MUNSON HEALTHCARE

Treatment Considerations in Adults and Children with Laboratory Confirmed SARS-CoV-2 (COVID-19)

Developed in collaboration by the MHC Antimicrobial Stewardship Committee and Infectious Diseases Section

Purpose:
The purpose of this document is to provide guidance for the management of patients with laboratory confirmed and suspected SARS-CoV-2 infection, the virus that causes COVID-19.

Clinical symptoms:
COVID-19 causes a range of symptoms including fever, cough, shortness of breath, and ranges from uncomplicated upper respiratory tract viral infection to pneumonia, acute respiratory distress syndrome (ARDS), sepsis, and septic shock.

Supportive care: Appropriate treatment of concomitant pneumonia, respiratory failure, ARDS, sepsis, septic shock.

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Table 1: Outpatient treatment of mild COVID-19 (symptomatic, not requiring oxygen or increase in baseline oxygen)		
	Paxlovid	**Molnupiravir**
Preference per NIH Guidelines	Preferred	Alternative
Core Criteria	• Mild to moderate COVID-19 (symptomatic COVID, NOT requiring oxygen or increase from baseline supplemental oxygen) • Patient tests positive for SARS-CoV-2 (PCR, other NAAT, or antigen, including home test) • Outpatient or not hospitalized for COVID-19 • At high risk for disease progression and hospitalization or death (see risk factors below)	
FDA Provider Fact Sheet	Paxlovid – Fact sheet for Providers	Molnupiravir – Fact sheet for Providers
FDA Patient/Caregiver Fact Sheet	Paxlovid - Patients and caregivers	Molnupiravir – Patients and caregivers
Age/Weight	≥12 YO & ≥40 kg	≥18 YO (no weight criteria)
Start within (x) days of symptoms: (symptom onset date is day ZERO)	5 days	5 days
Duration of therapy, route	5 days, oral	5 days, oral
First line/alternative	First Line	Alternative
Relative risk reduction in hospitalization or death	88%	30%
Further Criteria	First line for mild-moderate COVID-19 at high risk for progression to severe disease with at least 1 of the CDC risk factors below (not an inclusive list): • Age ≥65 years of age • Adults with BMI >25 kg/m², or if 12 to 17 years of age, have BMI ≥85th percentile for their age and gender based on CDC growth charts • Pregnancy (Paxlovid or Remdesivir x 3 days preferred, Molnupiravir contraindicated) • Chronic kidney disease • Diabetes • Immunosuppression • Cardiovascular disease or hypertension • Chronic lung diseases • Sickle cell disease • Neurodevelopmental disorders or other conditions that confer medical complexity • Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation [not related to COVID 19])	Same high-risk criteria as Paxovid Alternative **ONLY** if patient cannot get Paxlovid due to drug interactions, impaired kidney/liver function, or supply.
Contraindications (not including allergy)	Renal impairment eGFR < 30 mL/min Child-Pugh Class C liver disease Certain drug interactions (See below)	Contraindicated in Pregnancy. Males of reproductive age should use reliable contraception during treatment and 3 months after last dose; females, during treatment and 4 days after last dose.
Drug Interactions (Paxlovid only)	FDA Paxlovid eligibility screening checklist and drug interaction checking: https://www.fda.gov/media/158165/download Paxlovid drug interaction checker: Liverpool COVID-19 Drug Interaction Website A guide to drug interactions with Paxlovid can be found at: MI Medicine Tool	
Management of Disease Relapse (Paxlovid only)	There have been reports of relapse (a positive test with symptoms after testing negative) in patients receiving Paxlovid. The prevalence of relapse during the Omicron surge is currently unknown. At this time, there are no data to support a 2nd course of Paxlovid if symptoms recur. For more information, see this message from the FDA.	

