Antiviral/Immunologic Agents for the Treatment of COVID-19 (Highly Suspected or Proven)
Infectious Diseases Section, VA Greater Los Angeles Healthcare System
January 26, 2023

MANAGEMENT OF MODERATE COVID-19 (symptomatic patients who do not require new or increased use of supplemental oxygen)

Available therapeutics (listed in order of preference, assuming availability and satisfaction of drug-specific eligibility criteria):

- **Nirmatrelvir 300 mg with ritonavir 100 mg (Paxlovid)** orally twice daily for 5 days, initiated as soon as possible and within 5 days of symptom onset **(AIIa*)**
- **Remdesivir 200 mg** IV on Day 1, followed by **remdesivir 100 mg** IV daily on Days 2 and 3, initiated as soon as possible and within 7 days of symptom onset **(BIIa);** *limited to use in patients hospitalized for reasons other than respiratory disease due to COVID-19*
- **Molnupiravir 800 mg** (**Lagevrio)** orally twice daily for 5 days, initiated as soon as possible and within 5 days of symptom onset in those aged ≥18 years **ONLY** when none of the above options can be used **(CIIa)**.

* Strength of recommendation and level of evidence

Medication	Administration	Timing after onset	Efficacy*	Other
Nirmatrelvir /ritonavir (PAX)**	Po BID x 5 days	≤5 days	EPIC-HR trial: (n=-2,224) 0.8% (PAX) vs. 6.3% (PLO)	Renal dose adjustment; multiple drug interactions
Remdesivir	IV qd x 3 days	≤7 days	PINETREE trial: (n=562) 0.7% (RDV) vs. 5.3% (PLO)	Monitoring required
Molnupiravir***	Po BID x 5 days	≤5 days	MOVe-OUT trial: (n=1408) 6.8% (MOV) vs. 9.7% (PLO)	No dose adjustment.
* Death or hospitalization by day 28 or 29; studies done when Delta predominated				
** Multiple drug-drug interactions due to ritonavir -				
*** **Use molnupiravir only if other alternatives are not accessible or clinically appropriate**. Not recommended in pregnancy and lactation due to potential embryo-fetal toxicity. Reliable, consistent contraception required during therapy and for 4 days after (females) of childbearing potential or 3 months after last dose (males) of reproductive potential				
Note: Hyperlinks lead to EUA Fact Sheet for healthcare providers				

Medication Specific considerations

Intravenous therapies

Remdesivir: Remdesivir has full FDA approval for patients with moderate COVID-19 (i.e., symptomatic but not requiring new or increased use of supplemental oxygen and at high risk of disease progression (3-day regimen). See the section on management of hospitalized patients with severe/critical covid-19 COVID-19 for the use of remdesivir in more serious ill patients.

At GLA three days of remdesivir is the preferred therapy for inpatients with moderate COVID-19 who are at high risk for disease progression. *Initiation of the three-day remdesivir regimen requires infectious diseases approval.*

Dosing to prevent disease progression in high-risk patients with moderate disease

- 200mg IV x1 on day one, 100mg IV qd on days two and three.

Eligibility

- The patient is within 7 days of symptom onset (earlier is better)
- ALT < 5x upper limit of normal
- eGFR > 30 mL/min unless patient is on hemodialysis (relative contraindication). Remdesivir may still be considered on a case-by-case basis with Infectious Diseases approval for eGFR <30.

Potential adverse effects:

- Hepatotoxicity (self-limiting, reversible)
- Nephrotoxicity (mostly over concern for accumulation of cyclodextrin in intravenous preparation, though amount is small and dialyzable)

Oral therapies

Completion of the PRIMARY CARE COVID-19 OUTPAT THERAPEUTICS APPROVAL NOTE allows primary care providers to prescribe oral antiviral medication, i.e., nirmaltrevir/ritonavir (paxlovid) and molnupiravir for the treatment of outpatients with recently diagnosed COVID-19 who are at high risk for disease progression as defined by the CDC.

