ANMC COVID-19 Clinical Guidance

Contents:

COVID-19 Clinical Presentation

COVID-19 infection has an extremely wide range of clinical presentation, ranging from common asymptomatic infection, mild upper respiratory illness symptoms, other non-respiratory symptoms to respiratory failure. Non respiratory complaints that may be signs of COVID-19 infection include headache, nausea, vomiting, abdominal pain or diarrhea. Finally, anosmia and dysgeusia are more common in COVID-19 in comparison to other upper respiratory viral infections.

The cardinal symptoms of influenza are fever, dry cough, headache and severe myalgias. Influenza is less likely than COVID-19 to present as mild illness in adults, and can present with gastrointestinal symptoms in children. In the event of a patient with an influenza-like illness, both influenza and COVID-19 should be evaluated. Co-infection with COVID-19 and other respiratory infections, including influenza, occurs and therefore during the pandemic COVID-19 infection should be evaluated despite a confirmed diagnosis of an alternative viral infection.

Clinical Comparison of COVID-19 and Influenza Illness

	COVID-19	Influenza
Symptoms	• Fever, cough, shortness of breath, headache, myalgias, loss of appetite, vomiting and diarrhea. • Patients can present with isolated gastrointestinal symptoms such as diarrhea. • Patients often have no or mild symptoms. • Anosmia or dysgeusia are common. • Consider COVID-19 in patients with isolated fever without a clear diagnosis.	• Fever, cough, headache, myalgias (often severe), fatigue and weakness. • Mild presentations are less common but possible. • Children can present with predominant gastrointestinal symptoms such as nausea and vomiting.

COVID-19 Symptom Spectrum and Reported Frequency (symptoms may vary based on circulating strain)

- Fever (77–98%)
- Cough (46%–82%)
- Myalgia or fatigue (11–52%)
- Shortness of breath (3-31%) at illness onset
- Anosmia or Dysgeusia (loss of sense of smell or altered taste perception)
- Headache (3-10%)
- Myalgias (11-15%)
- Loss of appetite (78.6%)
- Diarrhea (34%)
- Vomiting (3.9%)
- Abdominal Pain (1.9%)
- Rhinorrhea (4-6%)
- Sore throat (5-14%)

Considerations on Tests for COVID-19 available at ANMC

Several available nucleic acid amplifications test for COVID-19 are performed at ANMC. Laboratory validation of these available nucleic acid tests show very high sensitivities for SARS-CoV-2, however false-negative testing is not uncommon in COVID-19 and therefore the pretest probability of COVID-19 should be considered when interpreting a negative test result. The viral replication and load of SARS-CoV-2 rises during the first several days of COVID-19 illness, therefore repeating COVID-19 test may be useful if suspicion for COVID-19 remains high. The testing sensitivity is higher in lower respiratory tract samples in patients that present later in disease course with severe illness. When COVID-19 is the primary diagnostic consideration and PCR testing for SARS-CoV-2 is negative Infectious Diseases consultation should be considered. Due to the high prevalence of infection and variable presentation, we recommend providers have great latitude in deciding whom to test for COVID-19, and not adhere to a rigid algorithm.

The IDSA has released diagnostic guidelines for COVID-19. Patients with a high pre-test probability of COVID-19 who initially test negative by PCR, regardless of which PCR used, should be treated as suspected COVID-19 and receive a repeat PCR in 24-48 hours. If the patient has lower respiratory tract signs/symptoms a lower tract sample is preferred for the repeat test. Please refer to the IDSA COVID-19 diagnostic algorithm and guideline for further details: https://www.idsociety.org/practice-guideline/covid-19-guideline-diagnostics/

During the influenza season, the recommended evaluation for patients presenting with an influenza-like illness includes testing for both COVID-19 and Influenza. ANMC has several testing options available for COVID-19 and influenza and there are currently no stand-alone tests for influenza.

ANMC COVID-19 Nucleic Acid Amplification Testing Options

COVID-19 Molecular (In-House) Rapid: Abbott ID Now Point of Care Test. Isothermal nucleic acid amplification test.

General recommendations for use:

- Early diagnosis on symptomatic patient being admitted to appropriately start COVID-specific therapy
- Pre-operative testing if feasible to guide appropriate infection control precautions and avoid delay in urgent surgery
- Prior to admission into dual occupancy room if feasible and supply is not limited
- If high suspicion for COVID-19, no alternative diagnosis and COVID-19 Molecular (In-House) Rapid is negative, recommend repeating COVID-19 testing with COVID-19 PCR (In-House)

COVID-19 PCR (In-House): Abbott m2000 or Hologic Panther Test. PCR test.

