MANAGEMENT OF COVID-19 PATIENTS ADMITTED TO FLAGLER HOSPITAL

As with any protocol, this protocol serves to provide evidence-based, comprehensive recommendations to guide our multidisciplinary team in patient care, with the expectation that expert practitioners will modify and customize as necessary the present protocol to meet individual patient needs. This Protocol is not intended to replace the physician's judgment; it is intended to provide guidance to the physician for the group of patients described in this Protocol.

All patients with confirmed COVID-19 infection will be eligible to be included in this protocol.

OBJECTIVE:
To optimize and standardize the management of patients with confirmed COVID-19 infection in patients admitted to Flagler Hospital.

MONITORING AND INTERVENTIONS
All patients with confirmed severe or critically ill COVID-19 infection will have a pulmonary (Drs Aduen, Husain, or Usman) and infection disease consultation (Drs. Manikal or Dhillon). For patients with mild to moderate category the consultation will be at the discretion of the PCP or ED physicians.

PATIENT PLACEMENT AND TRANSMISSION-BASED PRECAUTIONS

- Patients with suspected or confirmed COVID-19 infection **not receiving aerosol-generating procedures,** should be placed in a single-person room with the door closed and dedicated bathroom. Airborne and Contact precautions will be initiated. Personnel protective equipment (PPE) must include disposable gowns, gloves, masks, and eye protection.
- For patients who will be **undergoing aerosol-generating procedures or surgical procedure that might pose higher risk for transmission** (e.g., that generate potentially infectious aerosols or involving anatomic regions where viral loads might be higher, such as the nose and throat, oropharynx, respiratory tract) fit-tested N-95 mask or a powered air-purifying respiratory (PAPR) will be used and if possible will be placed in an airborne Infection Isolation Rooms, also referred to as negative pressure rooms.
    - Definite **aerosol-generating procedures defined by the WHO:**
        - Intubation, noninvasive positive pressure ventilation, tracheotomy, cardiopulmonary resuscitation, bronchoscopy, and sputum induction.
    - Possible aerosol-generating procedures:
        - High-flow oxygen and nebulization
- Providers are trained regarding applying and removing PPE. Fit testing is performed by Employee Health upon hire and annually.
- Regular cleaning of environmental surfaces will be performed following CDC guidelines.
- In general, patients who are hospitalized for CODID-19 infection should be maintained in Transmission-Based Precautions for the time period described for patients with severe to critical illness.

ISOLATION FOLLOWING CDC RECOMMENDATIONS - updated August 22, 2023, as follows:

- **Patients with mild to moderate illness who are *not* moderately to severely immunocompromised**:
    - Isolate for 10 days after symptom onset.

- **Patients with severe and critical illness who are *not* moderately to severely immunocompromised:**
    - Isolate for at least 10 days and up to 20 days after symptom onset, and after fever ends (without the use of fever-reducing medication) and symptoms are improving.
    - Serial testing prior to ending isolation can be considered in consultation with infectious disease.
- **Patients who are moderately or severely immunocompromised regardless of COVID-19 symptoms or severity:**
    - Isolate for at least 20 days and end isolation in conjunction with serial testing in consultation with infectious diseases.
    - The criteria for serial testing to end isolation are:
        - Negative result from at least two consecutive respiratory specimens collected ≥ 24 hours apart (total of two negative specimens) tested using an antigen test or nucleic acid amplification test.
    - if a patient was symptomatic, there should be resolution of fever for at least 24 hours (without the taking fever-reducing medication) and improvement of other symptoms.

If symptoms recur (e.g., rebound) patients should be placed back into isolation until they again meet the healthcare criteria to discontinue Transmission-Based Precautions for COVID-19 infection unless an alternative diagnosis is identified.

- Re-testing for COVID-19 infection is suggested if symptoms worsen or return after ending isolation and precautions.

If a patient has persistently positive nucleic acid amplification tests beyond 30 days, additional testing could include molecular studies (e.g., genomic sequencing) or viral culture, in consultation with infectious disease.