[1] **Severe immunocompromise**: Solid organ transplant, bone marrow transplant, hematologic malignancy, on b-cell depleting therapy (i.e., on rituximab)

[2] **Moderate immunocompromise**: Primary immunodeficiency, active malignancy and receiving chemotherapy, autoimmune diseases requiring immunosuppressive therapy (hydroxychloroquine or sulfasalazine alone is not sufficient), advanced or untreated HIV infection

[3] **Up-to-date with vaccines**: a person has received all recommended COVID-19 vaccines, including any booster dose(s) when eligible

Table 2: Inpatient treatment of mild/moderate to severe COVID-19

Severity of illness	Consideration
Inpatients	
Mild illness • Symptomatic, not requiring oxygen or increase in baseline oxygen	• **Supportive care** • Remdesivir x 3 days (200 mg day 1, then 100 mg daily on days 2-3), may be an option in certain high-risk patients when started within 7 days of symptom onset. • Not recommended: Dexamesthasone, tocilizumab, or baricitinib
Moderate illness • Low-flow supplemental oxygen	• **Supportive care** • Dexamethasone 6 mg daily for up to 10 days (or until discharge if sooner). Exceptions: Minimal supplemental oxygen (1-2 L) with < 7 days of symptoms. • Remdesivir x 5 days • Not recommended: Paxlovid, Molnupiravir • If patient is started on Paxlovid or Molnupiravir and progresses to moderate, or severe disease, it is reasonable to stop these therapies and initiate the next level of care.
Severe illness • High-flow nasal cannula (HFNC), non-invasive mechanical ventilation (NIMV), or invasive mechanical ventilation (IMV)	• **Supportive care** • Dexamethasone 6 mg daily for up to 10 days. • Tocilizumab x 1 (If unavailable, suggested alternative is Baricitinib). Strong recommendation to wait until blood cultures are negative for 48 hours before initiating tocilizumab. • HFNC and NIMV: It's uncertain if remedesivir confers a clinical benefit in this population. If patient's oxygen requirement is felt to be related to other reasons beyond COVID-19, it may be reasonable to utilize Remdesivir x 5 days. • Note: if remdesivir is started and the patient progresses to severe disease, it is reasonable to continue remdesivir, but should be based on clinical judgement. ○
See individual drug summaries in Table 3 for specific information in special populations (e.g. pediatrics & pregnancy) **Risk factors for severe disease:** Age ≥65 years, chronic cardiovascular, pulmonary, hepatic, renal, hematologic, or neurologic conditions, immunocompromised, pregnant women, residents of nursing homes or long-term care facilities.	

Table 3: Dosing and additional considerations for treatment options for the management of COVID-19