General recommendations for use:

- Patients WITH symptoms
- COVID-19 PUI if Rapid testing not indicated or remains PUI after a negative Rapid

COVID-19 PCR Asymptomatic Screen (In-House): Abbott m2000 or Hologic Panther Test. PCR test.

General recommendations for use:

- Asymptomatic screen, preferred test when time allows
- After high risk exposure, ideally > 2 days following exposure and guided by infection control/employee health

The test platform used is determined behind the scenes in the lab and based on supplies on hand among other factors. If interested, providers can click into the test result details to view which test was actually performed.

Considerations on COVID-19 Antigen Testing

COVID-19 antigen testing is a highly specific but less sensitive testing modality when compared to COVID-19 PCR testing. Antigen testing has potential advantages of rapid turnaround time, increased testing availability, and lower cost. Therefore, it may be advantageous as a testing modality for large volume and higher frequency of asymptomatic screening in a higher risk population (e.g. frequent screening of nursing home residents, frontline healthcare workers). COVID-19 Antigen testing is less reliable at excluding COVID-19 in symptomatic patients compared to a NAAT test.

Recommendations on IgM/IgG Testing for COVID-19

The role of antibody testing for COVID-19 has not yet been well defined. We are still learning the test performance in a clinical setting. Most references do not recommend using serologic studies to make a diagnosis of acute COVID-19, however the test may be useful in conjunction with Infectious Diseases consultation for admitted patients who are highly suspected of COVID-19 but have negative PCR results. The use of any serologic test to diagnose an acute infection will often require acute and convalescent samples to demonstrate appearance of IgM or a four-fold increase in IgG titers. The COVID-19 serologic test should not be used in place of PCR based testing to make a diagnosis of acute COVID-19.

We have yet to learn if IgG positive results will confer immunity to reinfection with COVID-19. It is also not known if IgG antibody titers wane over time, or how long IgM titers persist after acute infection. Interpretation of serologic results in a low prevalence setting is challenging. A positive serologic test has a high likelihood of being a false positive result even with a highly specific test. For example, if the disease prevalence is 1% and the test specificity is 99% there will be an equal number of false positive and true positive results. In a low prevalence setting the COVID-19 antibody has highest utility for patients with a high pre-test probability for resolved illness, such as a known exposure plus a history of COVID-19 consistent illness. We recommend a discussion between the provider and patient prior to testing COVID-19 serologies. Until further research is available we do not recommend routinely instructing patients they are immune to COVID-19 if an IgG is positive.

Please see the following table to help guide interpretation of test results. Infectious Diseases consultation is recommended if there are questions on how to interpret serologic results. The interpretation of serologic testing should always be done in the context of the clinical history.

Test Results			Clinical Interpretation
PCR	IgM	IgG	
+	-	-	Active COVID-19 infection in a window period of infection
+	+	-	Active COVID-19 infection
+	+	+	Active COVID-19 infection
+	-	+	Active COVID-19 infection
-	+	-	Possible early COVID-19 with false negative PCR or false positive IgM result
-	-	+	Possible recovered COVID-19 infection or false positive IgG result
-	+	+	Active COVID-19 with false negative PCR or recovering recent COVID-19

Recommendations on Treatment of COVID-19

Hospitalized but not requiring supplemental oxygen

- No dexamethasone or other corticosteroids recommended
- If at high risk for progression to severe disease, consider remdesivir x3 days.

Hospitalized and requiring supplemental oxygen

- Remdesivir plus dexamethasone
- Dexamethasone (when combination therapy with remdesivir not able to be used)

Hospitalized and requiring oxygen delivery through High-Flow device or Noninvasive ventilation

- Remdesivir plus dexamethasone
- Dexamethasone (when combination therapy with remdesivir not able to be used)
- For patients who were recently hospitalized with rapidly increasing oxygen needs and systemic inflammation (hsCRP >7.5 mg/dL):
  - Add baricitinib PO or tocilizumab IV. Treatment decisions should be based on drug availability and patient comorbidities.
    - Do not use baricitinib and tocilizumab in combination. This has not been studied and is recommended against at this time.

Hospitalized and requires mechnical ventilation

- For most patients: Dexamethasone
- Patients within 24 hours of admission to the ICU: Dexamethasone plus tocilizumab
  - Do not use baricitinib and tocilizumab in combination. This has not been studied and is recommended against at this time.

