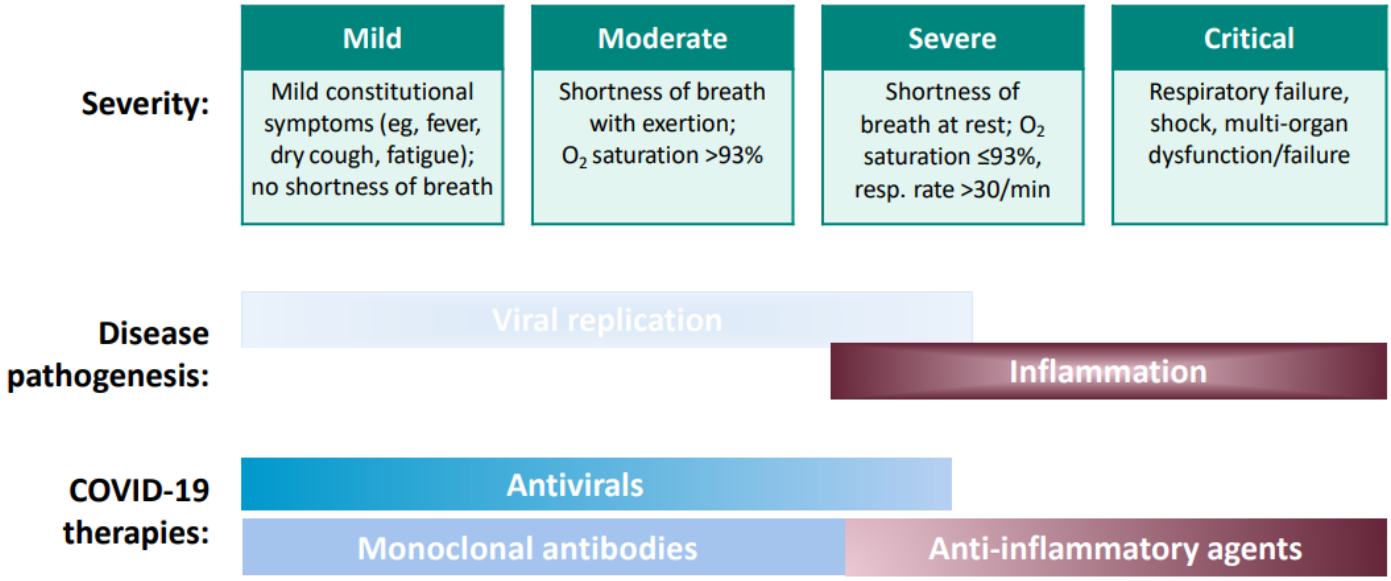
**RRH Adult INPATIENT Antiviral Treatment Guidelines for Confirmed COVID-19 Patients**

**INTERIM -- Current as of 01.20.2022**

## General Considerations

- The following is to provide guidance; this document will evolve as the scientific community learns more about this novel virus and the pandemic.
- The decision for treatment must be made on a case-by-case basis in conjunction with **Infectious Diseases and/or Pulmonary discussion**.
- The risks of prescription need to be considered in the context of potential benefits.
- The Infectious Disease Society of America (IDSA), National Institutes of Health (NIH) COVID-19 Treatment Guidelines, and World Health Organization (WHO) in addition to the primary literature provide guidance to this document as to which medications should and should not be given outside of clinical trials.
- This is a living guideline that will be frequently updated as new data emerges.

## Characteristics, Diagnosis, and Management of COVID-19 (RG *NEJM* 2020: 1757-1766)




The World Health Organization (WHO) Ordinal Scale measures illness severity, and is used by many centers as a metric for worsening or improvement. Severe studies on COVID use the ordinal scale in determining which level of severity may gain the most benefit from specific treatments.

| WHO Ordinal Scale | |
|---|---|
| 1 | Ambulatory, at baseline |
| 2 | Ambulatory, limitation of activities, + new home O2 needs |
| 3 | Hospitalized, no O2 therapy, not requiring medical care |
| 4 | Hospitalized, no O2, but requiring medical care related to COVID-19 |
| 5 | Hospitalized, on low-flow supplemental O2 |
| 6 | Hospitalized, on HFNC or NIV |
| 7 | Hospitalized, IMV or ECMO |
| 8 | Death |