For all others: a test-based strategy is no longer recommended except to discontinue isolation or precautions earlier than would occur under the strategy outlined above. Two negative tests 48 hours apart will be accepted.

LABORATORY AND ANCILLARY TESTS

Tests will be ordered based on clinical necessity. Initially the following baseline studies will be ordered:

- CBC with differential, CMP, CPK, C-reactive protein (CRP), procalcitonin (PCT), LDH, troponin, ferritin, D-dimer, INR/P, PTT, fibrinogen, CXR and EKG. CT chest will only be considered if it is likely to change management.

Limit transport and movement of the patient outside of the room to medically essential purposes only including imaging studies that are not portable

CLASSIFICATION

In general, adults with COVID-19 infection can be grouped into the following severity of illness categories. However, the criteria for each category may overlap with other conditions and a patient's clinical status may change over time.

Asymptomatic or Presymptomatic Infection: Individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test or an antigen test), but who have no symptoms that are consistent with COVID-19.

Mild Illness: Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have dyspnea or abnormal chest imaging and who have saturation of oxygen (SpO_2) ≥94% on room air.

Moderate Illness: Individuals who show clinical or radiographic evidence of lower respiratory disease (dyspnea or lung infiltrates <50%) and who have saturation of oxygen (SpO_2) ≥94% on room air.

Severe Illness: Individuals who have SpO_2 <94% on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mmHg, respiratory frequency >30 breaths per minute, or lung infiltrates >50%.

Critical Illness: Individuals who have respiratory failure requiring high flow nasal canula (HFNC) or noninvasive ventilation (NIV) or invasive mechanical ventilation (IMV), septic shock, and/or multiple organ dysfunction.

TREATMENT

There is no indication for antibiotics unless superimposed bacterial pneumonia is suspected. If bacterial infection is suspected, obtain bacterial cultures, prior to initiation of empiric antibiotic and initiate antibiotics according to the suspected source of infection. Based on cultures and procalcitonin results, antibiotics might be discontinued if there is no evidence of a bacterial infection.

If the patient requires bronchodilators medications can be administered either by metered dose inhaler or nebulization. If a nebulizer is required, use appropriate PPE and airborne precautions as follows:

- The use of MDI with spacer is recommended for spontaneously breathing patients in need of aerosol therapy.
- For patients on a ventilator:
    - The vibrating mesh nebulizer is preferred. If necessary, place an additional filter on the expiratory limb of the ventilator circuit during nebulization.
    - It is essential to avoid opening the ventilator circuit to add medication or change nebulizers, because this generates aerosol from condensate that may be infectious
- If a patient with suspected or confirmed COVID-19 must unavoidably use a nebulizer, infection control procedures must be followed. These procedures include:
    - Pre-nebulization − Washing hands − Ensure the device is clean − Ensure adequate protection for health care workers and bystander hosts
    - During nebulization − Use of a negative-pressure room, if accessible, but if this is not available and there is no alternative, a single room with the door closed must be used. Mouthpiece preferred over facemask.
    - Post-nebulization − When therapy is completed, the equipment is placed in a patient setup bag with patient name and date written on the outside of the setup bag.
    - Disposables are used for single patient use only and can be discarded when therapy is discontinued.
    - If ordered nebulizer treatment is being discontinued due to COVID infection, the Respiratory Therapist should obtain a replacement MDI order from patient's attending or treating pulmonologist.

Nebulizer to MDI replacement guideline:

- 2.5 mg nebulized albuterol equivalent to 4 puffs albuterol
- 0.5 mg nebulized ipratropium equivalent to 4 puffs ipratropium

Management of Hypoxemia

- If patient has sustained O2 Sat <94% on RA, initiate O2NC 1 to 6 L/min to keep O2Sat 90-96%.
- Encourage use of incentive spirometry, early mobilization and self proning as tolerated.
- Acapella or Aerobika (PAP) therapy should be avoided if possible
- If O2 Sat cannot be maintained ≥90% and RR <30/min with O2 by nasal cannula, initiate HFNC or BiPAP or intubation. Endotracheal intubation will be required as with any patient with hypoxemia.
- Mechanical ventilatory support will be provided using a lung protective strategy following ABCDEF Flagler Hospital Protocol.

