COVID-19 Task Force Guideline for Patient Management

Updated: January 11, 2021

Disclaimer: At this time, remdesivir is the only FDA approved therapy for COVID-19 infection. In COVID-19 patients with acute hypoxemic respiratory failure, new treatments are being compared to the combination of dexamethasone and remdesivir in NIH clinical trials.

After review of the existing literature, a task force has agreed upon the following guidance for overall management of patients with COVID-19 infection.

Currently, clinical trials are enrolling patients to study new treatments. As a result, data continues to be released after both peer review and alternate pathways. This guidance document will continue to be updated as new data becomes available.

Algorithm has been approved by the FMOLHS System COVID Task Force for utilization as a guidance document.

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COVID-19 Outpatient Treatment Algorithm

****An FDA EUA has been granted to the monoclonal antibody bamlanivimab as well as casirivimab + imdevimab for outpatient use. Patients should be informed of both the experimental nature of the drug and known adverse drug effect profile in true shared decision making if medication prescription is undertaken. Decadron is not indicated for use in the care of the non-hypoxemic patient as data from the RECOVERY trial demonstrated no benefit and potential harm in this population.**

Clinical Category	Supportive Care	Antiviral Therapy
COVID-19 diagnosis: outpatient testing Low risk (*lack of high risk criteria*)	• Acetaminophen PRN • Ibuprofen PRN	Consider fluvoxamine PO x 15 days (*see additional information on page 6*)
COVID-19 diagnosis: outpatient testing High risk (*BMI ≥35, CKD, DM, age ≥65, immunosuppression, OR age ≥55 with HTN/COPD/CVD*)	• Acetaminophen PRN • Ibuprofen PRN	Consider bamlanivimab 700mg x1 (*see limitations of authorized use on page 8*)

COVID-19 Inpatient Treatment Algorithm

****Disclaimer: Remdesivir is the only FDA approved therapy in COVID-19; other agents are under investigation for the treatment of COVID-19. Treatment efficacy has been demonstrated with length of stay impact by remdesivir. Dexamethasone 6mg/day has been added as the RECOVERY randomized control trial demonstrated mortality benefit in those with acute hypoxemic respiratory failure. An FDA EUA has been granted to high titer convalescent plasma within 3 days of COVID-19 diagnosis. Most treatments remain experimental and require that patients are informed of both the experimental nature of the drug and potential risks. This continues to be best achieved within the confines of a clinical trial. Providers may be contacted by research personnel if inclusion criteria are met.**

Clinical Category	Supportive Care	Antiviral Therapy
Suspicion of COVID-19 • Non-pulmonary signs or symptoms	• Acetaminophen PRN	None
Suspicion of COVID-19 • Dyspnea, SpO2 ≤92% or • Bilateral infiltrates on CXR, clin hx, elevated community prevalence	• Acetaminophen PRN • Albuterol MDI PRN • Higher enoxaparin DVT prophylaxis may be considered (Avoid decadron on patients not requiring supplemental oxygen to maintain oxygen saturation >90%)	None
Confirmed COVID-19 • Requiring < 5L NC	• Higher enoxaparin DVT prophylaxis (40mg or 30mg BID)* **Therapeutic anticoagulation NOT recommended unless confirmed VTE** • Dexamethasone 6 mg daily for up to 10 days (if requiring supplemental O2) • Acetaminophen PRN • Albuterol MDI PRN	Remdesivir x 5 days (See remdesivir use criteria) **+/-** High titer convalescent plasma within 3 days of diagnosis - NCATS Funded RCT PassItON (BR Market)
Confirmed COVID-19 • Requiring >5L NC • Requiring mechanical ventilation	• Higher enoxaparin DVT prophylaxis (40mg or 30mg BID)* **Therapeutic anticoagulation NOT recommended unless confirmed VTE** • Dexamethasone 6 mg QD x10 days[3] • Acetaminophen PRN *Link to pain and sedation algorithm on page 3*	Remdesivir x 5 days (See remdesivir use criteria) + baricitinib x 14 days **+/-** High titer convalescent plasma within 3 days of diagnosis - NCATS Funded RCT PassItON (BR Market)

General Treatment Considerations

Standardization of medication times:
In an effort to limit nursing exposure and preserve PPE, please utilize standardized medication administration times. Preferably select times which may coincide with other required actions, such as lab draws.