## COVID-Negative -- Pre-exposure prophylaxis in high-risk

- Tixagevimab + Cilgavimab (Evusheld)

Criteria:

1a) Who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments **AND**

1b) May not mount an adequate immune response to COVID-19 vaccination

OR

2) For whom COVID vaccination is not recommended due to a history of severe adverse reaction

## COVID-Positive -- Ambulatory, Symptomatic, Non-severe, at risk for progression to severe illness

- Agent choice hinges on time from symptom onset:
  - 1-5 days: *Nirmatrelvir + Ritonavir (Paxlovid)
  - 1-10 days: *Sotrovimab infusion
  - 1-7 days: Remdesivir (Veklury) IV
  - 1- 5 days: *Molnupiravir (Lagevrio)

- No hypoxia
- No signs of respiratory distress
- See EUA for full details for *

## COVID-Positive -- Hospitalized, Non-Severe (including nosocomial)

- **OS 4 - Not on supplemental oxygen**
  - Remdesivir (Veklury) IV - duration 3-5 days

## COVID-Positive -- Hospitalized, Severe

- **OS 5 - On supplemental oxygen**
  - Dexamethasone (Dex) + Remdesivir 5 days (RDV)
  - Cannot take Dex: Baricitinib + RDV
  - Cannot take either Dex nor RDV: Baricitinib alone
  - Progressive despite Dex + RDV: Consider adding Tocilizumab

- SpO2 <90 on room air
- Respiratory rate >30 in adults
- Signs of severe respiratory distress

- **OS 6 - On HFNC (10 LPM or more) or Non-Invasive Ventilation or CPAP**
  - Dex + RDV + consider adding ONE of the following based on criteria: Baricitinib or Tocilizumab
    - *Patients who have already received tocilizumab are not candidates for baricitinib*

## COVID-Positive -- Hospitalized, Critical

- **OS 7 - on mechanical ventilation and/or ECMO**
  - Dex + RDV + Baricitinib
  - Dex + RDV + Tocilizumab if within 24 hours of intubation

- Requires life sustaining treatment
- Mechanical Ventilation
- ECMO
- Acute respiratory distress syndrome

| Potential clinical considerations for addition of Nirmeltrevir + Ritonavir (Paxlovid)<br>• Recommended for outpatient use.<br>  ○ Can be continued if started as an outpatient and the patient is subsequently hospitalized.<br>• Can be prescribed for COVID-19 infected patients at high risk for progression to severe disease, who are hospitalized for reasons other than COVID-19. | |
|---|---|
| Age 12 years and older, weight >40kg | No data in pregnancy or breastfeeding |
| Symptom duration < 5 days total | Not recommended for eGFR < 30 mL/min |
| Mild to moderate symptoms, no hypoxia | Not recommended for Child-Pugh C liver disease |
| Significant drug-drug interactions (see EUA for details) - common: lipid-lowering agents, anticoagulants, antiarrhythmic | Pills should be swallowed whole and cannot be crushed |
| HIV or HCV ritonavir-containing regimens can continue concomitantly without dose adjustments | No lab monitoring required |

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR PAXLOVID (fda.gov)

| Potential clinical considerations for addition of Molnupiravir (Lagevrio)<br>• Recommended for outpatient use.<br>  ○ Can be continued if started as an outpatient and the patient is subsequently hospitalized.<br>• Can be prescribed for COVID-19 infected patients at high risk for progression to severe disease, who are hospitalized for reasons other than COVID-19. | |
|---|---|
| Age 18 years and older | Embryo-fetal toxicity - Not recommended in pregnancy or child-bearing age unable to use contraception during therapy and for 4 days after |
| Symptom duration < 5 days total | Not recommended during breastfeeding and for 4 days after the last dose. May consider pumping and discarding breast milk. |
| Mild to moderate symptoms, no hypoxia | No lab monitoring required |

