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Guideline for therapeutic management of hospitalized adult patients with confirmed COVID-19

Contents

Criteria and Principles

This guidance is intended to provide a framework for therapeutic management of adult patients with confirmed COVID-19 managed in the hospital setting. Given the rapid evolution of the epidemic, this will be a living document that is subject to change as new data emerge.

Infection prevention, diagnostic testing, and specimen collection guidance are available on the DUHS COVID-19 page.

See separate guidance for Pediatric patients <18 years of age and guidelines for ambulatory management of COVID-19 in adults.

- Approach to treatment should be similar to other respiratory viral illnesses which can have severe manifestations and/or secondary infectious complications.
- Antibiotics for secondary bacterial infections should include agents outlined in Hospital-acquired/Ventilator-acquired Pneumonia or Community Acquired Pneumonia guidance. Co-infection at the time of initial presentation is uncommon. Risks for hospital-acquired infection increase with length of stay and severity of illness. The principles of antibiotic de-escalation still apply.
- DUHS supply of COVID-19 therapeutics may be limited or under critical shortage. Updates are available on this dashboard.

When to Consult ID

- General ID consultation is **recommended** for cases in which diagnostic and/or therapeutic management is complex.
- Some COVID-19 therapeutics require ID consultation for inpatients (**Figure 1, Table 3**).
- Transplant ID consultation is **recommended** for cases in which diagnostics and/or therapeutic management is complex and is **required** for inpatients with severe or critical laboratory-confirmed COVID-19 in: Solid organ transplant, Hematopoietic cell transplant, Active hematologic malignancy.

Figure 1. GENERAL ID Approval Requirements for use in HOSPITALIZED Patients

	*General ID Approval Required?***	*Consult (C) or Per Protocol (PP)*
EUA COVID-19 Monoclonal Antibody Products*	N/A: No active agents	N/A
Nirmatrelvir/Ritonavir (Paxlovid)	No	none
Molnupiravir (Lagevrio)	Yes	C with chart review note
Remdesivir	No	None
Dexamethasone	No	None
Baricitinib	Yes, if not per protocol <u>Per Protocol</u> Laboratory-confirmed SARS-CoV2 Primary team attending-level approval Requiring high-flow or non-invasive mechanical ventilation (OS6) No high-complexity features: pregnancy, active thrombosis or new stroke/MI, active non-COVID infection	PP or C

***ID consultation requirement for use depends on individual, hospital-level approval processes. Review and verification of required documentation by an ID pharmacist may replace full ID consultation at Duke Regional and Duke Raleigh Hospitals.*
*As of 11/30/22, there are NO EUA monoclonal antibody products active against circulating variants.

Management Guidelines by Clinical Severity

Table 1. Clinical Severity Criteria for COVID-19 Disease

Severity	**COVID-19 Ordinal Score**	**Description**	**Clinical Criteria**
Asymptomatic or Pre-symptomatic		Positive test without clinical disease	No symptoms
Mild		Upper respiratory tract disease	Upper respiratory symptoms Normal chest exam, chest imaging, and oxygenation

Moderate	4 – No oxygen requirement	Lower respiratory tract disease without hypoxia	Radiographic infiltrates by imaging OR Abnormal chest exam (rales/crackles) AND SpO2>94% on room air
Severe	5 -- Low flow oxygen requirement 6 – High- flow oxygen or non-invasive ventilation	Lower respiratory tract disease with hypoxia	RR>30 breaths per minute OR SpO2≤94% on room air OR PaO2/FiO2<300 OR Lung infiltrates >50% on imaging
Critical	7 – Mechanical ventilation or ECMO	Lower respiratory tract disease and acute respiratory failure	Requiring mechanical ventilation or ECMO OR Shock requiring vasopressors OR Multiple organ dysfunction

High-Risk Criteria for progression to severe disease and/or complications

- Age ≥65 years
- having cardiovascular disease, chronic lung disease, sickle cell disease, diabetes, cancer, obesity, or chronic kidney disease
- pregnant
- being a cigarette smoker
- being a recipient of transplant or on immunosuppressive therapy
- unvaccinated or functionally unvaccinated due to immune compromised status

Treatment of asymptomatic patients with positive SARS-CoV2 tests

- Asymptomatic hospitalized patients found to have incidental positive SARS-CoV2 tests should receive supportive care and clinical monitoring.
- Symptom onset date is necessary to guide use of COVID-19 therapeutics. If patients do not have symptoms of COVID-19 disease, there is unknown benefit of COVID-19 therapeutics.