Adapted from the NIH COVID Guidelines Figure 2. Therapeutic Management of Hospitalized Adults with COVID-19 Based on Disease Severity

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Remdesivir

ANMC Infectious Diseases recommends Remdesivir for the treatment of patients admitted with severe COVID-19 pneumonia **(pulmonary infiltrates with oxygen saturation ≤94%).** In this group Remdesivir has been shown to shorten time to recovery and duration of symptoms, and is associated with a trend towards decreased mortality that was not statistically significant. The benefit of Remdesivir was not demonstrated in patients requiring mechanical ventilation or ECMO.

Remdesivir can be considered in patients admitted to the hospital due to moderate COVID-19 **(defined in study as pulmonary infiltrates with oxygen saturation > 94%).** In this group Remdesivir had a statistically significant improvement in clinical status at day 11 of unclear clinical importance.

ANMC Infectious Diseases recommends a 5-day course of Remdesivir for patients that are admitted and require oxygen support to maintain O2 sat > 94%, but does not routinely recommend for patients that require mechanical ventilation. If the patient is discharged from the hospital prior to completing remdesivir the medication can be discontinued early.

ANMC Infectious Diseases recommends Remdesivir for 3 days for patients admitted with COVID and high risk for progression to severe disease, but only have mild symptoms.

Remdesivir is FDA approved for adults and pediatrics aged ≥28 days of age and weighing ≥3kg. There is no special documentation required to use Remdesivir.

Avoid the use of Remdesivir if GFR < 30 or ALT is > 10 X upper limit of normal (400 units/L).
Recommended lab monitoring:

- eGFR (SCr for full-term neonates 7-28 days old)
- Liver Function Tests should be done at baseline and repeated daily while receiving Remdesivir

Dosing:

- Adults and Pediatrics ≥40kg:
    - Loading dose of 200 mg IV once
    - Followed by maintenance dose of 100 mg IV every 24 hours
- Pediatrics 3.5kg to 40kg:
    - Loading dose of 5 mg/kg IV once
    - Followed by maintenance dose of 2.5 mg/kg IV every 24 hours

Corticosteroids

Dexamethasone 6 mg PO or IV daily for up to 10 days is recommended for hospitalized adults with severe COVID-19 defined as SpO2 ≤94% or critically-ill that are requiring oxygen therapy or mechanical ventilation. This is based on the RECOVERY trial demonstrating survival benefit.

ANMC Infectious Diseases recommends against dexamethasone for patients with non-severe COVID-19 defined as SpO2 >94% not requiring supplemental oxygen in accordance with the IDSA and NIH COVID-19 Treatment Guidelines.

Baricitinib

Hospitalized patients with severe COVID-19 on high-flow devices or noninvasive ventilation (e.g. BIPAP) can receive baricitinib 4 mg PO daily for up to 14 days while hospitalized in combination with remdesivir and dexamethasone. The benefits for starting baciritinib on patients who are mechanically ventilated are uncertain; however, completion of a previously started course would be ok if progressed to ventilation and able to take oral tablets. Do not use in combination with tocilizumab as this has not been studied and is not recommended at this time. Baricitinib should be avoided in patients with suspected co-infection, including bacterial, fungal, and tuberculosis. If severe infection or reactivation of infection develops while on therapy, discontinuation of baricitinib is recommended.

Tocilizumab

Tocilizumab is recommended for patients admitted for severe COVID-19 and hsCRP >7.5 mg/dL (CRP > 75 mg/dL). This treatment recommendation is based largely on data from the RECOVERY (https://www.medrxiv.org/content/10.1101/2021.02.11.21249258v1) and REMAP-CAP trials (https://www.nejm.org/doi/full/10.1056/NEJMoa2100433?query=RP). Tocilizumab should be used in addition to dexamethasone and other standard of care, but has not been studied to be given in addition to baricitinib. Tocilizumab should be avoided in patients with suspected co-infection, including bacterial, fungal, and tuberculosis. Dosing was studied as a single IV infusion over 60 minutes based on body weight (800 mg if >90kg; 600 mg if >65kg and ≤90 kg; 400 mg if >40 kg and ≤65 kg; and 8mg/kg if ≤40 kg). A second dose could be considered 12 to 24 hours later, if the patient's condition had not improved.

Monoclonal Antibodies

ANMC Infectious Disease recommends monoclonal antibody therapy for patients with mild-moderate COVID-19 with risk factors of developing severe disease. The beneficial effects of the monoclonal antibody treatment are most likely achieved when the treatment is given earlier in course of COVID-19 infection. The EUA allows for use within 7 days of symptom onset and the potential benefit is maximized when given earliest in disease course. Therapy option should be selected based on anticipated susceptibility to current predominant variant in Alaska. Administration of Monoclonal Antibodies has been performed at Municipality of Anchorage infusion site through the end of June 2022.