- Ex: 0300, 0900, 1500, 2100
    - Consider drawing AM labs at the same time as AM medication doses are administered.
- Avoid frequency of more than TID if possible
    - Teams caring for critical care patients bundle medications and care delivery such as ventilator assessment. As a result, qid medication administration is difficult to bundle with other activities in a timeline that maximizes PPE efficiency.

Pain and Sedation:
The increased number of critical care level patients nationwide has and can contribute to significant drug shortages of medications used for pain and sedation. Inventory is being monitored closely and guidance documents have been created to assist clinicians in selecting appropriate regimens.

Treatment algorithm for selecting regimens:
https://fparchives.com/ololrmc/documents/Analgosedation Guidance Document.pdf
Medication info sheet:
https://fparchives.com/ololrmc/documents/FMOLHS%20Analgosedation%20Guidance.pdf

Adjunct Antibiotics:

- In an effort to maximize PPE efficiency, antibiotics that are given less frequently and/or can be given as a push are generally preferred.
- Initial CAP therapy (If warranted prior to COVID + test return. For example, patient presents with Lactic acid >4 or test turnaround time is greater than 60 minutes)
    - Ceftriaxone PLUS atypical coverage (doxycycline OR azithromycin)
    - Beta-lactam allergy: Levofloxacin
- Gram negative coverage
    - Ceftriaxone OR Cefepime (Pseudomonal coverage) OR meropenem (ESBL coverage)
    - In general, piperacillin-tazobactam is considered second line given its inability to be delivered as a push and the associated volume required for administration.
- MRSA coverage
    - A MRSA nasal PCR should be ordered for all patients who are COVID confirmed/rule out and have MRSA coverage initiated
        - See full protocol on page 11 for operational guidance
    - Linezolid- preferred if bacteremia is not suspected
    - Vancomycin- only if contraindication to linezolid or bacteremia is suspected
- Elevated rates of acute kidney injury (AKI) can be seen in COVID-19 patients. Thus, avoidance of potential AKI risk with vancomycin paired with the challenge in timing of level blood draws to guide dosing has moved vancomycin to second line.
- Co-infections and secondary infections in COVID-19 patients on *presentation* have a low incidence in literature reported to date (8% in meta-analysis).[1] Thus, empiric use of antibiotics on all COVID-19 patients is not recommended. Clinical judgment for initiation is recommended on a case by case basis.

Corticosteroids

- The **RECOVERY** trial (dexamethasone 6mg daily x 10 days vs none) showed a mortality reduction in patients on supplemental oxygen. No benefit was seen in patients not requiring oxygen support.[2]
- The **CoDEX** trial (dexamethasone 20mg daily x 5 days, followed by dexamethasone 10mg daily x 5 days vs none) showed a significance increase in ventilator free days over 28 days.[3]
- A multicenter randomized control trial **(CAPE COVID)** evaluated continuous hydrocortisone 200mg daily x 7 days, followed by hydrocortisone 100mg daily x 4 days, then 50mg daily x 3 days (14 total days) vs placebo. There was no significant difference in the primary outcome of treatment failure (death or continued mechanical ventilation or high-flow oxygen therapy) at 21 days. This study was stopped early and likely underpowered to detect a difference.[4]
- The **REMAP-CAP** trial, a multicenter open-label trial, randomized patients to hydrocortisone 50mg q6h x 7 days or hydrocortisone 50mg q6h while in shock up to 28 days, or no intervention. The study was stopped early; therefore a definitive conclusion cannot be made. However, the results suggest benefit in the primary outcome of days free of organ support with fixed dose hydrocortisone compared to no hydrocortisone.[5]
- **Key points: Glucocorticoids have shown clear mortality benefit and reduction in ventilator-free days in patients with COVID-19. Currently, an optimal dosing strategy and timing of corticosteroids are still unclear.**
- **Key points: The task force recommends initiation of dexamethasone at 6 mg/day (IV or oral) for up to 10 days in patients with COVID-19 who are mechanically ventilated and in those who require supplemental oxygen but who are not mechanically ventilated. CoDEX dosing may be considered in mechanically ventilated patients. Task force recommends against the use of dexamethasone in patients with COVID-19 who do NOT require supplemental oxygen (defined as the need to maintain an oxygen saturation >90 percent)**
    - **Adverse drug events to be monitored include delirium and hyperglycemia.**

