody for an inpatient must be reviewed by Infectious Diseases.

Remdesivir (Veklury)

Remdesivir is a nucleotide prodrug of an adenosine analog that inhibits viral replication by binding to the viral RNA polymerase. It is currently FDA approved for the treatment of COVID-19 in hospitalized persons aged ≥12 years and weighing ≥40 kg.

Remdesivir has been studied in clinical trials with mixed results. The NIH sponsored ACTT-1 trial demonstrated a five day reduction in time to clinical recovery compared to placebo but no statistical difference in 30 day mortality. The benefit was most apparent in hospitalized patients using low flow supplemental oxygen; no benefit was seen in those persons not using oxygen (mild-to-moderate disease) or in those persons requiring high flow oxygen, mechanical ventilation, or ECMO. The WHO Solidarity study was a large, multinational, open label study that did not demonstrate a decrease in in-hospital mortality.

Currently, both the NIH and IDSA recommend the use of remdesivir in persons with severe COVID-19. Both recommend against the routine use of remdesivir in critically ill COVID patients requiring mechanical ventilation and/or ECMO; such decision should be made on a patient-by-patient basis.

At Stony Brook Medicine, remdesivir is recommended for persons with COVID-19 and hypoxemia (O2 saturation <94%). The duration of therapy is five days (longer courses have not been shown to provide added benefit).

Remdesivir is not recommended in persons with severe renal impairment (CrCl or eGFR <30) due concerns about the accumulation of the preservative sulfobutylether beta-cyclodextrin sodium. Clinical trials are underway to assess the safety of remdesivir in persons with severe renal insufficiency.

Remdesivir is not recommended in persons with abnormal liver function, defined as an ALT or AST greater than 5 times the upper limit of normal (ULN). Liver function tests should be monitored while on remdesivir and the drug discontinued if the ALT or AST rise to >10 times the ULN.

Use of remdesivir requires ID approval.

Corticosteroids

Persons with severe COVID-19 can develop a systemic inflammatory response that leads to lung injury and multiorgan dysfunction. Corticosteroids have been demonstrated to improve outcomes in persons with COVID-19 and hypoxemia. The largest study to demonstrate this was the RECOVERY trial, a randomized, open label trial in hospitalized patients with COVID-19. Dexamethaxone 6mg for 10 days was compared to standard of care. RECOVERY demonstrated a 28-day mortality benefit based on the severity of illness. Among patients who required supplemental oxygen but not mechanical ventilation, an 18% risk reduction was noted. In persons on mechanical ventilation, a 36% risk reduction was seen. No benefit was seen in persons not on oxygen.

Dexamethasone 6mg (or its equivalent) is recommended in all patients with COVID-19 who require supplemental oxygen. There are no head-to-head studies comparing the different corticosteroids. Dexamethasone is recommended based on the RECOVERY trial; however, the use of other corticosteroids (i.e. methylprednisolone) is not expected to yield less benefit.

In critically ill patients, higher doses of corticosteroids may be beneficial. A well-done retrospective study showed improved severity-adjusted mortality (16% VS 26%) with 1-2 mg/kg methylprednisolone/day compared to usual dexamethasone 6 mg dose in ICU patients (Ko JJ, J Intens Care Med 2021) and a smaller randomized trial from Iran (Ranjbar K, BMC Infect Dis, 2021) showing a similar benefit of methylprednisolone 2 mg/K/d over dexamethasone, 19% v 38%, (p=0.07). Considering a relative potency ratio ~ 5:1 methylprednisolone:dexamethasone, the doses used in these studies favor higher steroid doses overall.

The duration of therapy is 10 days or until hospital discharge.

Corticosteroids are not recommended for the treatment of COVID-19 in persons who do not need supplemental oxygen.

Baricitinib (Olumiant)

Baricitinib is an oral Janus kinase inhibitor currently approved for the treatment of rheumatoid arthritis. In addition to immune modulating effects, baricitinib is postulated to have antiviral activity and to prevent SARS-CoV2 from entering lung cells.

The benefit of baricitinib was first shown in the NIH ACTT-2 study. In this multicenter, randomized, double blind study, baricitinib with remdesivir was compared to remdesivir alone. Overall, the trial demonstrated a reduction in time to recovery of one day in the baricitinib group. However, the benefit was pronounced in the cohort that was on high flow oxygen therapy (10 vs. 18 days for the baricitinib and placebo recipients, respectively). Of note, few patients in ACTT-2 received corticosteroids.

The COV-BARRIER study looked at the effect of baricitinib versus placebo in patients receiving standard of care (primarily dexamethasone). Preprint data from multicenter, randomized, double blind study demonstrated a 38.2% reduction in mortality, though there was no statistical difference in disease progression. The effect was again most pronounced in persons on high flow oxygen or noninvasive mechanical ventilation at baseline.

While baricitinib can be given as a substitute for corticosteroids, there appears to be a more pronounced benefit when it is given in conjunction.

At Stony Brook Medicine, immune modulator therapy is recommended in persons with COVID-19 on high flow oxygen or noninvasive mechanical ventilation.

Baricitinib is not recommended in persons already receiving other immune modulator therapy, whether for COVID-19 or for other indications (i.e. autoimmune disease). Baricitinib is not recommended in persons with severe renal impairment (CrCl or eGFR <30), neutropenia (ANC <1000/mm^3), or severe hepatic impairment.

Use of baricitinib for COVID-19 treatment requires ID approval.