When there are medication shortages, will consider limiting to one or more of the following tier groups of risks (with Tier 1 being the highest priority):

- TIER 1 RISK GROUP
    - Immunocompromised individuals not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection due to their underlying conditions, regardless of vaccine status (see NIH Immunocompromising Conditions) OR
    - Unvaccinated individuals at the highest risk of severe disease (anyone aged >=75 years or anyone aged >=65 years with additional risk factors).
- TIER 2 RISK GROUP
    - Unvaccinated individuals at risk of severe disease not included in Tier 1 (anyone aged >=65 years or anyone aged <65 years with clinical risk factors).
- TIER 3 RISK GROUP
    - Vaccinated individuals at high risk of severe disease (anyone aged >=75 years or anyone aged >=65 years with clinical risk factors).
- TIER 4 RISK GROUP
    - Vaccinated individuals at risk of severe disease (anyone aged >=65 years or anyone aged <65 with clinical risk factors)

Infectious Diseases approval is NOT required to prescribe oral COVID therapeutics. However, consultation with Infectious Diseases is available for complicated cases

Additional drug-specific criteria
Nirmatrelvir/ritonavir (Paxlovid)

Eligibility

- The patient is within 5 days of symptom onset
- The patient has at least one high-risk criteria for progression to severe disease, as defined by the CDC (e.g. age ≥ 65 years, obesity/overweight, pregnancy, chronic comorbidities, eGFR is ≥ 30 mL/min)
- Patient does not have severe hepatic impairment (Child-Pugh Class C)

Drug-drug interactions: See complete list at Liverpool COVID-19 Interactions (covid19-druginteractions.org)

Contraindicated drugs:

Anticancer drugs: Apalutamide
Anticonvulsant: Carbamazepine, Phenobarbital, Phenytoin
Antimycobacterials: Rifampin
Herbal products: St. John's Wort (*hypericum perforatum*)

Medications that should not be taken during the duration of treatment with Paxlovid

Alpha-1-adrenoreceptor antagonist: Alfuzosin
Analgesics: Pethidine, Piroxicam, Propoxyphene
Antianginal: Ranolazine
Antiarrhythmic: Amiodarone, Dronedarone, Flecainide, Propafenone, Quinidine
Anti-gout: Colchicine
Antipsychotics: Lurasidone, Pimozide, Clozapine
Ergot derivatives: Dihydroergotamine, Ergotamine, Methylergonovine
HMG-CoA reductase inhibitors: Lovastatin, Simvastatin
PDE5 inhibitor: Sildenafil (Revatio®) when used for pulmonary arterial hypertension (PAH)
Sedative/hypnotics: Triazolam, oral Midazolam

Other drugs of concern (partial list)

Anticoagulants: warfarin, direct acting oral anticoagulants, e.g., rivaroxan, apixaban
Antifungals: azole antifungals
HIV or HCV protease inhibitors
Immunosuppressives (levels increased): cyclosporine, tacrolimus, sirolimus

Dosing and Administration

eGFR ≥ 60 mL/min: 300 mg (2 tablets) of Nirmatrelvir and 100 mg (one tablet) of ritonavir each Q12h for 5 days
eGFR ≥ 30 - 59 mL/min: 150 mg (1 tablets) of Nirmatrelvir and 100 mg (1 tablet) of ritonavir each Q12h for 5 days

Molnupiravir

Use molnupiravir only if other alternatives are not accessible or clinically appropriate. Molnupiravir is not recommended in pregnancy and lactation due to potential embryo-fetal toxicity. Reliable, consistent contraception required during therapy and for 4 days after (females) of childbearing potential or 3 months after last dose (males) of reproductive potential