Remdesivir

- The **ACTT-1** trial (remdesivir 200mg x1 day, followed by 100mg x 9 days vs placebo) showed shorter time to recovery in the remdesivir group, with those on supplemental oxygen benefiting most from therapy.[9]
- An interim analysis of the WHO **SOLIDARITY** trial did not show any difference in mortality, ventilation initiation, or time to discharge when comparing remdesivir to its placebo.[10]
- A randomized, open-label trial **(SIMPLE-1)** evaluating 5-day vs 10-day courses of remdesivir showed no significant difference in efficacy when comparing 5- vs 10-day courses after adjustment of disease severity. Of note, only 44% of patients in the 10-day group completed a full course of therapy. Few mechanically ventilated or ECMO patients were included in the analysis.[11]
- A randomized open-label trial **(SIMPLE-2)** compared standard of care, up to 5-day course of remdesivir, and up to a 10-day course of remdesivir in patients with moderate COVID-19 in a 1:1:1 fashion. The study found a statistically significant, but not clinically significant, difference in clinical status at day 11 in those receiving a 5-day course of remdesivir versus standard of care. There was no significant difference in clinical status at day 11 in those receiving a 10-day course of therapy versus standard of care.[12]
- The NIH COVID-19 Treatment guidelines have recommended that remdesivir be prioritized for use in patients requiring supplemental oxygen but who are not mechanically ventilated **first** in areas where remdesivir supply is limited. Duration of therapy is 5 total days. There is uncertainty regarding whether remdesivir confers clinical benefit in patients who require high-flow oxygen, non-invasive ventilation, mechanical ventilation, or ECMO.[13]
- **Key points: The task force recommends initiation of remdesivir 200mg x 1 day, followed by remdesivir 100mg x 4 days (5 days total therapy) in patients requiring supplemental oxygen. If mechanical ventilation is utilized, symptoms should have started within 7 days of mechanical ventilation initiation. (*See page 6 for full inclusion/exclusion criteria*). Remdesivir should NOT be initiated in those NOT requiring supplemental oxygen.**

Baricitinib

- Baricitinib, a selective Janus kinase (JAK) 1 and 2 inhibitor, has been studied for use in combination with remdesivir for COVID-19 infection.
- In the **ACTT-2** trial, baricitinib 4mg daily x 14 days or until hospital discharge (or 2mg daily if CrCl <60mL/min) in combination with remdesivir was compared to remdesivir alone. Overall, patients receiving combination therapy recovered about one day sooner than those only receiving remdesivir. The recovery time benefit of combination therapy was seen most in patients in patients receiving noninvasive ventilation or high-flow oxygen (10 days in combination vs 18 days in remdesivir group).[15]
- Though baricitinib carries a warning for risk of thrombosis, rates of this adverse event were similar between both groups. Given this risk, consider use of dopplers to evaluate active VTE prior to initiation of baricitinib.
- **Key points: Baricitinib may be considered in patients failing steroid therapy who have advanced to ICU status requiring high-flow oxygen. The dosing is baricitinib 4mg daily x 14 days or until hospital discharge (considering renal function) in combination with remdesivir (200mg x1 followed by 100mg x9 days for 10 days total).**

Hydroxychloroquine

- Several studies have been performed to evaluate for a possible benefit with hydroxychloroquine, some with the combination of azithromycin. Overall, studies have shown no impact on mortality, transfer to ICU, ARDS, mechanical ventilation requirements.[16-18]
- The **ORCHID** trial evaluating hydroxychloroquine versus placebo was stopped by the NIH for futility. Results of the trial found no significant difference in their primary outcome of improvement in clinical status at 14 days. [19]
- QTc prolongation is a known adverse effect of hydroxychloroquine and may be more pronounced when combined with azithromycin.[20] QT prolongation >500ms occurred in >20% of patients in one study.[21]
- **Key points: The task force recommends against the routine use of hydroxychloroquine in treatment of COVID-19 patients outside of a clinical trial due to the lack of evidence showing benefit and evidence of potential harm.**