Pharmacological management based as recommended by NIH guidelines reviewed in December 2023

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy		Recommendations for Anticoagulant Therapy
	Clinical Scenario	Recommendation	
Hospitalized for Reasons Other Than COVID-19	Patients with mild to moderate COVID-19 who are at high risk of progressing to severe COVID-19[a,b]	See Therapeutic Management of Nonhospitalized Adults With COVID-19.	For patients without an indication for therapeutic anticoagulation: • **Prophylactic dose of heparin**, unless contraindicated **(AI)**; **(BIII)** for pregnant patients
Hospitalized but Does Not Require Supplemental Oxygen	All patients	The Panel **recommends against** the use of **dexamethasone (AIIa)** or other systemic corticosteroids **(AIII)** for the treatment of COVID-19.[c]	
	Patients who are at high risk of progressing to severe COVID-19[a,b]	**Remdesivir**[d] **(BIIb)** for patients who are immunocompromised; **(BIII)** for other high-risk patients	
Hospitalized and Requires Conventional Oxygen[e]	Patients who require minimal conventional oxygen	**Remdesivir**[d,f] **(BIIa)**	For nonpregnant patients with D-dimer levels above the ULN who do not have an increased bleeding risk: • **Therapeutic dose of heparin**[h] **(CIIa)** For other patients: • **Prophylactic dose of heparin**, unless contraindicated **(AI)**; **(BIII)** for pregnant patients
	Most patients	Use **dexamethasone plus remdesivir**[f] **(BIIa)**. If remdesivir cannot be obtained, use **dexamethasone (BI)**.	
	Patients who are receiving dexamethasone and who have rapidly increasing oxygen needs and systemic inflammation	Add 1 of the following immunomodulators:[g] *Preferred* • **PO baricitinib (BIIa)** • **IV tocilizumab (BIIa)** *Alternatives* • **IV abatacept (CIIa)** • **IV infliximab (CIIa)**	
Hospitalized and Requires HFNC Oxygen or NIV	All patients	**Dexamethasone** should be administered to all patients **(AI)**. If not already initiated, promptly add 1 of the following immunomodulators: *Preferred* • **PO baricitinib**[g,i] **(AI)** *Preferred Alternative* • **IV tocilizumab**[g,i] **(BIIa)** *Additional Alternatives (Listed in Alphabetical Order)* • **IV abatacept**[g,i] **(CIIa)** • **IV infliximab**[g,i] **(CIIa)** Add remdesivir to 1 of the options above in certain patients (for examples, see footnote).[j]	For patients without an indication for therapeutic anticoagulation: • **Prophylactic dose of heparin**, unless contraindicated **(AI)**; **(BIII)** for pregnant patients For patients who are started on a therapeutic dose of heparin in a non-ICU setting and then transferred to the ICU, the Panel recommends switching to a **prophylactic dose of heparin**, unless there is another indication for therapeutic anticoagulation **(BIII)**.
Hospitalized and Requires MV or ECMO	All patients	**Dexamethasone** should be administered to all patients **(AI)**. If the patient has not already received a second immunomodulator, promptly add 1 of the following (listed in alphabetical order): • **PO baricitinib**[j,k] **(BIIa)** • **IV tocilizumab**[j,k] **(BIIa)**	

The combination of the antiviral remdesivir and the antiinflammatory dexamethasone are considered the best treatment options for patients who require supplemental O2 with the addition of immunomodulators (baricitinib or tocilizumab) for those with respiratory failure requiring HFNC, NIV or IMV associated with a significant inflammatory response.