Treatment of symptomatic patients not requiring supplemental oxygen (Ordinal Score 4)

- For patients with COVID-19 respiratory symptoms, early in disease course (<5-7 days from symptom onset) with high-risk of disease progression (e.g., multiple comorbidities or immunocompromised), can be treated to reduce the risk of progression to severe disease.
    - EUA Nirmatrelvir/ritonavir (Paxlovid), renally dosed oral BID x 5-day dose pack (Table 3, Dispensing information here)

      OR
    - Remdesivir 200 mg IV loading dose, followed by 100mg IV daily for 2 more days

- Dexamethasone or other steroids should be avoided unless otherwise indicated (e.g. COPD exacerbation). Steroids may worsen disease or prolong shedding if given early in the disease course.
- Note that EUA agents require patients to have high-risk criteria, within 5 days of symptom onset, and most are only allowed if not hospitalized due to COVID-19 (**Table 3**).

Treatment of patients requiring low-flow supplemental oxygen (Ordinal Score 5)

- Remdesivir 200 mg IV loading dose, followed by 100mg IV daily for 4 more days. Remdesivir is expected to have the greatest benefit early in the course of the disease (e.g. < 7 days).
- Consider adding dexamethasone 6mg PO/IV daily x 10 days within the context of patient-specific risks, duration of symptoms, and clinical trajectory.
    - RECOVERY trial allowed enrolling physicians to exclude patients if they believed there was a contraindication to short-term, low-dose corticosteroids.
    - Patients later in their disease course (>7 days from symptom onset) and/or with evidence of hyperinflammation were most likely to benefit.
    - Alternative steroid equivalents may be considered when dexamethasone is unavailable: prednisone 40mg PO daily or hydrocortisone 80mg IV BID x 10 days

Treatment of patients requiring high-flow oxygen or non-invasive mechanical ventilation (Ordinal Score 6)

- Remdesivir 200 mg IV loading dose, followed by 100mg IV daily for 4 more days PLUS Dexamethasone 6mg PO/IV daily x 10 days. Remdesivir is expected to have the greatest benefit early in the course of the disease.
- Baricitinib plus dexamethasone may be considered for patients with significant systemic signs of inflammatory response (elevated CRP, ferritin, and/or D dimer) and progressive hypoxia requiring HFNC or non-invasive ventilation.
    - ID consult is recommended for review of high-complexity cases to evaluate risk/benefit of baricitinib or not meeting per protocol criteria. Transplant ID consult is required for transplant or heme malignancy patients.
    - Baricitinib use “per protocol” must:
        - Be approved by a primary team attending-level physician.
        - Have NO high-complexity features: pregnancy, active thrombosis or new stroke/MI, active non-COVID infection.
    - Risk/benefit of secondary infection must be evaluated.
    - Consider holding baricitinib in lymphopenia <200, neutropenia <500, or if significant elevations of AST/ALT.
    - Patients given baricitinib should also be on VTE prophylaxis.
    - When used in combination with dexamethasone, baricitinib is dosed based on renal function for 14 days or until hospital discharge (**Table 3**).

Treatment of patients requiring mechanical ventilation or ECMO (Ordinal Score 7)

- Dexamethasone 6mg PO/IV daily x 10 days
- Remdesivir is NOT recommended for initiation in mechanically ventilated patients, but such patients may complete a 5-day course if initiated prior to illness progression.

- Baricitinib plus dexamethasone may be considered on a case-by-case basis for patients with critical disease and high inflammatory markers; ID consult required.**

Investigational agents

- For inpatient clinical trial enrollment, refer to Research Protocol Summary page for inclusion/exclusion and contact the Principle Investigator if patient/caregiver is interested.

High Titer COVID-19 Convalescent Plasma (CCP)

- High titer COVID-19 convalescent plasma (CCP) is an investigational blood product available under EUA. CCP is not recommended for use outside of clinical trials, is not considered standard of care, but may be considered for patients who are unable to receive recommended treatments and/or those with impaired humoral immunity.
- ID bedside consult** is required to discuss risks, potential benefits, and availability of high-titer CCP.
- Availability of high-titer CCP is difficult to anticipate. There may be delay from the time of request to administration, especially for rare blood types.
- Dose: 1-2 units of ABO compatible COVID-19 convalescent plasma intravenously, Duration: Once

Additional agents **were reviewed and are currently NOT recommended for use at DUHS outside of clinical trials for COVID-19 based on lack of efficacy data:** lopinavir/ritonavir, ruxolitinib, nitazoxanide, darunavir/ritonavir, darunavir/cobicistat, ribavirin, interferon, IVIG, hydroxychloroquine, chloroquine, ivermectin, hydroxychloroquine/azithromycin combination therapy, and monoclonal antibody infusion.