Antiviral therapy	Dosing & Duration	Comments
Remdesivir (3-day regimen) **See Eligibility Criteria** 3-day duration is extrapolated from the PINETREE study. ****<u>The CDC definition of 'up-to-date'</u>:** received primary series and the most recent recommended booster dose.	<u>Adult</u>: 200mg IV load, then 100mg IV q24h days 2-3 <u>Pediatric dosing (≥28 days of age):</u> 3 kg to <40 kg: 5 mg/kg IV load, then 2.5 mg/kg q24h days 2-3 ≥40 kg: 200 mg IV load, then 100 mg IV q24h days 2-3 <u>Duration</u>: 3 days or until hospital discharge whichever comes first	**Eligibility criteria:** 1. Not on supplemental O_2 or increase over baseline oxygen requirements 2. Duration of symptoms ≤ 7 days 3. PCR or antigen confirmed COVID-19 4. LFTs < 10x upper limit of normal, 5. <u>At least one of the following risk factors for severe disease</u>: ○ Age ≥ 75 years old ○ Solid-organ transplant recipient ○ Hematologic malignancy ○ HSCT or CAR-T recipient within 2 years ○ Receiving a significantly immunosuppressing agent (e.g., anti-CD20 or B-cell depleting agents within last year, biologic agents, high dose steroid (i.e., >20 mg prednisone or equivalent per day when administered for >2 weeks), or chemotherapeutic agents considered severely immunosuppressive ○ Moderate to severe primary immunodeficiencies (e.g., familial hemophagocytic lymphohistiocytosis, DiGeorge syndrome, Wiskott-Aldrich syndrome) ○ Advanced or untreated HIV infection (CD4 cell count < 200/mL or history of AIDS-defining illness) ○ **Patients NOT up to date with or ineligible for vaccination**** AND one of the following: ▪ Pregnant ▪ Chronic lung disease: ▪ Hypertension: systemic or pulmonary ▪ Cardiovascular or cerebrovascular disease ▪ Diabetes mellitus: Type 1 or 2 ▪ Obesity (BMI ≥30) ▪ Chronic kidney disease: any stage ▪ Chronic liver disease ▪ Sickle cell disease ▪ Neurodevelopmental disorders ▪ Medical-related technological dependence (i.e., tracheostomy, positive pressure ventilation)
Remdesivir (5-day regimen) *Patients not hypoxic and those requiring mechanical ventilation or ECMO will not meet the eligibility criteria because existing data does not demonstrate that remdesivir confers a clinical benefit in these patients (clinical recovery or mortality). Exceptions to the eligibility criteria may be considered on an individualized basis.*	<u>Adult</u>: ≥40 kg: 200mg IV on day 1, then 100mg IV q24h x 4 days <u>Pediatric</u>: 3.5 - 40 kg: 5 mg/kg IV load, then 2.5 mg/kg IV q24h x 4 days ≥40 kg: 200 mg IV load, then 100 mg IV q24h x 4 days Typical duration is 5 days, or until hospital discharge whichever comes first. Patients started on remdesivir and progress to requiring higher level of oxygen support (i.e. mechanical ventilation) should still complete a course of remdesivir.	• **The following criteria must be met prior to initiation:** 1. Laboratory confirmed SARS-CoV-2 infection by PCR from nasopharyngeal or respiratory sample 2. Radiographic evidence of pulmonary infiltrates (CXR or CT). 3. SpO2 ≤ 94% on room air or requires low-flow supplemental oxygen ≤ 6 L/min. (5-day duration) 4. LFTs < 10X upper limit of normal 5. Consideration for ≤ 7 days of symptoms (not a hard exclusion). Antivirals work better earlier in the disease course. • Baseline AST/ALT should be < 10 x ULN (or < 200). This is not an absolute contraindication, but these patients were excluded from clinical trials. • eGFR < 30 mL/min is NOT a contraindication to remdesivir. The risk of cyclodextrin accumulation to a toxic level with 5 days of therapy is small and benefit of remdesivir likely outweighs this small risk. • Adverse events include increased liver enzymes, injection site reactions, bradycardia, and potential to have drug-drug interactions with medications metabolized through cytochrome system. • <u>Pregnancy & Breastfeeding</u>: limited studies exist for remdesivir use in pregnant women. Remdesivir should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus. There is no information regarding the presence of remdesivir in human breastmilk, the effects on the breastfed infant, or the effects on milk production.