Tocilizumab

- Tocilizumab is an IL-6 inhibitor which has been evaluated for potential impact in patients with cytokine storm from COVID-19 infection.
- Early data from China showed possible benefit with the use of tocilizumab in 21 patients.[22]
- Preliminary data from the phase III **COVACTA** trial of tocilizumab in hospitalized patients with severe COVID-19 associated pneumonia showed no improvement in clinical status or mortality.[23]
- Recent data comparing the use of tocilizumab versus usual care in hospitalized patients with COVID-19 pneumonia (**RCT-TCZ-COVID-19**)[24] showed no benefit on disease progression in these patients. In non-ICU patients with moderate to severe COVID-19 pneumonia on oxygen support (**CORIMUNO-19**)[25] tocilizumab was no different than usual care when comparing mortality outcomes.
- The **BACC-BAY** trial compared tocilizumab versus standard of care in moderately ill hospitalized patients and found no difference in risk of intubation or death. Patients receiving tocilizumab did have significantly more neutropenia and infection rates.[26]
- Additionally, a retrospective analysis showed a higher incidence of secondary bacterial infections in patients with COVID-19 receiving tocilizumab versus those who did not receive tocilizumab.[27]
- **Key Points: At this time, the task force would recommend against the use of tocilizumab in COVID-19 due to its lack of benefit and possible increase in secondary infections.**

REGN-COV2 Antibody Cocktail

- REGN-COV2 is a combination of monoclonal antibodies (casirivimab and imdevimab) proposed to reduce viral load and symptoms associated with COVID-19 by blocking infectivity of SARS-CoV-2. Currently, a randomized, double-blind trial comparing the addition of REGN-COV2 versus placebo to standard-of-care is ongoing in both outpatient and inpatient settings.[28,29]
- Based on press release information, preliminary results from 275 non-hospitalized COVID + patients have shown a possible decrease in time to symptom resolution in a subset of patients who did not have measurable antiviral antibodies prior to treatment initiation. It is anticipated that a total of 1,300 outpatient participants will be recruited.[29]
- Currently, Phase 2 and 3 studies are ongoing, and REGN-COV2 is still under investigation for use.
- **Key points: At this time, preliminary data shows a possible benefit for symptom alleviation in non-hospitalized patients. REGN-COV2 is currently not recommended due to lack of peer-reviewed publications and is not currently available within the FMOL Facilities.**

Bamlanivimab:

- Bamlanivimab is a recombinant neutralizing human IgG1k monoclonal antibody which blocks spike protein attachment of SARS-CoV-2 to human ACE2 receptors.
- The **BLAZE-1** trial evaluated bamlanivimab administered as a one-time dose in high-risk patients with SARS-CoV-2 in the outpatient setting. Patients were randomized to receive one of 3 doses (700mg, 2800mg, 7000mg) or placebo.[30] The trial showed a potential decrease in viral load, with statistically significant decrease shown for the 2800mg dose.
- Based on the results of the **BLAZE-1** trial, the FDA issued an EUA for bamlanivimab 700mg x1 in high-risk outpatients with SARS-CoV-2 (limitations of authorized use outlined by FDA). FMOLHS will be allocated a small quantity.[31]
- Bamlanivimab is NOT recommended in hospitalized patients as demonstrated by the **TICO** trial, showing that there was no difference in clinical outcomes at day 5 in hospitalized patients when compared to placebo.[32]
- **Key points: At this time, data shows a possible benefit for increased viral clearance in non-hospitalized patients. Bamlanivimab is available to FMOLHS in an allocated quantity. See page 8 for current criteria for use.**

Fluvoxamine:

- Fluvoxamine is a selective serotonin reuptake inhibitor with potent affinity for the σ 1 receptor (S1R). The S1R has potential for immune modulation through cytokine production regulation through interaction with the inositol-requiring enzyme 1α.[33]
- The **STOP-COVID** trial evaluated the use of fluvoxamine versus placebo for 15 days (Day 1: 50mg, Day 2-3: 100mg BID, Day 4-15: 100mg TID) in 152 symptomatic outpatients with SARS-CoV2. The primary outcome of clinical deterioration within 15 days was statistically significant with no patients in fluvoxamine group experiencing clinical deterioration versus 6 in the placebo group.[34]
- Of note, patients were excluded if they were hospitalized, had unstable medical conditions including COPD, pulmonary hypertension, decompensated cirrhosis, CHF, were immunocompromised (organ transplant, bone marrow transplant, AIDs, on biologic agents, or high dose steroids >20mg of prednisone daily).
- **Key points: At this time, data shows potential benefit with fluvoxamine in non-hospitalized patients with few comorbidities. Dosing is as follows: Day 1: Fluvoxamine 50mg once; Day 2-3: Fluvoxamine 100mg BID; Day 4-15: Fluvoxamine 100mg TID.**
- **Key points: If medication is considered in the outpatient setting, providers should be mindful of drug-drug interactions with warfarin and concomitant selective serotonin reuptake inhibitors. Fluvoxamine is not recommended in those with the above-mentioned disease states, but bamlanivimab may be considered.**