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR MOLNUPIRAVIR (fda.gov)

| Potential clinical considerations for addition of Tocilizumab<br>(Requires Pulmonary and/or Infectious Diseases Consult for approval) | | |
|---|---|---|
| Total COVID-19 illness duration <21 days | CRP > 75 | No evidence for active bacterial or fungal infection |
| Worsening oxygenation despite remdesivir and corticosteroids | ALT and AST <5x ULN | No active malignancy |
| Oxygen requirement minimum 4-6 lpm | ANC > 1000 | No diverticulitis or evidence of bowel perforation |
| Within 48 hours of ICU admission or progressive respiratory failure and within 24 hours of intubation | Platelet >50,000 | No treatment with other immunomodulators that remain clinically active other than corticosteroids |

| Potential clinical considerations for addition of Baricitinib<br>(Requires Pulmonary or Infectious Diseases Consult for approval) | | |
|---|---|---|
| COVID-19 illness and unable to take corticosteroids | ANC is > 500 cells/µL | Use not recommended for patients who are on dialysis, have ESRD or have acute kidney injury |
| Evidence suggests greatest benefit for patients with Ordinal scale 6 (HFNC or NIIV or CPAP) | ALC is > 200 cells/µL | Prophylaxis for venous thromboembolism is recommended unless contraindicate |
| Not to be given with or in patients who have received tocilizumab | Hold if ALT or AST increase | Avoid in patients with known active tuberculosis |

## Adult Dosing

| | Baricitinib | Molnupiravir | Nirmatrelvir + Ritonavir | Remdesivir | Tocilizumab | Tofacitinib |
|---|---|---|---|---|---|---|
| **eGFR ≥60 ml/min** | 4 mg po once daily | 800 mg po twice daily | 300 mg + 100 mg po twice daily | 200 mg IV x 1, followed by 100 mg IV daily | 8 mg/kg IV once | 10 mg po BID |
| **eGFR 30 - <60 ml/min** | 2 mg po once daily | 800 mg po twice daily | 150 mg + 100 mg po twice daily | 200 mg IV x 1, followed by 100 mg IV daily | No dose adjustment | |
| **eGFR 15 - <30 ml/min** | 1 mg po once daily | 800 mg po twice daily | Use not recommended | Use not recommended | No dose adjustment | |
| **eGFR <15 ml/min or on renal replacement therapy** | Use not recommended | 800 mg po twice daily | Use not recommended | Use not recommended | No dose adjustment | |
| **Duration** | 14 days or until hospital discharge, whichever is sooner | 5 days | 5 days | Ordinal scale 1-3: 3 days<br><br>Ordinal scale ≥ 4: 5 days or until hospital d/c, whichever sooner | Once | 14 days or until hospital discharge, whichever is sooner |
| **Administration** | Orally with or without food.<br><br>Can be crushed and/or made into a slurry. | Orally, uncrushed, with or without food | Orally, uncrushed, with or without food | Intravenous only | Intravenous only | Orally with or without food.<br><br>Do not crush |

| **Therapeutic agents considered for the treatment of COVID-19, with International and RRH institutional guideline recommendation** | | | | |
|---|---|---|---|---|
| **Agent (in alphabetical order)** | Recommendation of IDSA[1] NIH[2], or WHO[3] | Strength of recommendation | Level of evidence | RRH suggestion |
| **Anakinra** (IL-1 receptor antagonist) | Insufficient data to recommend for or against use[2] | Knowledge gap[2] | | No |
| **Bamlanivimab** (Monoclonal antibody) | Bamlanivimab monotherapy not recommended in hospitalized patients with severe disease[1] | Strong[1] | Moderate[1] | No due to current circulating variant |
| | Bamlanivimab plus etesivimab: Recommend against use given the Beta and Gamma variants[3] | Strong[3] | High[3] | |
| **Baricitinib** (JAK inhibitor) | Baricitinib alone is not recommended[2] | Strong[2] | Low[2] | Case-by-case basis<br><br>(OS 5 or OS 6) |
| | Baricitinib with remdesivir:<br>Suggest use for hospitalized patients who cannot receive corticosteroids[1,2] | Conditional[1]<br>Moderate[2] | Low[1]<br>Moderate[2] | |
| | Baricitinib with remdesivir and steroids:<br>Insufficient data to recommend for or against use[1,2]<br>In severe or critical COVID-19, combined use recommended[3] | Knowledge gap[1]<br>Moderate[2] Low[2]<br>Strong[3] Moderate[3] | | |
| **Casirivimab plus imdevimab** | Ambulatory patients:<br>Recommended for use in patients with mild to moderate COVID-19 and are at high risk for | Conditional[1]<br>Strong[3] | Very low[1]<br>Moderate[3] | No |