Eligibility

- The patient is within 5 days of symptom onset
- Other treatments authorized for mild-moderate COVID-19 in high-risk patients are not accessible or clinically appropriate (PAXLOVID, monoclonal antibodies)
- The patient and/or caregiver has been informed that that females of childbearing potential should use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of molnupiravir, and that males of reproductive potential who are sexually active with females of childbearing potential should use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose

Dosing and Administration: 800mg orally q12h for 5 days (with or without food) with no dose adjustments recommended for renal or hepatic impairment

MANAGEMENT OF HOSPITALIZED PATIENTS WITH SEVERE/CRITICAL COVID-19

Key points:

- **Bacterial co-infection with SARS-CoV-2 is infrequent (<10%)**; empiric treatment for bacterial pneumonia should be reserved for more severe presentations. GLA pneumonia treatment guidelines are available at http://www.vaglaid.org/gla-guidelines; antimicrobial order sets in CPRS are concordant with these guidelines. Consider stopping antibiotics after 48-72 hours if micro data is negative, there is no neutrophilia/bandemia, purulent sputum or lobar infiltrate. Trending procalcitonin in critically ill patients can also be used as a tool to discontinue antimicrobial therapy.
- **Viral co-infection (e.g., influenza or other respiratory viruses) is uncommon** but can occur.

DEXAMETHASONE:

GLA recommendations

Reserve dexamethasone for patients with a significant, sustained oxygen requirement (i.e., at least 4 liters of nasal oxygen for 4 hours or more); Infectious Diseases consultation is strongly suggested for these patients, though use of dexamethasone does not require ID approval**.** Other considerations for corticosteroids may include:

- Exacerbation of obstructive lung disease
- Refractory shock (stress dose)
- Severe ARDS (e.g., PaO2/FiO2 ≤100 mmHg on ventilator settings that include PEEP ≥5 cm H2O)

Background

The RECOVERY trial demonstrated reduced 28-day mortality in patients receiving dexamethasone (6mg po/IV qd x 10 days) who were mechanically ventilated (35% reduction) or receiving supplemental O_2 (20% reduction); there was no significant benefit among those who did not require any respiratory intervention.

A recent retrospective analysis of outcomes within the VA (submitted for publication) shows evidence of increased 90-day mortality among persons receiving dexamethasone in the first 48 hours who were on no oxygen or only receiving low-flow nasal oxygen.

REMDESIVIR:

Remdesivir has full FDA approval for patients

- Who are with moderate COVID-19 (i.e., symptomatic but not requiring new or increased use of supplemental oxygen and at high risk of disease progression (3-day regimen)
- Who are hospitalized with laboratory-confirmed COVID-19 that require supplemental oxygen. A 5 day regimen is appropriate for most patients but up to 10 days may be given to persons with progressive, severe disease. Patients with a rapid clinical response can be discharged off therapy without completing a 5-day course.
    - The benefit of remdesivir is limited for patients who present with late-stage disease (e.g., require mechanical ventilation, or extracorporeal membrane oxygenation).

Dosing:
200mg IV x1 on day 1, 100mg IV qd on subsequent days.

Exclusion Criteria:

- ALT > 5x upper limit of normal
- eGFR < 30 mL/min if not on hemodialysis (relative contraindication; also consider continuing if eGFR falls below 30 mL/min while on therapy if potential benefit outweighs risk)

Potential adverse effects:

- Hepatotoxicity (self-limiting, reversible)
- Nephrotoxicity (mostly over concern for accumulation of cyclodextrin in intravenous preparation, though amount is small and dialyzable)

TOCILIZUMAB (anti-IL-6 receptor):

Tocilizumab has been studied as an adjunctive therapy for the inpatient management of COVID-19 with varying results (see Appendix A). We agree with NIH treatment guidelines that currently recommend a single intravenous dose of tocilizumab (8mg/kg actual body weight up to 800mg) in combination with dexamethasone in certain hospitalized patients who are exhibiting rapid respiratory decompensation due to COVID 19:

- Recently hospitalized patients (i.e., within first 3 days of admission) who have been admitted to the ICU within the prior 24 hours and who require invasive mechanical ventilation, noninvasive ventilation, or high-flow nasal cannula (HFNC) oxygen, OR
- Recently hospitalized patients not admitted to the ICU who have rapidly increasing oxygen needs and require noninvasive ventilation or HFNC oxygen and who have significantly increased markers of inflammation (CRP ≥ 7.5 mg/dL).