Ivermectin:

- Ivermectin is an anti-parasitic agent which has shown some anti-viral activity (including SARS-CoV-2) in vitro.[35]
- No studies exist to date evaluating ivermectin in treating patients with COVID-19, but clinical trials are ongoing.
- **Key points: The task force would recommend against the use of ivermectin use in treating COVID-19 due to the lack of clinical data.**

ACE/ARBs:

- In vitro studies have proposed ACE2 as a possible point of attachment for SARS-CoV-2.[36] Due to a possible increase of ACE2 receptor production in patients on ACE/ARB therapy, some experts have recommended against use of ACE/ARBs in patients with suspected/confirmed COVID-19.
- ACE/ARBs may have a lung protective effect through increases in ACE2 production.[37]
    - Ongoing clinical trials in the US on effect of ARBs on disease progression in SARS-CoV-2 (NCT04340557, NCT04311177, NCT04312009, NCT04360551, NCT04335123).
    - Previous trial on recombinant ACE2 administration was withdrawn (NCT04287686)
- Retrospective analysis of 12,594 patients tested for COVID-19: 5894 (46.8%) were positive, 1002 (17.0%) of them with severe illness. 4357 patients tested had hypertension, with 2141 receiving ACE/ARB therapy. No differences seen in rate of COVID (+) or severe illness. No increase in risk of COVID-19 infection or development of severe disease seen with ACE/ARB therapy in this study.[38]
- A small retrospective, single-center review of 614 COVID (+) patients with hypertension found that those who continued ACE/ARB therapy in-hospital, and who did not develop hypotension or acute kidney injury, did not have worse clinical outcomes as compared to those in the discontinued ACE/ARB group.[39]
- **Key points: At this time, recommendation is for best clinical judgment in care delivery. Long acting anti-hypertensives may be challenging in critically ill patients and in acutely ill patients given a desire to maintain net even to negative fluid status in ARDS patients.**

NSAIDs:

- Early reports (France) recommended against the use of NSAIDs due to the possibility of adverse outcomes. However, no data to validate the observational data has been published.
- Available guidelines have recommended caution with use and clinical judgment.
- **Key points: At this time, the task force would recommend appropriate clinical reasoning. Consider use of acetaminophen as first line therapy for fever/myalgias with addition of NSAIDS when benefits outweigh the risks in inpatient medication administration.**

Patients with prior COVID-19 vaccination:

- At this time, no data exists to guide treatment of patients with COVID-19 who previously received a COVID-19 vaccine.
- Bamlanivimab can still be given. However, the second COVID-19 vaccine dose should be delayed for at least 90 days after receiving bamlanivimab to avoid potential interference of the antibody therapy with vaccine-induced immune responses.
- **Key points: For vaccinated persons who subsequently develop COVID-19, prior receipt of an mRNA COVID-19 vaccine should not affect treatment decisions (including use of monoclonal antibodies, convalescent plasma, antiviral treatment, corticosteroids, etc.) or timing of such treatments.**

Consideration for the Initiation of Remdesivir in COVID-19

Given the results of the Adaptive COVID-19 Treatment Trial (ACTT)[9] and approval by the FDA's emergency use authorization process, hospitals now obtain a limited allocation of medication. In an effort to standardize delivery and receipt of the medication within FMOLHS hospitals, a proposed criterion for use and administration of the medication has been created. Intra-facility administration will use the pre-existing non-formulary process with pharmacy monitoring.

I.

Inclusion	**Exclusion**
Admitted ≥18 years	Pregnant/Breast Feeding
Positive COVID Test	GFR <30 ml/min or dialysis dependent
Required supplemental oxygen to maintain saturation >90% (>2 L nasal cannula)	ALT/AST > 5x upper limit of normal
Radiograph with evidence of pneumonia	Age < 18
<18 years but ≥40 kg and ≥12 years	Known Hypersensitivity
	*Platelet count less than 50K
	*Bilirubin > 2
	*EF less than 10%

*Trial Exclusion Language: Evidence of multiorgan failure including but not limited to coagulopathy (significant thrombocytopenia), hepatic failure (elevated bilirubin) or renal failure (low urine output or estimated glomerular filtration rate[eGFR]< 30mL/min), or significant cardiomyopathy (low cardiac output).