For patients hospitalized for reasons other than COVID-19 or those with mild to moderate disease not requiring supplemental oxygen who are at risk for clinical deterioration* will use one of the following therapeutic options in order of preference:

- Paxlovid orally twice daily for 5 days initiated as soon as possible and within 5 days of symptom onset.
- Remdesivir IV daily for 5 days initiated as soon as possible and within 10 days of symptom onset. Remdesivir can be extended for 5 days if they develop severe disease during the treatment.
- Molnupiravir 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

For patients with severe disease who require supplemental oxygen due to sustained O2 Sat <94% but do not require HFNC, NIV or IMV will use the combination of:

- Remdesivir for 5 days or until hospital discharge.
- Dexamethasone IV or orally for 10 days or until hospital discharge.
- Baricitinib (preferred) orally for 14 days or until hospital discharge or tocilizumab single dose IV will be initiated in patients with rapidly increasing oxygen needs and systemic inflammation.

For patients with critical illness who require HFNC or NIV but not intubated will use the combination of:

- Dexamethasone IV or orally for 10 days or until hospital discharge.
- Baricitinib (preferred) orally for 14 days or until hospital discharge or tocilizumab IV
- Remdesivir IV for 5 days or until hospital discharge will be optional in patients who are immunocompromised or patients who are ≤ 10 days from symptom onset.

For patients with critical illness who require intubation-IMV will use the combination of:

- Dexamethasone IV or orally for 10 days or until hospital discharge.
- Baricitinib (preferred) orally for 14 days or until hospital discharge or tocilizumab IV
- Remdesivir will not be routinely used.
    - If a patient has been receiving remdesivir and deteriorates requiring intubation and IMV, remdesivir should be continued until the treatment course is completed.
    - In patients who has been intubated for a short period of time, less than 24 to 48 hours, remdesivir might be added to dexamethasone in a case-by-case basis.

Paxlovid (nirmatrelvir 300 mg plus ritonavir 100 mg) orally twice daily for 5 days initiated as soon as possible and within 5 days of symptom onset.

- Before prescribing Paxlovid, clinicians should carefully review the patient's concomitant medications, including over-the-counter medications and herbal supplements, to evaluate potential drug-drug interactions.

Remdesivir 200 mg IV on Day 1 followed by 100 mg IV/d x4 days initiated as soon as possible and within 10 days of symptom onset. For inpatients, remdesivir can be extended for 5 days if they develop severe disease during the treatment.

- Before starting patients on remdesivir, ALT and INR will be performed and repeated as clinically indicated.
- It will be discontinued if a patient's ALT level increases to >10 times the upper limit of normal or any ALT increase with signs or symptoms of liver inflammation.
- Can be used without dose adjustment in patients with an estimated glomerular filtration rate (eGFR) of <30 mL/min, including those receiving dialysis.

Molnupiravir 800 mg 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

Dexamethasone 6 mg orally or IV once daily for up to 10 days as the preferred dose. However, a dose of 12 mg might confer a benefit in patients who require noninvasive or mechanical ventilation (higher probability of benefit and a lower probability of harm than dexamethasone 6 mg).

Baricitinib and Tocilizumab, when administered as a second immunomodulatory agent in combination with a corticosteroid, offers a survival benefit in certain patients with COVID who require supplemental oxygen and most patients who require HFNC, NIV, or mechanical ventilation or who are rapidly deteriorating with increasing oxygen needs, or those who are having a significant inflammatory response.

Baricitinib dosing:

- 4 mg/d x14 days or until hospital discharge.
- In patients with GFR 30-60 m/min/1.73m2 the dose will be 2 mg/d.
- In patients with GFR 15 to <30 mL/min/1.73m2 the dose will be 1mg/d.
- In patients with GFR <15 mL/min/1.73m2 will not be used

The use of baricitinib should be avoided in patients with any of the following:

- Patients on dialysis or with ESRD with GFR <15 m/min/1.73m2
- Immunocompromised patients (receiving high dose corticosteroids, biologics, T cell or B cell-targeted therapies, interferon, or JAK inhibitors) or with overwhelming infection.
- The following labs should be monitored at baseline, then days 3, 5, 8, 11 (all +/- 1 day) if patient remains hospitalized: GFR, absolute lymphocyte count, absolute neutrophil count, and aminotransferases (AST/ALT). Adjust dose based on EUA recommendations.