Antiviral therapy	Dosing & Duration	Comments
Dexamethasone	Adult dosing: 6 mg daily, maximum 10 days or until discharge from the hospital. Consider 20 mg daily x 5 days followed by 10 mg daily x 5 days as an option for patients with severe disease receiving ≥10 L/min HFNC, noninvasive positive pressure ventilation (e.g. BIPAP), or invasive mechanical ventilation. Shorter duration is reasonable in patients who rapidly improve. Durations >10 days are generally not recommended, but may be reasonable on a case by case basis for critically ill patients.	• NIH Guidelines recommends using dexamethasone (at a dose of 6 mg per day for up to 10 days) for the treatment of COVID-19 in patients who are mechanically ventilated (AI) and in patients who require supplemental oxygen but who are not mechanically ventilated (BI). • The NIH Panel recommends **against** using dexamethasone for the treatment of COVID-19 in patients who do not require supplemental oxygen (AI). • Unclear benefit in patients on low level supplemental oxygen (1-2 L) with < 7d of symptoms. • In the setting of a dexamethasone shortage, an equivalent total daily dose of an alternative glucocorticoid to dexamethasone 6 mg daily can be used (e.g., methylprednisolone 32 mg daily or prednisone 40 mg daily). • Pregnancy & Breastfeeding: Given the potential benefit of decrease in maternal mortality and the low risk of fetal adverse effects for this short course of therapy, the NIH Guidelines recommend using dexamethasone in pregnant women with COVID-19 who are mechanically ventilated (AIII) or who require supplemental oxygen but who are not mechanically ventilated (BIII).
Tocilizumab Guidance based on REMAP-CAP & RECOVERY randomized controlled trials, in accordance with NIH & IDSA COVID-19 Treatment guidelines.	Adult Dosing (≥18 years): >40-65 kg: 400 mg >65-90 kg: 600 mg >90 kg: 800 mg (max: 800 mg/dose) Pediatric Dosing (<18 years): <30 kg: 12 mg/kg ≥30 kg: 8 mg/kg (max: 800 mg/dose) Duration: One dose over 60 minutes *There are no data to inform risk vs. benefit of a second dose.*	If supply is inadequate, a suggested alternative is Baricitinib. Strong recommendation to wait until blood cultures are negative for 48 hours before initiating tocilizumab. Consider **Tocilizumab** (*in addition to* ***dexamethasone***) in: 1. Patients with rapidly increasing oxygen needs within 24-48 hours while on dexamethasone with either: a. ARDS (without evidence of bacterial or fungal pneumonia), OR b. HFNC > 6 L / min (FiO_2 >40%), noninvasive mechanical ventilation, or mechanical ventilation within 48 hours, with COVID-19 being the primary reason for respiratory failure. **Tocilizumab** is NOT recommended in the following scenarios: 1. Significant immunosuppression (e.g. ANC < 500) 2. Use of biologic immunomodulating drugs with increased risk of infection, or where opportunistic infection prophylaxis would be considered 3. ALT > 5 x upper limit of normal 4. Platelet count <50,000 cells/µL 5. High concern for systemic bacterial or fungal co-infection 6. High-risk for GI perforation 7. Receiving mechanical ventilation for longer than 48 hours 8. Patients who significantly improve with the initiation of enhanced oxygen support or corticosteroids; monitoring such patients for 12-24 hours is reasonable 9. Unlikely to survive >48 hours 10. Patient is currently receiving baricitinib **6.24.2021 – FDA issued an EUA for tocilizumab.** *Providers must provide FDA fact sheet for patients and document verbal consent in their note.* • Health Care Providers must review FDA Fact Sheet for Health Care Providers: https://www.fda.gov/media/150321/download • Health Care Providers must provide recipients with the Fact Sheet for Patients/Caregivers: https://www.fda.gov/media/150320/download