| | | | | |
|---|---|---|---|---|
| (Monoclonal antibody) | progression, or for post-exposure prophylaxis, as defined by the EUA criteria [1,3]<br>Insufficient data to recommend for or against use[2] | | | |
| | Hospitalized: Use not recommended[1]<br>Use not recommended except in a clinical trial[2] | Strong[1] | Moderate[1] | |
| **Chloroquine** | Use not recommended[1,2,3] | Strong[1,2] | Moderate[1]<br>High[2] | No |
| **Colchicine** | Ambulatory: Recommend against use, except in a clinical trial[2] | Moderate[2] | Moderate[2] | No |
| | Hospitalized: Recommend against use[2] | Strong[2] | High[2] | No |
| **Convalescent Plasma** | Ambulatory: Use not recommended except in a clinical trial[1] | Conditional[1] | Low[1] | No |
| | Hospitalized: Recommend against use[1,2,3] | Strong [1] | Moderate[1] | |
| **Corticosteroids** | In the absence of hypoxia, recommend against use[1,2,3] | Conditional[1,3]<br>Strong[2] | Low[1,3]<br>Moderate[2] | Case-by-case basis |
| | For hypoxemic patients, recommend use[1,2,3] | Strong[1,2,3] | Moderate[1,2]<br>Low[3] | |
| **Empiric broad-spectrum antibiotics** | Insufficient data to recommend in the absence of another indication[2] | Moderate[2] | Low[2] | Case-by-case basis |
| | Recommend against use unless there is a clinical suspicion for a bacterial co-infection[3] | | | |
| **Famotidine** | Use not recommended solely for the purpose of treating COVID-19 outside of a clinical trial | Condtional[1] | Very low[1] | No |
| **Fluvoxamine** (Antidepressant) | Ambulatory: Recommended only in the context of a clinical trial[1]<br>Insufficient evidence to recommend for or against use[2] | Knowledge gap[1]<br>Moderate[2] | Moderate[2] | No |
| **Hydroxychloroquine +/- Azithromycin** | Post-exposure prophylaxis or treatment: Use not recommended[1,2,3] | Strong[1,2,3] | Moderate[1-3]<br>Low[1] | No |
| **Interferons** | Use not recommended except in a clinical trial[2] | Strong[2] | Low[2] | No |
| **Ivermectin** (Antiparasitic) | Use not recommended except in a clinical trial[1,3]<br>Insufficient data to recommend for or against use[2] | Knowledge gap[1,2,3] | | No |
| | Use not recommended except in a clinical trial[1,3] | Conditional[1] | Very low[1] | |
| **Lopinavir + ritonavir** | Use not recommended[1,3] | Strong[1,2,3] | Moderate[1,2,3] | No |
| **Molnupiravir *(Lagevrio)*** Antiviral | For non-hospitalized patients with mild to moderate COVID-19, at risk for progression to severe disease<br>- ONLY when no other options can be used[1,2] | Conditional[1]<br>Optional[2] | Low[1]<br>Moderate[2] | Yes |
| **Nirmeltrevir + Ritonavir *(Paxlovid)*** (Antiviral) | Non-hospitalized patients with mild to moderate COVID-19, at risk for progression to severe disease[1,2] | Conditional[1]<br>Strong[2] | Low[1]<br>Moderate[2] | Yes |
| **NItazoxanide** | Use not recommended[2] | Moderate[2] | Moderate[2] | No |
| **Ozone** | Use not recommended | | | No |
| **Remdesivir** (Antiviral) | Non-hospitalized, symptomatic, at risk for progression to severe disease, able to access drug within 7 days of symptom onset[1,2] | Conditional[1]<br>Moderate[2] | Low[1]<br>Moderate[2] | Yes |
| | For hospitalized patients with no hypoxia, use not recommended[2,3] | Conditional[1]<br>Strong[2] Weak[3] | Very low[1]<br>Mod[2] Low[3] | Case-by-case basis |