We recommend checking CRP in all patients with COVID-19 who require supplemental oxygen to assess possible candidacy for tocilizumab. ID approval is required when tocilizumab is used for management of COVID-19, and requests for the medication must be made via the national VA Pharmacy Benefits Management EUA portal prior to drug administration. Please contact ID Pharmacy at x48643 for assistance in this process. Patients should be monitored for signs/symptoms c/w GI perforation (rare side effect). Also check strongyloides serology, QFTB and cocci serology when starting tocilizumab.

Exclusion criteria:

- Significant immunosuppression (particularly recent receipt of other biologic immunomodulating agents)
- Current documented or strongly suspected bacterial or fungal infection
- Known or suspected active tuberculosis or a history of incompletely treated latent or active tuberculosis
- AST or ALT > 10x upper limit of normal
- Absolute neutrophil count < 1000 cells/mm
- Platelet count < 50,000 cells/μL
- Active malignancy
- History of demyelinating disease

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 patients who are from strongyloidiasis-endemic areas.

BARICITINIB:

Baricitinib is a Janus kinase inhibitor that has anti-inflammatory effects. It is currently FDA-approved as an oral treatment for moderately to severely active rheumatoid arthritis. The FDA released an EUA for the use of baricitinib in combination with remdesivir for patients with COVID-19 who are hospitalized and requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). This EUA was based on clinical trial of hospitalized patients with COVID-19 in which baricitinib, in combination with remdesivir, was shown to reduce time to recovery within 29 days after initiating treatment compared to patients who received a placebo with remdesivir. The safety and effectiveness of this investigational therapy for use in the treatment of COVID-19 continues to be evaluated. Baricitinib is not authorized or approved as a stand-alone treatment for COVID-19.

The use of baricitinib may be considered by the Infectious Diseases consultation service in combination with remdesivir for the treatment of COVID-19 in hospitalized, non-intubated patients who require oxygen supplementation and cannot receive corticosteroids. Requests for baricitinib in the management of COVID-19 must be made via the national VA Pharmacy Benefits Management EUA portal prior to drug administration. Please contact ID Pharmacy at x48643 for assistance in this process.

SERAPH 100 MICROBIND AFFINITY BLOOD FILTER:

A blood filter that adsorbs bloodstream pathogens (including SARS-CoV-2) is currently being evaluated at GLA for critically ill patients with COVID-19. As patients are hospitalized, there will be a local team who will be involved with screening and enrolling patients. Potentially eligible trial participants include patients 18 years of age or older with confirmed COVID-19 admitted to the ICU with any one of the following:

a) Early acute lung injury (ALI) or acute respiratory distress syndrome (ARDS)
b) Severe disease defined as
    1. Dyspnea
    2. Respiratory rate $\geq$ 30 breaths/min
    3. Blood oxygen saturation $\leq$ 93%
    4. PaO2/FIO2 ration < 300 and/or
    5. Infiltrates involving > 50% of the lung within 24-48 hrs
c) Life-threatening disease defined as
    1. Respiratory failure
    2. Septic shock and/or
    3. Multi-organ system dysfunction or failure

Contraindications

a) Heparin induced thrombocytopenia
b) Thrombocytopenia < 30,000
c) Inability to tolerate anti-coagulation

d) Untreated hypercoagulability
e) Pregnancy
f) Medical futility
g) Allergy to ethylene oxide (Seraph 100 is sterilized with ethylene oxide)

Contact Jaime Betancourt, MD (VA 78542, 619-886-8572) for questions or potential candidates for enrollment.