Tocilizumab dosing: single intravenous dose of 8 mg/kg of actual body weight, up to 800 mg)

- >90 Kg: 800 mg IV
- 65-90 Kg: 600 mg IV
- 40-65 Kg: 400 mg IV
- <40 Kg: 8 mg/Kg IV

The use of tocilizumab should be avoided in patients with any of the following:

- Significant immunosuppression, particularly in those with a history of recent use of other biologic immunomodulating drugs
- Alanine transaminase >5 times the upper limit of normal
- High risk for gastrointestinal perforation
- Uncontrolled, serious bacterial, fungal, or non-SARS-CoV-2 viral infection

- Absolute neutrophil count <500 cells/ml or platelets <50.000 cells/ml

If baricitinib or tocilizumab are not available or not feasible to use, **tofacitinib or sarilumab** can be used as an alternative.
Either intravenous IV **abatacept or IV infliximab** can also be used as alternatives.

Anticoagulation and VTE prophylaxis

For nonpregnant patients with *who do not require low-flow oxygen and do not require ICU level of care* will use:

- Standard prophylactic dose of enoxaparin or unfractionated heparin unless contraindicated.

For nonpregnant patients *with D-dimer levels above the upper limit of normal who require low-flow oxygen but do not require ICU level of care and have no increased bleeding risk* will use:

- Therapeutic dose of enoxaparin or unfractionated heparin
- Intermediate dose of enoxaparin 1 mg/kg/d will be optional

For nonpregnant patients *who are receiving ICU level of Care (including patients on high-flow oxygen or non-invasive ventilation)* will use:

- Standard prophylactic-dose of enoxaparin or unfractionated heparin as VTE prophylaxis unless a contraindication exists.
- Intermediate dose of enoxaparin 1 mg/kg/d will be optional

The guideline revised the recommendation on the use of an intermediate dose of anticoagulation based on the results of the ANTICOVID trial in 2023 and previous studies and concluded that there is insufficient evidence to recommend either for or against the use of an intermediate dose of anticoagulation for VTE prophylaxis (this is a change from previous guideline in which it was against).

- **The ANTICOVID trial-NEJM March 22, 2023**, evaluated the effect of standard-dose prophylactic, high-dose prophylactic, and therapeutic anticoagulation in 334 patients with hypoxemic COVID-19 Pneumonia and found less venous or arterial thrombosis in patients treated with high-dose prophylactic but no mortality benefit.

- **The INSPIRATION trial-JAMA April 27, 2021,** multicenter study evaluated the effect of intermediate dose vs standard dose prophylactic anticoagulation in 600 critically patients and found no difference in venous or arterial thrombosis, treatment with ECMO, or mortality.

Enoxaparin is preferred over unfractionated heparin

- Enoxaparin 1mg/Kg sq q12h) if CrCl >30 mL/min minus 10% (rounding factor).
- Enoxaparin 0.8mg/Kg sq q12h if BMI ≥40 or weight >120 Kg and CrCl >30 mL/min minus 10% (rounding factor).
- Heparin IV infusion therapeutic dose following Flagler Hospital protocol without loading dose for patients with CrCl ≤30 mL/min.

Contraindications for therapeutic anticoagulation for COVID-19 due to an increased bleeding risk are as follows:

- Platelet count <50 x 10^9/L, hemoglobin <8 g/dL.
- Need for dual antiplatelet therapy.

- Known bleeding within the last 30 days requiring an emergency room visit or hospitalization.
- Known history of a bleeding disorder, or an inherited or active acquired bleeding disorder.

In patients without a VTE started on therapeutic-dose heparin, treatment should continue for 14 days or until hospital discharge, whichever comes first.

For patients started on therapeutic-dose heparin while on low-flow oxygen due to COVID-19 and then transfer to the ICU, will be switched from therapeutic to prophylactic-dose of enoxaparin or unfractionated heparin unless a VTE is confirmed.

Therapeutic-dose oral anticoagulants for VTE prophylaxis or prevention of COVID-19 progression in hospitalized patients are not indicated.

Full anticoagulation unless contraindicated will be recommended for patients with confirmed VTE or recurrent clotting of dialysis filter, lines/tubing despite 500 U/h of through circuit prefilter unfractionated heparin.