Tocilizumab (Actema)

Tocilizumab is an IL-6 receptor antagonist that has been shown in two large, multicenter clinical trials (RECOVERY and RECAP-MAP) to improve 28 day mortality in persons with COVID-19. In the RECOVERY trial, hospitalized persons with COVID-19 and elevated CRP (≥ 75 mg/L) was associated with a reduction in all-cause mortality (29 vs. 33%) and shorter time to discharge. The RECAP-MAP trial demonstrated lower mortality (28.0% vs. 35.8%) and shorter duration of organ support in persons with COVID-19 treated with an IL-6 inhibitor vs. standard of care alone within 24 hours of admission to the ICU. The majority of patients in these studies were on noninvasive mechanical ventilation or high flow nasal cannula (HFNC) at baseline.

Use of tocilizumab should be considered in the following scenarios:

- Recently hospitalized persons (<3 days) who have been admitted to the ICU within the past 24 hours and who require invasive mechanical ventilation, noninvasive ventilation, or HFNC oxygen
- Recently hospitalized persons (<3 days) not in the ICU who have rapidly increasing oxygen needs and require noninvasive mechanical ventilation or HFNC oxygen *and* who have significantly increased markers of inflammation (CRP ≥ 7.5 mg/dL).

Tocilizumab should be avoided in significantly immunosuppressed persons, particularly those who have recently received other biologic immunomodulating agents. It should also be avoided in persons with elevated liver transaminases (>5 times ULN); who are at high risk for gastric perforation; have an uncontrolled serious bacterial, fungal, or other viral infection; are neutropenic (ANC <500 cells/uL); or are thrombocytopenic (<50,000 cells/uL).

Tocilizumab should only be given in combination with corticosteroids.

The recommended dose of tocilizumab is approximately 8mg/kg (maximum dose 800mg). The drug is dispensed at doses of 400mg, 600mg, and 800mg. At this time, a single dose is recommended.

The effects of tocilizumab can be prolonged (half life estimated at 13 days). Patients who receive tocilizumab can be at risk for bacterial, fungal, and mycobacterial infections long after they receive the drug.

Use of tocilizumab for the treatment of COVID-19 requires ID approval.

Special Populations

Pregnancy

There is limited clinical data on the above therapeutics in pregnant women with COVID-19. Recommendations based on literature review is shown below:

Medication	Pregnancy	Breast Feeding
Casirivimab-imdevimab (REGEN CoV)	Recommended as pregnancy is considered a high risk factor for COVID-19 progression	No clinical data available.
Remdesivir	Case series based on pregnant women receiving remdesivir via compassionate use suggest safety during pregnancy	No clinical data available.
Baricitinib	No clinical data in COVID-19	No clinical data available.
Tocilizumab	Limited case reports and case series suggest it is safe when given to pregnant women. Clinical trials and post marketing data for rheumatoid arthritis and juvenile idiopathic arthritis suggest an increased risk of preterm labor; however, this was associated with long term use. No significant risk for fetal malformation was noted.	No clinical data available.

Given the paucity of data, use of the above COVID therapeutics should include shared decision-making between the pregnant individual and the health care provider, considering the potential maternal benefit and fetal risks.

Pediatrics

Clinical trial data involving children is scarce. Casirivimab-imdevimab has been approved for persons age 12 years and older with high risk factors for progression to severe COVID-19. Remdesivir has been approved for use in persons age 12 years and older. While tocilizumab and baricitinib have been used in children for autoimmune diseases, data on their use in the treatment of COVID-19 or multisystem inflammatory syndrome in children (MIC-C) is limited. Consultation with Pediatric Infectious Diseases is recommended.

Other Investigational Agents

Colchicine

- There is limited clinical experience for the use of colchicine in patients with COVID-19. The largest study (COLCORONA) looking at high dose colchicine in treating outpatients did not reach its primary endpoint of reducing hospitalizations and death. A slight reduction in hospitalizations was observed in persons with positive SARS-CoV2 PCR tests.
- In a randomized trial in hospitalized patients with COVID-19 (RECOVERY), no benefit was seen with regards to 28-day mortality or other secondary outcomes.
- At this time, use of colchicine for the treatment of COVID-19 is **not recommended**.

Ivermectin

- There is limited clinical trial data for the use of ivermectin in either outpatient or inpatient settings. Trials that have reported a benefit have methodological limitations such as small sample size, variance in ivermectin dose used, and confounding use of other COVID-19 therapeutics. Some clinical trials have not shown a benefit to using ivermectin in the management of COVID-19. Larger studies are underway to assess the benefit of ivermectin.
- At this time, use of ivermectin for the treatment of COVID-19 is **not recommended**.

Fluvoxamine

- There is limited clinical data on the use of fluvoxamine in patients with COVID-19. Small clinical studies have suggested a potential benefit with fluvoxamine; however, they have limitations that prevent generalizing their conclusions.
- At this time, use of fluvoxamine for the treatment of COVID-19 is **not recommended.**

High titer convalescent plasma

- High titer convalescent plasma is authorized by the FDA for use under the EUA for the treatment of hospitalized patients with COVID-19 and impaired immunity. While clinical trial data is limited, high titer convalescent plasma may be beneficial in persons with impaired humoral immunity (i.e. recent use of rituximab). Infectious Diseases consultation is recommended in such cases.
- Routine use of convalescent plasma is hospitalized patients is **not recommended**.

High dose vitamin C

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of vitamin C for the treatment of COVID-19 in non-critically ill or in critically ill patients.
- It is important to note that high circulating concentrations of vitamin C may affect the accuracy of point-of-care glucometers
- It is important to note that fluid volume may contribute to respiratory failure
- Routine use of high dose vitamin C is **not recommended**