ANTICOAGULATION:

In line with revised NIH guidelines on anticoagulation for COVID-19, we highlight key issues:

*For hospitalized, nonpregnant adults who require low-flow oxygen and **ARE NOT** receiving Intensive Care Unit level of care:*

- **Therapeutic-dose heparin** is recommended for patients who have a D-dimer above the upper limit of normal (ULN), require low-flow oxygen, and have no increased bleeding risk. LMWH is preferred over unfractionated heparin.

*For hospitalized, nonpregnant adults who **ARE** receiving Intensive Care Unit level of care (including patients who are receiving high-flow oxygen)*

- **Prophylactic-dose heparin** is recommended as VTE prophylaxis unless a contraindication exists.
- **Intermediate-dose** (e.g., enoxaparin 1 mg/kg daily) and **therapeutic-dose anticoagulation** for VTE prophylaxis are not recommended outside of a clinical trial.

MONOCLONAL ANTIBODY PROPHYLAXIS FOR IMMUNOCOMPROMISED PATIENTS: EVUSHELD (Tixagevimab + Cilgavimab):

The U.S. Food and Drug Administration announced on February 26, 2023, that EVUSHELD (tixagevimab + cilgavimab), SARS-CoV-2 spike protein-directed attachment inhibitor is no longer authorized in the United States for the pre-exposure prophylaxis of coronavirus disease 2019 (COVID-19).