Table 3. Summary of Agents for Treatment of COVID-19 disease

	Drug	Dose (Adult)	Potential Harms	Additional information
Antiviral	Remdesivir (Veklury)	200 mg IV loading dose day 1, followed by 100 mg IV daily for 4 days for **severe disease** 200mg IV loading dose day 1, followed by 100mg IV daily for 2 days for **mild/moderate** disease in high-risk patients, **within 7 days** of symptom onset	Elevation in ALT/AST, reversible Drug interactions: CYP-3A4 substrates or inhibitors*	Remdesivir is expected to have the greatest benefit early in the course of the disease.
	EUA Molnupiravir	800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, initiated **within 5 days** of symptom onset in high-risk patients NOT hospitalized due to COVID-19	Embryo-Fetal toxicity: NOT recommended for use in pregnancy or lactation. Bone and cartilage toxicity Mild reactions: diarrhea, nausea, dizziness.	Must meet High Risk criteria (see Ambulatory guideline). Typically reserved for outpatient or pending discharge scenarios and for whom other treatment options are not accessible or clinically appropriate. ID consult with chart review note required for inpatient use.** Drug supply: DUHS outpatient pharmacies PTOM process for patients started on therapy and admitted for a non-COVID reason
	EUA Nirmatrelvir/ritonavir (Paxlovid)	Renally dosed, PO twice daily for 5 days, initiated **within 5 days** of symptom onset in high-risk patients NOT hospitalized for severe or critical COVID-19. eGFR ≥ 60: 300mg nirmatrelvir (two 150mg tablets) + 100mg ritonavir PO BID eGFR 30 to 59: 150mg nirmatrelvir + 100mg ritonavir PO BID eGFR <30: Not recommended	**Significant CYP3A drug-drug interactions*** NOT recommended in severe renal impairment (eGFR<30) or severe liver impairment (Child-Pugh Class C) Hepatotoxicity HIV drug-resistance (if used in individuals with untreated or undiagnosed HIV infection) Mild reactions: dysgeusia, diarrhea, hypertension, myalgia	Meets High Risk criteria (see Ambulatory guideline). Reserved for patients with mild/moderate disease. Pharmacist drug-interaction review strongly encouraged. Dispensed in a 5-day dose pack. Ensure that patients who are being discharged before completion of the course leave the hospital with the remaining doses to complete the therapy once discharged. Do NOT send an additional prescription to an outpatient pharmacy.

				INPATIENT dispensing information and Tip Sheet available here.
Anti-inflammatory	Dexamethasone	6mg PO/IV daily x 10 days Alternative steroid equivalents may be considered when dexamethasone is unavailable: Prednisone 40mg PO daily x 10 days Hydrocortisone 80mg IV BID x 10 days	Hyperglycemia Neurological side effects (e.g., agitation/confusion) Adrenal suppression Risk of secondary bacterial and fungal infection. CYP-3A4 substrates or inhibitors*	Do NOT use in mild/moderate disease.
	Baricitinib	Daily dose based on renal function, for 14 days or until hospital discharge: eGFR ≥ 60: 4mg PO daily eGFR 30 to 59: 2mg once daily eGFR 15-29: 1mg once daily eGRF <15: not recommended In combination with dexamethasone. In patients with contraindications to steroids, baricitinib may be considered for use without dexamethasone.	Serious venous thrombosis, including pulmonary embolism. Concomitant VTE prophylaxis recommended. Risk of secondary bacterial, viral, and/or fungal infection. Screen based on individual risk factors. Drug-induced liver injury. Strong OAT3 inhibitor (dose adjustment needed)	Per Protocol: • Laboratory-confirmed SARS-CoV2 • Attending-level ordering • Requiring high-flow or non-invasive mechanical ventilation (OS 6) • NO high-complexity features: pregnancy, active thrombosis or new stroke/MI, active non-COVID infection. Other disease severity or locations restricted to ID consult.** Consider avoiding in lymphopenia <200 or neutropenia <500 Transplant ID consultation required for transplant or heme malignancy patients

Convalescent Plasma	High titer COVID-19 Convalescent Plasma	Under EUA: 1-2 units of ABO compatible high titer COVID-19 convalescent plasma intravenously, once	Transfusion related risks: Mild allergic (itching/hives, 1-2%) Infrequent (<1%): transfusion associated circulatory overload (TACO); anaphylactic reactions; transfusion transmitted infections (HBV, HCV, HIV, syphilis and unknown pathogens); transfusion associated lung injury (TRALI); febrile nonhemolytic transfusion reactions; hemolytic reactions. Theoretical risks: antibody-mediated enhancement of infection; blunted long-term immune response to infection which may increase risk of recurrence.	Restricted to ID consult.** May consider in patients unable to receive recommended therapies or with impaired humoral immunity. Availability and time to administration will vary based on ABO compatibility and other factors.

*Please utilize this link to review drug interactions: http://www.covid19-druginteractions.org/

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EUA=emergency use authorized by FDA which requires 1) specific clinical use criteria be met, 2) counseling and risk/benefit discussion with the patient/caregiver and provision of the FDA Fact Sheet, and 3) safety event reporting to the FDA.

Reviewed by: The guidance was approved on 3/24/20 by the DUHS PMMC which includes physician, pharmacist, and nursing leadership. An update was approved 4/17/20, 6/4/20, 6/29/20, 8/19/20, 10/5/20, 11/02/20, 12/14/20, 3/1/21, 4/23/21, 6/7/21, 8/16/21, 9/3/21, 1/10/22, 04/8/2022, 11/30/2022, 8/3/2023.

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