Antiviral therapy	Dosing & Duration	Comments
		Pregnancy and Nursing Mothers: • Tocilizumab is not currently recommended for the treatment of rheumatic and musculoskeletal diseases during pregnancy; however, given the increased risk of severe COVID-19 Disease in pregnancy, benefit of tocilizumab may outweigh the risk. • Tocilizumab may be harmful to newborns, and mothers should stop breastfeeding if receiving tocilizumab but may resume after discontinuation. Serious adverse events: • Gastrointestinal perforation, Anemia, Hepatitis, Infusion reaction, Neutropenia, Infection
Baricitinib Selective inhibitor of JAK 1&2 Non-formulary at MHC Should not be used in combo with tocilizumab Should be used in combination with dexamethasone, based on the results of the COV-BARRIER study.	Adult 4 mg PO q24hr *renal adjustment for eGFR: ≥ 60 mL/min: 4 mg PO q24hr 30-59 mL/min: 2mg PO q24hr 15-29 mL/min: 1mg PO q24hr <15 mL/min (contraindicated) Duration: Maximum 14 days, or until discharge Shorter duration is reasonable to consider in patients who have improved rapidly or are experiencing adverse events.	• May 10, 2022: FDA approved Baricitinib for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). • Criteria for Use ○ Can be considered in patients that meet criteria for tocilizumab, if tocilizumab is unavailable. ○ Not recommended in the following patients: ▪ Previously received tocilizumab ▪ Not requiring supplemental oxygen ▪ Requiring mechanical ventilation ▪ Patients with known active Tuberculosis ▪ Patients with AKI and eGFR < 15, or those with ESRD, or receiving dialysis. • Monitoring parameters: ○ Renal function (dosed based on eGFR) ○ Absolute lymphocyte count ○ Absolute neutrophil count ○ VTE prophylaxis present ○ AST/ALT ○ Platelets ○ Drug-drug interactions • Potential Adverse events: ○ Thromboembolic events: VTE, PE ○ Increased risk for infection
Paxlovid (Nirmatrelvir/ritonavir)	Dosing: eGFR ≥60 mL/min: Nirmatrelvir 300 mg + ritonavir 100 mg twice daily x 5 days eGFR 30-59 mL/min: Nirmatrelvir 150 mg + ritonavir 100 mg twice daily x 5 days eGFR <30 mL/min: Not indicated per manufacturers labeling* Must be initiated with 5 days of symptoms onset. Day 0 is the first day of symptoms. Duration: 5 days	• See table 1 for criteria • * eGFR < 30 mL/min - The manufacturer does not recommend use, however alternative dosing schemes have been suggested based on small studies in this patient population. ○ Alternative dosing schemes require manipulation of current packaging of the drug product and may result in dosing errors. ○ Use could be considered on a case-by-case basis after discussion between the provider and pharmacist. • Contraindicated in liver impairment, Child Pugh class C • Multiple drug interactions exist. Resources for Drug interaction checking. ○ https://www.covid19-druginteractions.org/ • FDA fact sheet for HCP • FDA fact sheet for patients/caregivers

Antiviral therapy	Dosing & Duration	Comments
Molnupiravir A large, open-label randomized controlled trial (PANORAMIC) of over 25,000 patients randomized to molnupiravir vs supportive care did not demonstrate an association of molnupiravir at preventing hospitalization or death. Additionally, a reduction in time to symptom relief was not seen in the MoVE-OUT trial (blinded RCT), calling this finding further into question. Currently, molnupiravir is still available through the FDA EUA, but it is unlikely to decrease risk of progression to severe disease.	Dosing: 800 mg twice daily x 5d Must be initiated with 5 days of symptoms onset. Day 0 is the first day of symptoms.	• Considered alternative when other therapies are unavailable (e.g. Paxlovid,) • Avoid in pregnancy • Men who are sexually active with a woman of reproductive age should use reliable contraception during treatment and 3 months after last dose; • Women of reproductive age should use reliable contraception during treatment and 4 days after last dose. • FDA fact sheet for HCP • FDA fact sheet for patients/caregivers

Do not use (therapies without any supportive evidence and/or associated with potential harm): ivermectin, hydroxychloroquine, hydroxychloroquine + azithromycin, lopinavir/ritonavir, nitazoxanide, oseltamivir, baloxavir, interferon, ribavirin, IVIG

