Nebraska Medicine
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Revision Date: 2/28/2023

COVID-19 Antiviral and Pharmacotherapy Information

Supportive therapy is the cornerstone of treatment. *Recent IDSA and NIH guidelines reinforce this general approach to pharmacological treatment, with data for only a few specific therapies in certain circumstances[32,40]. The treatment framework below is adapted from the NIH, which is routinely updated at* www.covid19treatmentguidelines.nih.gov/therapeutic-management/.

Patient Profile	Recommendation
Not hospitalized for COVID-19, but at high-risk of progression:* Follow ambulatory guidance	• **PREFERRED** •**Nirmetrelvir/ritonavir (Paxlovid)** PO BID x 5 days, within 5d of symptom onset; or •**Remdesivir** IV daily x 3 days, within 7 days of symptom onset • **ALTERNATIVE** • **Molnupiravir** 800mg PO BID x 5 days, within 5 days of symptom onset - only if preferred therapies not available •Should **NOT** use **Dexamethasone** or **Baricitinib**
Hospitalized, but does Not require Supplemental Oxygen	•Patients at high-risk of COVID-19 progression (see text at bottom for additional details): **Remdesivir** IV daily x 3 days, if symptomatic • Oral antivirals above can be continued, if admitted for reason other than COVID-19, rather than using IV therapy •Should NOT use **Dexamethasone** or **Baricitinib**
Hospitalized and Requires Supplemental Oxygen	• **SUPPLEMENTAL OXYGEN ≤5L/min:** •**Remdesivir** x 5 days or until discharge if sooner • **SUPPLEMENTAL OXYGEN >5L/min**: •**Remdesivir plus Dexamethasone** or **Baricitinib (**See text for additional details on patient criteria and adverse effects to guide choice)
Hospitalized and Progressive Respiratory Failure Requiring High Level Oxygen Delivery / Non-invasive Mechanical Ventilation	•**Dexamethasone plus Baricitinib** +/- Remdesivir (can continue if already on, but starting may have limited benefit) •As an alternative to baricitinib, tocilizumab can be considered. Consult ID (See text for additional details on anti-inflammatory combination therapy)
Hospitalized and Requires Invasive Mechanical Ventilation or ECMO	•**Dexamethasone plus Baricitinib** •As an alternative to baricitinib, tocilizumab can be considered. Consult ID (See text for additional details on anti-inflammatory combination therapy)

*Patients with high-risk criteria for progression may benefit from early treatment before requiring oxygen. Examples include, but are not limited to: age ≥65, BMI ≥35, immunosuppression, or other chronic health conditions. See guidleines

Anticoagulation recommendations also contained in NIH Guideline Tables for COVID-19 Treatment
https://www.covid19treatmentguidelines.nih.gov/tables/therapeutic-management-of-hospitalized-adults/

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Therapies below have been tiered based on the available data, current availability, toxicity profile, and practical considerations specific to Nebraska Medicine. Updates are expected during this fluid situation.

Preferential:

» **Remdesivir (Veklury)** FDA-approved antiviral for adults and children
- Dosing: 200mg IV once, then 100mg IV daily. Duration of 3 days for outpatients and those admitted for reasons other than COVID-19. Duration of 5 days is standard for inpatients requiring oxygen (can discontinue earlier if ready for discharge). Ten days of therapy was studied, although no additional benefit has been identified from a longer course in most cases.
  - In patients with renal disease, no dose adjustment is required. Although limited data exist, benefit is likely to outweigh risk of accumulation, and remdesivir may be given to this population, including those on hemodialysis
- Adverse Effects: Generally mild severity – monitor for *LFT abnormalities*, infusion-related reactions, and self-limited GI intolerance
- Patient Criteria: Patients at high-risk of progression or requiring low-levels of supplemental oxygen have the most benefit of treatment. By the time patient reaches the point of requiring high-flow oxygen or mechanical ventilation, inflammation is the primary driver of disease and antiviral therapy is unlikely to provide additional benefit.
- Cost: $3,744 per 5-day course AWP

» **Dexamethasone**
- Dosing: 6mg PO or IV once daily for up to 10 days (discontinue prior to discharge or when recovered)
- Adverse Effects: Hyperglycemia, GI bleeding, secondary infections, delirium, hypertension, fluid retention, insomnia
- Patient Criteria: Recommended for patients with COVID-19-related ARDS that are requiring higher levels of supplemental oxygen, high-flow/non-invasive oxygen delivery or mechanical ventilation
- Cost: $12 per 10-day course AWP.

» **Baricitinib (Olumiant)** FDA approved for adults, Emergency Use Authorization for children
- Mechanism: JAK and AAK1 inhibitor (anti-inflammatory agent) proposed for use to counter COVID-19 cytokine storm.
- Dosing: 4mg PO daily (adjusted for renal function) for up to 14 days until recovered or discharged (2mg/d if 2-8 years old)
- Adverse Effects: Short-term treatment of COVID-19 was very well-tolerated. Monitor Scr and CBC
- Criteria: Hospitalized patients requiring supplemental oxygen or higher-levels of respiratory support.
  - *For children, use SmartPhrase in note before ordering: ".baricitinibEmergencyUse".*
  - Contraindications: eGFR <15 mL/min or on dialysis; neutropenia (ANC <500/mL); lymphopenia (ALC<200/mL); known active tuberculosis
  - Recommended with dexamethasone for patients with progressive respiratory failure, needing high-flow, noninvasive or mechanical ventilation.
  - Consider as an option for patients on supplemental oxygen >5L/min, high-flow, noninvasive ventilation, or progressive respiratory failure.
- Cost: $2,500 per 14-day course AWP.

