Stony Brook Medicine COVID-19 Treatment Guidelines

Summary Recommendations

	Definition		Treatment Recommendations
Post-exposure prophylaxis	No symptoms High risk contact with infected person*		Observation
Mild	Oxygen saturation >94% on room air Chest X-ray without evidence for pneumonia	Symptoms ≤ 5 days	In persons with high risk factors:** • Nirmatrelvir-ritonavir • Remdesivir (3 day) • Molnupiravir
Moderate	Oxygen saturation >94% on room air Chest X-ray with evidence for pneumonia	Symptoms ≤ 5 days	In persons with high risk factors:** • Nirmatrelvir-ritonavir • Remdesivir (3 day) • Molnupiravir
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 4 days • Dexamethasone 6mg IV/PO daily x 10 days • Consider systemic anticoagulation if D-dimer elevated above ULN
		Using high flow oxygen (high flow nasal cannula, noninvasive mechanical ventilation)	• Dexamethasone 6mg IV/PO daily x 10 days • Consider addition of Remdesivir 200mg x1 then 100mg IV x 4 days • Consider use of either tocilizumab or baricitinib
Critical (Hospitalized)	PaO_2/FiO_2 <100 Requiring mechanical ventilation Requiring ECMO		• Dexamethasone 6mg IV/PO daily x 10 days • Consider addition of Remdesivir 200mg x1 then 100mg IV x 4 days • Consideration for tocilizumab within 24 hours of admission

* 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.

**Persons with high risk factors for progression to severe COVID-19 are detailed in https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

Medication Dosages

Medication	Dose (Adult)	Contraindications	Laboratory Monitoring	ID Approval Needed for Inpatients
Nirmatrelvir-ritonavir	eGFR>60 300mg-100mg PO BID x 5 days eGFR 30-60 150mg-100mg PO BID x 5 days eGFR<30 Not recommended	Check for potential drug interactions** eGFR<30		Yes
Molnupiravir	800mg PO BID x 5 days	Caution in persons of reproductive age	Pregnancy testing prior to use in patients who may become pregnant	***
Remdesivir (Veklury)	200mg IV on day 1 100mg IV daily on days 2-4*	ALT or AST >200 IU/L Discuss with ID/ASP‡ if eGFR<30	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 eGFR 15-30 1mg PO daily x 14 days eGFR <15 Not recommended	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

** Use of references such as the University of Liverpool COVID drug interaction checker (https://covid19-druginteractions.org/checker) is advised for guidance regarding specific medications

*** Not available in SBUH formulary

‡ ID: Infectious Diseases, ASP: Antimicrobial Stewardship Program

Nirmatrelvir-ritonavir (Paxlovid)

Nirmatrelvir is a 3CL-like protease inhibitor, an enzyme specific to coronaviruses, and is the main component of Paxlovid. Ritonavir is added to increase the half-life of the nirmatrelvir via inhibition of the CYP3A pathway.

In the EPIC-HR Phase 2/3 clinical trial, nirmatrelvir-ritonavir reduced the risk of hospitalization and death by 89% in high-risk persons when given within 3 days of symptom onset. If given within 5 days, the risk of hospitalization and death was reduced by 88%.[1] It was authorized by the FDA for emergency use for the outpatient treatment of mild-moderate COVID-19 in high-risk persons.

Adverse events were similar in the nirmatrelvir-ritonavir and placebo groups (23 vs. 24%). Noted adverse effects with nirmatrelvir-ritonavir include impaired sense of taste, diarrhea, increased blood pressure, hepatotoxicity, and myalgias.

Nirmatrelvir-ritonavir is approved for use under the EUA for the treatment of mild-moderate COVID disease with a symptom duration of five days or less in persons aged 12 years and older who weigh at least 40 kg and who have risk factors for progression to severe COVID disease. It is not approved for persons with severe COVID disease or for pre- or post-exposure prophylaxis.