| | | | | |
|---|---|---|---|---|
| | For hypoxemic patients, recommend use over no antiviral treatment in hospitalized patients[1,2] | Conditional[1] Strong[2] | Moderate[1] High[2] | |
| | For hypoxemic patients, use not recommended[3] | Low[3] | Low[3] | |
| | On mechanical ventilation and/or ECMO, use not recommended[1] | Conditional[1] | Low[1] | |
| **Sotrovimab** (Monoclonal antibody) | Ambulatory patients: Recommended for use in patients with mild to moderate COVID-19 and are at high risk for progression, as defined by the EUA criteria [1,2] | Conditional[1] Strong[2] | Moderate[1,2] | Yes |
| **Tixagevimab Plus Cilgavimab (*Evusheld*)** (Monoclonal antibody) | Recommended for adults and adolescents (aged 12 years and weight >40 kg) who do not have SARS-CoV-2 infection, who have not been recently exposed to an individual with SARS-CoV-2 infection AND:<br>- are moderately to severely immunocompromised and may have an inadequate immune response *or*<br>- are not able to be fully vaccinated due to severe reactions to the COVID vaccine[2] | Conditional[1] Moderate[2] | Low[1] Moderate[1,2] | Yes |
| **Tofacitinib** (JAK inhibitor) | Hypoxic but not on NIIV or MV, tofacitinib is suggested rather than no tofacitinib (eligible patients should not have received or later receive an IL-6 inhibitor).[1] | Conditional[1] | Low[1] | Case-by-case basis<br><br>(OS 5 or 6 and no baricitinib available) |
| | Use as an alternative if baricitinib is not available or not feasible to use.[2] | Moderate[2] | Moderate[2] | |
| **Tocilizumab** (IL-6 inhibitor) | Among hospitalized adults with progressive severe or critical COVID-19 with elevated markers of systemic inflammation, suggest use in addition to standard of care.[1]<br><br>Within 24 hrs of ICU admission and invasive or noninvasive mechanical ventilation or high-flow oxygen: insufficient data to recommend for or against use[2] | Conditional[1] Moderate[2] | Low[1] High[2] | Case-by-case basis<br><br>(Progressive OS 5, 6, or 7) |
| | No ICU care or who are admitted to the ICU but do not meet the above criteria: use not recommended except in a clinical trial[2] | Moderate[2] | Moderate[2] | |
| | Recommend use in severe or critical COVID-19[3] | Strong[3] | High[3] | |

[1] IDSA – Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America 2021; Version 5.1.1. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed January 20, 2022.
[2] NIH – COVID-19 Treatment Guidelines. National Institutes of Health. https://www.covid19treatmentguidelines.nih.gov/ . Accessed January 20, 2022
[3] WHO – https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.2 . Accessed January 20, 2022

In the event a novel agent of purported anti-SARS-CoV-2 effectiveness emerges in the literature, this living guideline will be updated following critical review of the published evidence by the COVID Executive Pharmacy and Therapeutics Committee. This committee consists of representatives from the Departments of Infectious Diseases, Pulmonary/Critical Care, Pharmacy, the Pharmacy and Therapeutics Chair, and RRH Incident Command.

Agents not listed in the current guidelines but felt potentially beneficial to an acutely ill hospitalized patient with COVID-19 infection may be reviewed on a case-by-case basis by the COVID Execute Pharmacy and Therapeutics Committee, with the expectation of a decision to either prescribe or not prescribe within 48 hours.