Supplement A: Tocilizumab COVID-19 randomized controlled trials

Trial	Journal	Site	N (toci)	Entry criteria	Dose	Pt characteristics	Notable results
RECOVERY	Lancet	UK	2022	Req O2 or <92%, CRP>7.5	400-800mg (wt based), optional 2nd dose at 12-24h (29% got)	Mean age 64; 41% non-inv resp supp (HFNC, CPAP, BIPAP), 14% MV; median CRP 14.3, ferritin 947, 82% on corticosteroids. ~17% in toci arm didn't get it; ~3% in usual care arm did	31% vs 35% 28d mortality (RR 0.85; CI 0.76-0.94), more pronounced in men (RR 0.80; CI 0.71-0.91) vs women (RR 0.97; CI 0.80-1.18) and in pts on corticosteroids (RR 0.79; CI 0.70-0.89) vs not (RR 1.16, CI 0.91-1.48); RR 0.84 for prog to MV/death (CI 0.77-0.92); RR 0.72 for HD/HF need (CI 0.58-0.90).
REMAP-CAP	NEJM	Int'l	353	Resp (at least HFNC) or cardiovasc support (enroll within 24h of need for either)	8mg/kg up to 800mg, optional 2nd dose at 12-24h	Mean age 62; 29% HFNC, 41% NIV, 30% MV, 18% pressors, median CRP 15, ferritin 912, >80% on corticosteroids, RDV in 33%	Median organ-free support 10d vs. 0 in control (OR 1.64 CI 1.25-2.14; calc up to 21d); hosp mortality 28% vs. 35.8% (OR 1.64; CI 1.14-2.35); 90d mortality HR 1.59 (CI 1.24-2.05); resp support-free d OR 1.73 (1.13-2.27), CV support-free d OR 1.68 (1.25-2.24), time to ICU d/c HR 1.42 (1.18-1.70), time to hospital d/c HR 1.41 (1.18-1.70), authors state similar effect across CRP subgroups
COVACTA	NEJM	Int'l	294	O2 ≤ 93%, PaO2/FiO2 < 300, no active coinfxn	8 mg/kg up to 800mg, optional 2nd dose at 8-24h if febrile or worse on ordinal scale	Mean age 61; 3% no req O2, 27% just on O2, 32% on NIV/HFNC, 15% just MV, 23% MV+pressors or ECMO; median CRP 15.7; 36% corticosteroids (vs 55% in placebo); antivirals in 30%	No sig change in 7-cat ordinal scale at d28 (median 1.0 vs 2.0); 19.7% vs 19.4% 28d mortality; median d to hosp d/c 20 vs 28d; median ICU stay 9.8 vs 15.5d; clin failure among non-MV 29% vs 42% (HR 0.61, CI 0.40-0.94); serious AE 34.9% vs 38.5%
EMPACTA	NEJM	Int'l (80% US)	249	Hospitalized, 02 < 94%, no MV/CPAP/BiPAP	8mg/kg up to 800mg, optional 2nd dose at 8-24h if febrile or clin worse	Mean age 56; 10% not req O2, 65% just on O2, 26% on HFNC; median CRP 12.5, ferritin 1401, 80% on corticosteroids, RDV in 53%	12% vs 19.3% 28d MV/mortality (HR 0.56; CI 0.33-0.97); clin failure HR 0.55 (0.33-0.93), 28d mortality 10.4% vs 8.6% (2.0%; CI -5.2-7.8); serious AE 15.2% vs 19.7%
BACC Bay	NEJM	MA	161	2 of T>38, infiltrates, O2 need to maintain >92% plus CRP >5, ferritin >500, d-dimer >2.74, or LDH >250	8mg/kg up to 800mg (no 2nd dose)	Median age 62 (vs 56.5); 14% no O2, 83% just on O2, 3% on HFNC/NIV; median CRP 11.6, ferritin 723; RDV 33% vs 29%; 11% vs 6% corticosteroids (no dex)	10.6% vs 12.5% MV/death by d28 (non-adj HR 0.83 (0.38-1.81); adj HR 0.66 (0.28-1.52)); clin worsening HR 1.11 (0.59-2.10): 18% vs 14.9% d14, 19.3% vs 17.4% d28; MV duration 15 vs 28d (not sig); serious infections 8.1% vs 17.1% (p=.03)
TOCIBRAS	BMJ	Brazil	65	Supp O2 for 93% or MV <24h plus 2 of D-dimer >2.74, CRP >5, ferritin >300, or LDH >ULN	8mg/kg up to 800mg (no 2nd dose)	Median age 57; 60% just supp O2, 23% HFNC/NIV, 17% MV; mean CRP 16, ferritin 1271; pressors 14%; no RDV; corticosteroid 69% vs 73%	Early stop for death 17% vs 3% by d15 (OR 6.42 (1.59-43.2); 28% vs 20% death/MIV by d15 (OR 1.54 (CI 0.66-3.66)); hosp stay in d/c alive 11.9 vs 14.8d (RR 0.75 (0.58-0.94); serious AE 16% vs 11%
CORIMUNO-TOCI-1	JAMA IM	France	64	>3L O2, no MV/ICU, WHO-CPS score ≥5 (on 10pt ordinal scale)	8mg/kg, repeat 400mg d3 if O2 not improved by 50%, open label	Median age 64; corticosteroids in 33% (vs 61% placebo); median CRP 11.9, antivirals in 11% vs 24%	24% vs. 36% need for NIV/MV/death at d14 (HR 0.58 (0.30-1.09)); death at d28 10.9% vs 11.9 % (HR 0.92 (0.33-2.53)); serious AE 32% vs 43% (DSMB resigned when positive effect claimed in interim analysis)
RCT-TCZ-COVID	JAMA IM	Italy	60	PaO2/FiO2 200-300 plus T>38 plus CRP >10 or 2x baseline; no NIV/MV	8mg/kg up to 800mg, repeat dose at 12h, open label	Median age 62; median CRP 10.5 vs 6.5; ferritin 646 vs 534; no RDV; 9.8% corticosteroids	28.3% vs 27% clin worsening by d14 (RR 1.05 (0.59-1.86)) 10% vs 8% ICU adm by d14 (RR 1.26 (0.41-3.91)); 1.7% vs 1.6% d14 mortality; 3.3% vs 1.6% 30d mortality (RR 2.10 (0.20-2.26))