Nirmatrelvir-ritonavir is not recommended for use in persons with severe renal impairment (eGFR <30 mL/min) or severe hepatic impairment (Child-Pugh Class C).

Providers must be cautious in persons who are being treated with drugs that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions and that are potent CYP3A inducers which can significantly reduce plasma concentrations and effectiveness of nirmatrelvir-ritonavir. As the list of potential drug interactions is extensive, use of a reference guide such as the University of Liverpool COVID drug interaction checker (https://covid19-druginteractions.org/checker).

Inpatient use of nirmatrelvir-ritonavir requires approval from Infectious Diseases or Antimicrobial Stewardship.

Molnupiravir (Lagevrio)

Molnupiravir is a prodrug to a nucleoside analog that interacts with the viral RNA polymerase to introduce mutations that ultimately have an antiviral effect (a mechanism referred to as "error catastrophe").

In the MOVe-OUT Phase 2/3 clinical trial, molnupiravir reduced the risk of hospitalization and death by 30% when given to high-risk adult persons within 5 days of symptom onset.[2]

No serious adverse events were noted in the study. Common adverse effects of molnupiravir include nausea, diarrhea, headache, rashes, insomnia, and liver test abnormalities.

Molnupiravir is approved for use under the EUA for the treatment of mild-moderate COVID disease with a symptom duration of five days or less in persons aged 18 years and older who have risk factors for progression to severe COVID disease. It is **not** approved for use in persons with severe COVID disease or for pre- or post-exposure prophylaxis.

Molnupiravir is contraindicated in pregnant women as *in vitro* studies raised concerns about potential teratogenic effects. Women of childbearing age should be assessed for pregnancy. Women of childbearing age should use appropriate contraception while on molnupiravir and for at least four days after treatment. Breastfeeding is not recommended while on treatment and for at least four days afterwards. Males of reproductive potential should use contraception during treatment and for at least three months after the last dose.

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. It also has emergency use authorization for persons with mild-moderate COVID-19 disease with symptoms for seven days or less.

The benefit of remdesivir has been demonstrated in the PINETREE study. In persons with mild-moderate COVID-19 disease, symptoms of seven days or less, and risk factors for progression to severe disease, a three day course of remdesivir reduced the risk of hospitalization by 87%.[3]

Remdesivir has been studied in persons with severe COVID-19 disease 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.[4] 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.[5]

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. However, there are clinical studies that suggest a potential benefit to using remdesivir in persons with critical disease.[6] 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).

There have been concerns about using remdesivir is in persons with severe renal impairment (CrCl or eGFR <30) due concerns about the accumulation of the preservative sulfobutylether beta-cyclodextrin sodium. Case series suggest five day courses or remdesivir are safe in this population.[7] Randomized clinical trials are underway to assess the safety of remdesivir in persons with severe renal insufficiency. Use of remdesivir in this population should be considered on a case-by-case basis.

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 approval from Infectious Diseases or Antimicrobial Stewardship.

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.[8] Dexamethasone 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 6 mg (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 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.[9] A smaller randomized trial from Iran showed a similar benefit of methylprednisolone 2 mg/K/d over dexamethasone, 19% v 38%, ($p=0.07$).[10] 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.

Systemic Anticoagulation (Unfractionated heparin, Low Molecular Weight Heparin)

COVID-19 has been associated with inflammation and a prothrombotic state. Studies have reported varying incidences of venous thromboembolism is patients with COVID-19. Clinicians should be aware of this risk and have a low threshold to investigate in the appropriate clinical scenarios (i.e. rapid deterioration of pulmonary, cardiac, or neurologic function; sudden, localized loss of peripheral perfusion).

All hospitalized patients should receive at least a prophylactic dose of heparin unless they have a contraindication.