The EUA eligibility criteria for the monoclonal antibodies for the treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization, is listed below.

- High risk defined as **one or more** of the following criteria:
    - Age ≥ 65 years of age
    - BMI ≥ 25, or if 12-17, have BMI ≥ 85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm
    - Pregnant
    - Chronic kidney disease
    - Diabetes
    - Immunosuppressive disease or receiving immunosuppressive treatment
    - Cardiovascular disease (including congenital heart disease) or hypertension
    - Have chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis, and pulmonary hypertension)

- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Have a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19))
- Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and authorization of COVID-19 monoclonal antibody treatment under the EUA is not limited to the medical conditions or factors listed above. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extraprecautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

- Monoclonal antibodies are **not authorized** for use in patients:
  - who are hospitalized *due to* COVID-19, OR
  - who require oxygen therapy *due to* COVID-19, OR
  - who require an increase in baseline oxygen flow rate *due to* COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.

Close contact is defined as being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example).

Oral Antiviral Agents

The FDA has authorized EUA for two oral antiviral agents in the outpatient setting for mild-to-moderate symptomatic COVID-19 and who are at a high risk for progression to severe COVID-19. Therapy should be considered, when available, in patients who meet all of the following criteria:

- High risk for progression to severe disease
- Within 5 days of symptom onset

These agents are not authorized for pre-exposure or post-exposure prevention of COVID-19.

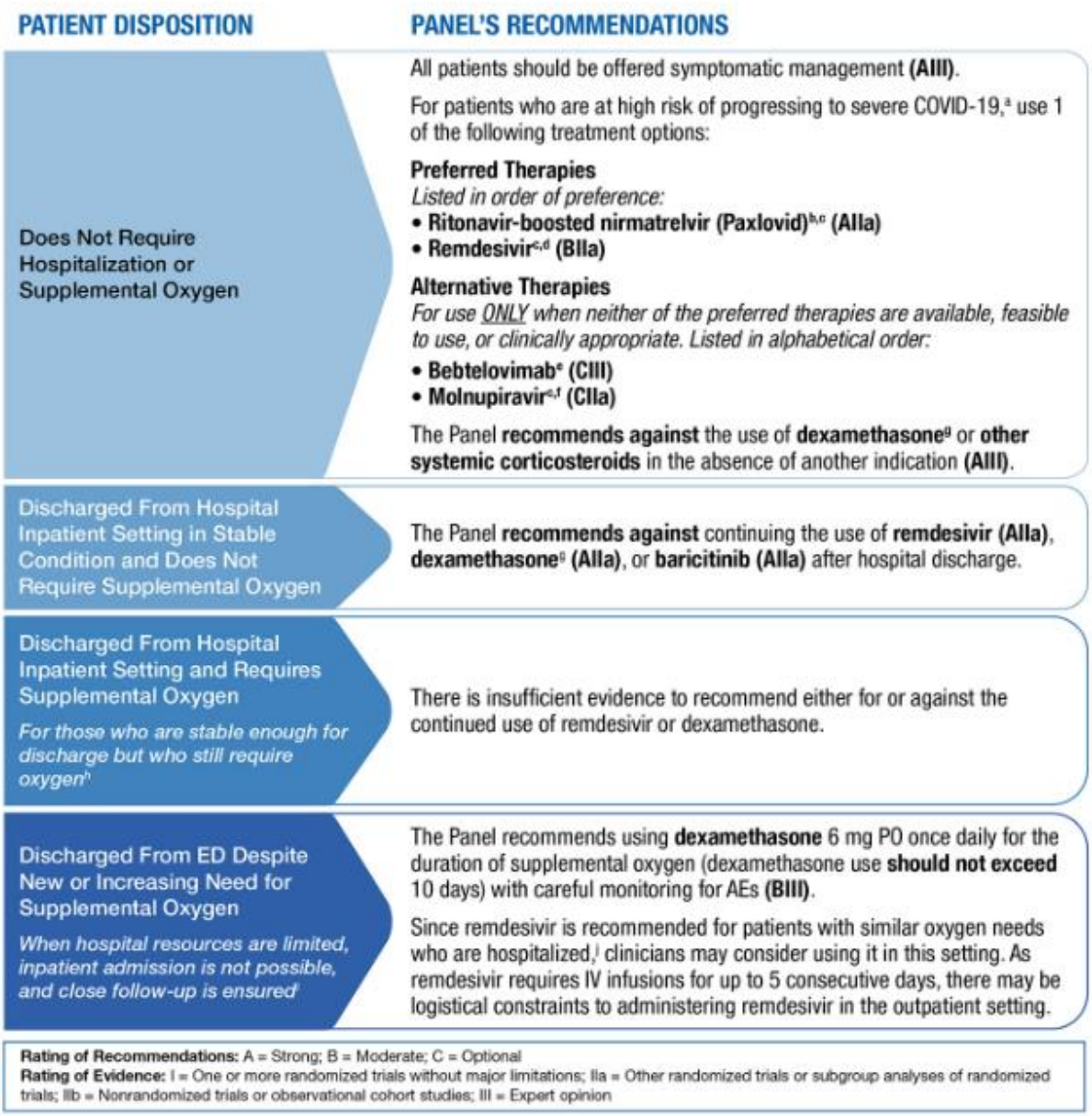
Patients hospitalized for COVID-19 with moderate-to-severe disease should not receive these agents due to a lack of data on efficacy. If a patient was previously started on therapy prior to hospitalization, medication can be continued up to 5 days to complete the original treatment duration utilizing the previously dispensed home supply; if worsening COVID leading to infection, adjust therapy per disease severity.