» **Nirmetrelvir/ritonavir (Paxlovid)** Emergency Use Authorization (EUA) for adults and children
- Mechanism: Protease inhibitor (antiviral)
- Dosing: Pack of 300 mg Nirmetrelvir (2 x 150mg) + 100mg ritonavir (1 tab) po BID x 5 days. If CrCl 30-60, give renal dose pack with 150 mg Nirmetrelvir (1 tab) + 100 mg ritonavir (1 tab) po BID.
- Adverse Effects: Dysguesia, diarrhea. Caution with numerous drug interactions
- Criteria: Patients with symptoms who are not hospitalized due to COVID-19, but at high-risk of progression. Must be started within 5 days of symptom onset. Considered safe in pregnancy
- Cost: Currently free to patients after being purchased from government. After that supply runs out/FDA-approval granted, cost may increase to several hundred thousand dollars per course.

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Situational: Efficacy unproven, and/or risk to benefit may favor use in select patients only

» **Molnupiravir (Lagevrio)** Emergency Use Authorization for adults only
- Mechanism: An oral antiviral that works as a ribonucleoside analogue integrated into the transcribing RNA and leads to an unrecoverable number of errors in future replication cycles.
- Criteria: Molnupiravir can be used in outpatient adults with ≤5 days of COVID-19 symptoms and having at least one high-risk criteria in whom preferred therapies are not appropriate. Results of the phase 3 MOVe-OUT trial demonstrated a reduction in patients progressing to hospitalization or death from 9.7% down to 6.8%, though after adjustment for unbalanced baseline characteristics and additional analysis looking specifically at COVID-19 related hospitalization or death, this difference was not statistically significant.
  - Molnupiravir was also studied for use as post-exposure prophylaxis in the MOVe-AHEAD study but found to have limited benefit for household contacts.
- Precautions: Molnupiravir should not be used in patients <18 years of age or in pregnant or breastfeeding patients. Contraception is recommended during therapy and for 4 days after last dose in female patients or 3 months after last dose in male patients of reproductive potential.
  - Adverse effects appear similar to placebo, and very rarely lead to discontinuation.
- Cost: Currently free to patients after being purchased from government. After that supply runs out/FDA-approval granted, cost may increase to several hundred or even thousand dollars per course.

» **Tocilizumab (Actemra)** FDA approved for adults and Emergency Use Authorization (EUA) for children
- Mechanism: IL-6 inhibitor (anti-inflammatory) on formulary for cytokine release syndrome (CRS) in oncology patients receiving CAR-T cell therapy
- Dosing: 8mg/kg IV once (max 800mg), or 12 mg/kg IV once for patients <30kg
- Adverse Effects: Neutropenia can be long lasting so risk of secondary infection is possible. In one report, superinfections were identified in 54% of tocilizumab-treated patients compared to 24% of untreated COVID patients. In long-term use for RA, intestinal perforation has been reported although this is rare with one-time doses.
- Criteria: Hospitalized patients requiring steroids and supplemental oxygen or other respiratory support.
  - Contraindications: neutropenia (ANC <1000/mL); thrombocytopenia (plts <50/mL); transaminitis (AST/ALT >10x ULN)
  - *For Pediatrics, use SmartPhrase in note before ordering: ".tocilizumabEmergencyUse"*
  - Tocilizumab is an alternative to baricitinib in triple therapy, and is preferred when baricitinib contraindications exist. In this case, the benefit of tocilizumab is only in combination with dexamethasone, not as a replacement to it. Baricitinib and tocilizumab should not be used at the same time.
  - Consultation with infectious diseases service is recommended before use
- Cost of single dose: $5,000 AWP

» **Convalescent Plasma** - Emergency Use Authorization (EUA)
- Early evidence suggested use for patients administered therapy as early in the disease process as possible, or for those with impaired humoral immunity. However, product needs to have a high-titer of Covid antibodies from currently circulating variants, which is difficult to elucidate.

Not Recommended (alphabetical order): Risk/benefit ratio does not favor use

» **Fluvoxamine**

» **Hydroxychloroquine**

» **Interferons**
- Typically used in combination with ribavirin, interferons have been studied for patients with other coronaviruses, with mixed results. Evaluated in addition to remdesivir in the ACTT-3 RCT, which demonstrated no additive benefit for the addition of interferon. Interferon's long-term adverse effect profile is generally unfavorable, and this was confirmed even for short-term treatment of COVID-19, with double the rate of adverse events despite receiving only four doses of interferon.

» **Ivermectin**
- Three large randomized controlled trials reported that the use of ivermectin did not provide a clinical benefit for patients with mild to moderate COVID-19

» **Lopinavir/ritonavir**

» **Nitazoxanide**

» **Oseltamivir**

» **Ribavirin (oral)**

» **Zinc**

Other Drug Class Guidance

» **Anticoagulants**
- Published guidelines from all relevant associations recommend that COVID-19 inpatients receive pharmacologic VTE prophylaxis (unless contraindicated). Either a low-molecular-weight heparin or fondaparinux can be used to reduce administration frequency, though heparin may be preferred in ICU patients due to its shorter half-life.
- Currently, the role of therapeutically dosed anticoagulation is limited to a narrow group of patients experiencing progressive respiratory failure with no contraindications

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