Treatment recommendations for nonhospitalized patients with COVID-19 infection at high risk for disease progression*

Use one of the following therapeutic options in order of preference:

- Paxlovid (nirmatrelvir 300 mg plus ritonavir 100 mg) orally twice daily for 5 days initiated as soon as possible and within 5 days of symptom onset.
    - Paxlovid) has significant and complex drug-drug interactions, primarily due to the ritonavir component of the combination.
    - Before prescribing Paxlovid, clinicians **should carefully review the patient's concomitant medications**, including over-the-counter medications and herbal supplements, to evaluate potential drug-drug interactions.
- Remdesivir 200 mg IV on Day 1 followed by remdesivir 100 mg IV on Days 2 and 3 initiated as soon as possible and within 7 days of symptom onset.
- Molnupiravir 800 mg 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

Use of tixagevimab plus cilgavimab (Evusheld) as pre-exposure prophylaxis for severely immunocompromised patients.

IV infusions must be administered in settings in which health care providers have immediate access to medications to treat severe infusion reactions such as anaphylaxis and the ability to activate the emergency medical system.

When IV infusion is not feasible or would lead to delay in treatment, SQ injection of casirivimab plus imdevimab can be used as an alternative route of administration.

The viral rebound and symptom recurrence phenomenon

- The frequency, mechanism, and clinical implications of these events are unclear.
- Can be seen in patients who have completed treatment with Paxlovid and also in the absence of treatment. However, it seems more frequent post Paxlovid treatment.

- To date, the recurrence of COVID-19 symptoms following the use of Paxlovid has not been associated with progression to severe COVID-19. Therefore, concerns about the recurrence of symptoms should not be a reason to avoid using Paxlovid.
- There is insufficient data on the efficacy of administering a second or a longer course of Paxlovid to treat viral rebound or symptom recurrence.

Convalescent Plasma

- The NIH guideline updated in December 2023 still recommends against the use of convalescent plasma for the treatment of COVID-19 in hospitalized patients who are immunocompetent and insufficient evidence to recommend either for or against the use of high-titer convalescent plasma for the treatment of COVID-19 in hospitalized or nonhospitalized patients who are immunocompromised. However,
    - In immunocompromised patients with prolonged and symptomatic COVID-19 with evidence of ongoing SARS-CoV-2 replication, without definitive data, some Panel members would use convalescent plasma
    - A more recent study: Convalescent Plasma for Covid-19–Induced ARDS in Mechanically Ventilated Patients NEJM October 26, 2023, evaluated the effect of high-titer CCP with neutralizing antibody titer of at least 1:160 in 475 patients with Covid-19–induced ARDS within 5 days after the initiation of invasive mechanical ventilation and found significantly reduced mortality at day 28.

Optional management

Vit C 1000 mg q12h PO, Vit D3 2000-4000 Uqd PO and Zinc 75-100 mg qd PO x10 days.

- A more recent analysis published in JAMA 2023 "Vit C for COVID-19 (LOVIT-COVID and REMAP-CAP)" concluded that high-dose vit C supplementation is much more likely to be harmful than helpful in COVID-19. The trial was terminated after pre-defined statistical thresholds for harm and futility were met.
    - Among critically ill patients, there was only a 9% likelihood of any benefit, vs a 92% likelihood of harm.
    - For non-critically ill patients, a 3% chance of benefit, 97% chance of harm.

*High risk is defined as patients who meet at least one of the following criteria:

- BMI ≥35
- Chronic kidney disease
- DM
- Immunosuppressive disease or currently receiving immunosuppressive treatment
- 65 years of age or older
- 55 years of age or older AND have:
    - Cardiovascular disease
    - HTN
    - COPD/other chronic respiratory disease

Transportation

For patients on nasal cannula or high flow nasal cannula, patients must wear a procedure mask.
For patients on BiPAP, RT will supply filters for transport.
For patients on ventilators, do not use transport ventilators, rather keep the patient on their existing ventilator.

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- 65 years of age or older
- 55 years of age or older AND have:
    - Cardiovascular disease
    - HTN
    - COPD/other chronic respiratory disease