In hospitalized patients who require low flow oxygen, do not require ICU level care, and who have elevated d-dimer serum levels, the NIH recommends the use of a therapeutic dose of heparin based on a several clinical studies looking at noncritically ill patients.[11,12,13] A meta-analysis of therapeutic heparin showed significant evidence of benefit in 5 important effectiveness outcomes (death or invasive mechanical ventilation, death or organ support, ventilator-free days alive, organ support–free days alive, and major thrombotic events.[14] However, this benefit has not been well demonstrated in critically ill patients with COVID-19.[15,16]

Use of therapeutic doses of heparin should be considered in hospitalized patients who are using low flow oxygen, do not require ICU level care, have serum d-dimer levels above the upper limit of normal, and do not have a contraindication to therapeutic anticoagulation. Contraindications for the use of therapeutic anticoagulation in patients with COVID-19 include a platelet count $<50 \times 10^9$/L, hemoglobin <8 g/dL, the need for dual antiplatelet therapy, bleeding within the past 30 days that required an emergency department visit or hospitalization, a history of a bleeding disorder, or an inherited or active acquired bleeding disorder.

Low molecular weight heparin is preferred as this was more often used in the clinical trials. Oral anticoagulants specifically for the treatment of COVID-19 have not been well studied and is not recommended.

In patients who have received therapeutic doses of heparin, treatment should continue for 14 days or until they are transferred to the ICU or discharged from the hospital, whichever comes first.

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.[17] 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).[18] 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 or Antimicrobial Stewardship approval.

Tocilizumab (Actemra)

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.[19] 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.[20] 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 or Antimicrobial Stewardship 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
Nirmatrelvir-ritonavir	Can be offered to patients based on risk-benefit assessment. Case series suggest safety of this treatment in pregnant women.[21]	No human data. Animal data suggests safety with lactation.
Molnupiravir	**Not recommended.**	**Not recommended**
Remdesivir	Case series based on pregnant women receiving remdesivir via compassionate use suggest safety during pregnancy.[22]	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 less robust compared to adults. Of the available therapies, the IDSA has recommended the following:

- Nirmatrelvir/ritonavir is suggested for patients age ≥12 years
- Molnupiravir is suggested for patients age ≥18 years
- Tocilizumab is suggested for patients age ≥2 years
- Baricitinib is suggested for patients age ≥2 years
- Remdesivir is indicated for all ages
- Dexamethasone is indicated for all ages

Consultation with Pediatric Infectious Diseases is recommended.

Other Agents

Monoclonal Antibodies

- Based on *in vitro* studies, the available monoclonal antibodies (bamlanivimab-etesevimab, casirivimab-imdevimab, sotrovimab, bebtelovimab) are ineffective against the currently circulating SARS-COV-2 Omicron subvariants (i.e. BQ.1, BQ.1.1, XBB).[23] **Monoclonal antibodies for the acute treatment of COVID-19 are no longer available as the FDA has revoked the emergency use authorizations.**
- While Evusheld (tixagevimab/cilgavimab) still has an FDA EUA for pre-exposure prophylaxis of COVID-19, *in vitro* data shows that it is also ineffective against the circulating Omicron subvariants. **Use of Evusheld is not recommended at this time**.

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.[24]
- 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.
- Use of colchicine for the treatment of COVID-19 is **not recommended**.

Ivermectin

- Randomized clinical trials have not demonstrated a benefit to ivermectin.[25,26]
- 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. One randomized study demonstrated a reduction in the proportion of patients who experienced the composite endpoint of emergency setting observation for >6 hours or hospitalization due to progression of COVID-19. However, fluvoxamine did not impact the incidence of COVID-19 hospitalizations, mortality, or time to symptom resolution.[27]
- 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**.

References

NIH COVID Treatment Guidelines
https://www.covid19treatmentguidelines.nih.gov/

IDSA Guidelines on the Treatment and Management of Patients with COVID-19
https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#HowtoApproachaPatientWhenConsideringPharmacologic%C2%A0TreatmentsforCOVID-19

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