II.

Criteria for Discontinuation
Development of ALT levels ≥5 upper limit of normal
Development of AST levels ≥5 upper limit of normal
Bilirubin ≥ 2
Acute anaphylactic reaction during infusion
Estimated GFR drops to < 30 ml/min*

*due to decreased renal clearance of sulfobutylether-beta-cyclodextran sodium in remdesivir formulation

III. **Duration of therapy:** 5 days (loading dose of 200mg on day 1, followed by 100mg on day 2-5)[10,11]

IV. **Population Selection[9-11]:**

- Medication is recommended for use in patients requiring supplemental oxygen (>2 L nasal cannula to maintain saturation of greater than 90%) within the first 14 days of symptom onset.
- Medication is recommended for potential use in patients on mechanical ventilation only if within the first 7 days of symptom onset.

Consideration for the Initiation of Bamlanivimab in COVID-19

For non-hospitalized adult patients (≥18 years old) with symptomatic mild-to-moderate COVID-19, **bamlanivimab** may be considered, as authorized by Emergency Use Authorization (EUA) by the Food and Drug Administration (FDA) on 11/10/20. Due to limited medication supply, patients being considered for banlanivimab should meet all of the following criteria:

I. **Authorized use criteria** *(Patients must meet all of the following criteria)*

a. Non-hospitalized
b. ≤7 days from initial symptom onset
c. Age ≥18 years
d. Weight ≥40kg
e. High risk for progressing to severe COVID-19 and/or hospitalization (Must meet ≥1 criteria below)

General risk factors:	Immunosuppressive/high risk disease:
• BMI ≥35 *OR* • Chronic kidney disease *OR* • Diabetes *OR* • Age ≥65 *OR*	• HIV infection with CD4 count ≤200 *OR* • Solid organ or stem cell transplant *OR* • Sickle cell disease
Age ≥55 AND one of the following:	**Receiving immunosuppressive treatment:**
• Cardiovascular disease *OR* • Hypertension *OR* • COPD *OR* • Other chronic respiratory illness	• Chemotherapy in the past year *OR* • Immunosuppressant use for autoimmune disease *OR* • Prednisone ≥20 mg/day (or equivalent) for ≥14 days

II. **Limitations of Authorized Use**

a. Bamlanivimab is not authorized for use in patients:
   i. Who are hospitalized due to COVID-19, OR
   ii. Who require oxygen therapy due to COVID-19, OR
   iii. 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.
b. Benefit of treatment with bamlanivimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

III. **Dose:** Single intravenous (IV) infusion of 700 mg over at least 60 minutes

IV. **Contraindications:** None

V. **Monitoring:**

a. No laboratory monitoring indicated
b. Clinical monitoring for 60 minutes post infusion

VI. **Special considerations:**

a. In patients who have received the first COVID-19 vaccine dose, bamlanivimab can still be given.
b. The second COVID-19 vaccine dose should be delayed for at least 90 days after receiving bamlanivimab to avoid potential interference of the antibody therapy with vaccine-induced immune responses.

VII. **Adverse Effects and Precautions:**

a. Symptoms including nausea, diarrhea, dizziness, headache, pruritus, and vomiting were observed in clinical trials, though at rates comparable to placebo.
b. Potential for serious hypersensitivity reaction, including anaphylaxis or infusion related reactions
    i. Signs and symptoms of infusion reactions may include: fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, dizziness.
    ii. If an infusion reaction occurs, stop drug infusion and contact provider for further instructions.
    iii. If anaphylaxis occurs, standard protocol should be followed

VIII. **Restrictions, Approvals, and Ordering:**

a. The EUA Fact Sheet should be provided to the patient and/or caregiver and documentation that it was reviewed should be placed in the clinical record.
b. Medication errors and/or serious adverse events should be reported to the OLOL Main Pharmacy. They will assist with submitting the required FDA Medwatch reports within 7 days of event.

IX. **Obtaining the medication**

a. After patients have patients have confirmed desire to receive bamlanivimab and the provider/pharmacy have confirmed that the patient meets appropriate criteria, the dose can be requested from pharmacy.