Nirmatrelvir/Ritonavir (Paxlovid®) is authorized for patients ≥12 years of age and weighing at least 40kg. Significant drug-drug interactions may be present due to ritonavir use as a boosting agent. Patients on concurrent medications should be assessed for potential interactions. Dosing is 300mg (two 150mg tablets) nirmatrelvir and 100mg (one 100mg tables) ritonavir twice a day for 5 days. Co-administration with dexamethasone is not recommended due to severe drug interaction potential with increased dexamethasone concentrations (>2 fold increase has been noted).

Molnupiravir (Lagevrio®) is authorized for patients ≥18 years of age because it may affect bone and cartilage growth. Use is not recommended in pregnancy as it may cause fetal harm. Testing for pregnancy should be done prior to prescribing for females of childbearing potential to assess risk vs benefit and documentation of discussion.

Females of childbearing potential are advised to use a reliable method of birth control correctly and consistently during treatment with molnupiravir and for four days after the final dose. Breastfeeding women should discard milk during and for 4 days after receipt of molnupiravir. Males of reproductive potential who are sexually active with females of childbearing potential are advised to use a reliable method of birth control correctly and consistently during treatment with molnupiravir and for at least three months after the final dose. Dosing is four 200mg capsules twice a day for 5 days.

Figure 1. Therapeutic Management of Nonhospitalized Adults With COVID-19



https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/nonhospitalized-adults--therapeutic-management/

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Anticoagulation Recommendations for Hospitalized COVID-19 Patients

Increased thrombotic risk in patients with COVID-19 was recognized early in the pandemic and data on the use of therapeutic anticoagulation in hospitalized patients has evolved. There are several studies demonstrating variable results of anticoagulation, which appears to be dependent on the level and stage of COVID-19 infection. In general the greatest benefit appears to be in patients that are early in a severe COVID-19 illness, hospitalized, but not requiring high flow O2 or critically ill.

The recommendation below is consistent with the NIH treatment guidelines

Therapeutic-dose low molecular weight heparin is recommended for nonpregnant adult patients admitted to the hospital due to COVID-19, requiring low-flow O2, have an elevated D-dimer, are *not* requiring care in the CCU, and without contraindication to anticoagulation.

Recommended duration of therapeutic anticoagulation is 14 days unless discharged sooner.

Prophylactic-dose anticoagulation is recommended for admitted patients with COVID-19 who are not receiving therapeutic anticoagulation unless a contraindication exists.

Antibiotic Therapy

Patients who are admitted for COVID-19 and are suspected of having a co-existing or secondary bacterial pneumonia should have antibiotic regimens chosen that minimize frequency of dosing and are consistent with ANMC Antimicrobial Stewardship Guidelines.

Provider Fact Sheets:
Paxlovid (Nirmatrelvir/Ritonavir)- https://www.fda.gov/media/155050/download;
Lagevrio (Molnupiravir)- https://www.merck.com/eua/molnupiravir-hcp-fact-sheet.pdf
Bebtelovimab- https://www.fda.gov/media/156152/download

Patient Fact Sheets:
Paxlovid (Nirmatrelvir/Ritonavir)- https://www.fda.gov/media/155051/download;
Lagevrio (Molnupiravir)- https://www.merck.com/eua/molnupiravir-patient-fact-sheet-english.pdf
Bebtelovimab- https://www.fda.gov/media/156153/download

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