Developed:	03/2020
Expedited P&T Approval:	03/19/20
Revision History:	**5/14/2024**: Criteria updated for remdesivir 3-day duration, dexamethasone high-dose removed, Paxlovid & Molnupiravir details updated, removed specific VTE prophylaxis and treatment recommendations **12/29/23:** added recommendation to wait until blood cultures are negative for 48 hours before initiating tocilizumab. **11/15/22:** Bebtelovimab removed from outpatient & ED treatment options due to high circulation of BQ omicron subvariants that are likely resistant to Bebtelovimab. **9/2/22:** Added FDA Paxlovid eligibility screening checklist & drug interaction checking link to table 1 **7/13/22:** Updated Bebtelovimab criteria for use **5/18/22:** FDA approved Baricitinib on May 10th, 2022 for patients with severe COVID-19 **5/11/22:** Added information about relapse after taking Paxlovid **3/30/22:** Removed sotrovimab from list of recommended therapies due to reduced activity against the BA.2 subvariant and high frequency of circulating BA.2 in Michigan. Paxlovid, Bebtelovimab, and Molnupiravir are still believed to be active against BA.2. **3/3/22:** Removed tiered prioritization from Table 1. Relocated remdesivir from Table 1 into the "inpatient" treatment recommendations for mild COVID-19 in Table 2. **3/1/22:** New VTE prophylaxis recommendations. **2/1/22:** Updated eligibility criteria for treatment of mild COVID-19 **1/21/22:** Added prioritization criteria & treatment consideration for mild COVID-19 in the inpatient and outpatient settings. Added recommendations for remdesivir 200 mg x1, then 100 mg daily on days 2 & 3 for patients with mild COVID-19. **1/10/22:** Added higher dose dexamethasone option (20 mg daily x 5 days followed by 10 mg daily x 5 days) as an consideration for patients with severe disease receiving in critically ill patients receiving ≥10 L/min HFNC, noninvasive positive pressure ventilation (e.g. BIPAP), or invasive mechanical ventilation. (note: stress ulcer prophylaxis recommended for patients on higher doses of dexamethasone). Added Paxlovid & Molnupiravir to outpatient recommendations with a link to MHC provider page for more detailed, updated information. **11/18/21:** Removed drug interaction between tocilizumab and direct oral anticoagulants (DOACs). Updated remdesivir section: patients started on remdesivir who progress to requiring HFNC or mechanical ventilation should complete the course of remdesivir. **10/19/21:** Added clarity to Tocilizumab exclusion: use of concomitant biologic immunomodulating drugs with increased risk of infection, or where opportunistic infection prophylaxis would be considered. (NOTE: COVID-19 monoclonal antibody is NOT immunomodulating). **9/3/21:** Updated outpatient treatment guidance. Removal of convalescent plasma. Updated tocilizumab shortage information, with suggested alternative of baricitinib. **8/24/21:** Updated tocilizumab shortage information **7/6/2021:** Updated tocilizumab emergency use authorization (EUA) information **4/7/2021:** Updated tocilizumab criteria for use **3/26/2021:** Added information & guidance on tocilizumab **12/23/20:** Added information & guidance on Baricitinib. Added clarity to remdesivir criteria for use. Updated VTE prophylaxis and treatment. **10/29/20:** Updated Remdesivir criteria for use: added criteria for ≤ 10 days of symptoms. Updated remdesivir FDA approval. Removed remdesivir exclusion of eGFR < 30 mL/min. Softened remdesivir contraindication when baseline AST/ALT > 5 x ULN. Updated dexamethasone and convalescent plasma information. **7/28/20:** Revised recommendations for remdesivir and dexamethasone. **6/24/20:** Removed HCQ and Tocilizumab. Updated Remdesivir information. Added dexamethasone for critically ill patients with further information to follow based on results of the RECOVERY Trial. **5/14/20:** Added Remdesivir Emergency Use Authorization (EUA) information. Added additional information about ivermectin, nitazoxanide. Updated VTE prophylaxis section. **4/17/20:** Downgraded recommendations for investigational therapies outside of a clinical trial per the IDSA COVID-19 treatment guidelines. Added information on convalescent plasma. Removed nitazoxanide and lopinavir/ritonavir. **4/9/20:** added recommendations for Vit C, Zn^{2+}, thiamine, & melatonin. Added recommendations for VTE prophylaxis. Added QTc prolongation risk stratification **4/2/20:** reduced HCQ dose. Added proposed mechanisms of action. **3/25/20:** removed azithromycin due to limited data. Added alt. HCQ dosing for outpatients. Added statement regarding ACEI/ARBs & NSAIDs. Updated Remdesivir compassion use program to Expanded Access. **3/20/20:** added recommendation to NOT use hydroxychloroquine prophylactically outside of clinical trial ongoing in Minnesota. **03/19/20:** Removed lopinavir/ritonavir. Added nitazoxanide for alternative in pregnancy. Added azithromycin in combination with hydroxychloroquine based on preliminary data[24]