X. **Administration**

a. Spike and prime the medication using a Polyvinylchloride (PVC) infusion set containing a 0.20/0.22 micron in-line polyethersulfone (PES) filter.
b. Administer the infusion solution via pump at a rate of 200mL/hr (over 60 minutes).
c. Clinically monitor patients during administration for signs of infusion reactions (listed above).
d. If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care.
e. Once infusion is complete, flush the infusion line to ensure delivery of the required dose.
f. Discard unused product.
g. Clinically monitor patients for at least 1 hour after infusion is complete.

MRSA Nasal Swabs for De-escalation of Anti-MRSA Therapy in Pneumonia

Background: Empiric antimicrobial therapy in pneumonia remains a challenge, especially among COVID-19 patients where sputum cultures are more difficult to obtain. De-escalation of anti-MRSA coverage is usually guided by the results of sputum cultures (which can take >48hrs) or negative blood cultures at 48hrs. Due to the potential increased risk of AKI in COVID-19 patients, the task force has recommended against the use of vancomycin for MRSA coverage in the absence of severe sepsis or concerns for bloodstream infections. Linezolid, recommended as the first-line option for COVID patients, continues to demonstrate supply issues due increased usage nationally.

Plan: In an effort to decrease rates of anti-MRSA therapy, the task force recommends the implementation of routine MRSA nasal swabs for all COVID-19 patients (suspected or confirmed) requiring anti-MRSA therapy. Nasal MRSA PCR tests are widely utilized for the purposes of deescalating anti-MRSA therapy in the treatment of pneumonia. Many studies have shown that negative MRSA nasal PCR are very reliable in ruling out MRSA involvement in pneumonia (negative predictive value >98%).

Process:

Step 1: Ordering of MRSA nasal swab

1. COVID order set
    a. Can be selected under the labs section (not pre-checked)
    b. Under the anti-MRSA therapy section (will be automatically added when linezolid or vancomycin are selected)
2. Ordered manually by providers at the time of placing order for anti-MRSA therapy
    a. Search MRSA nasal under orders
3. Ordered by clinical pharmacist when reviewing patients on anti-MRSA therapy
    a. If no order has been placed, the clinical pharmacist will place an order per protocol
    b. The swab will not be ordered if the patient has received anti-MRSA therapy for >48 hours

Step 2: Sample collection

1. RN will collect nasal swab sample during next entry into patient room
2. MRSA nasal swab kits will be stocked with usual culture supplies (different than RVP swab)

Step 3: Result

1. Negative result
    a. Provider can discontinue MRSA coverage if no alternative indication exists
        i. Consider utilizing standard practices for de-escalation in patients with an alternative source of infection or severe sepsis
        ii. Lower NPV shown in some studies (~94%) in patients with VAP
    b. Clinical pharmacist will call provider to discuss if they identify the result first
2. Positive result
    a. Utilize standard practices (ex: sputum culture results, negative blood cultures, clinical status) for de-escalation in these cases.
    b. Positive MRSA nasal swab does not mean that the patient has MRSA pneumonia (very low positive predictive value ~30%)

Note: The negative predictive value of MRSA nasal swabs is lower for alternative infection sites. Use of MRSA nasal swabs for de-escalation of anti-MRSA therapy in infections **other** than pneumonia is **NOT** recommended.

COVID-19 Anticoagulation Recommendations

Disclaimer: At this time, there are no published RCTs to determine a standard dosing strategy for venous thromboembolism (VTE) prophylaxis in patients with COVID-19 infection. The current standard of care VTE prophylaxis is enoxaparin 40mg daily (nl GFR). Potential increased dosing strategies may be implemented based on clinician's evaluation given reported increased risk of VTE in COVID + patients.

****Based on a press release, the NIH sponsored ACTIV-4, REMAP-CAP, and ATTACC trials comparing therapeutic anticoagulation strategies have been halted due to futility. It is NOT recommended to use therapeutic anticoagulation in patients with COVID-19 infection unless there is a co-existing accepted indication where therapeutic anticoagulation is necessary.[6]**

Background:
Patients with COVID-19 infection have been reported to have elevated rates of VTE, which may be caused by the disease state itself or elevated presence of risk factors such as immobility. As a result, additional guidance on VTE prophylaxis and treatment was created. An internal quality OLOLRMC dataset of 51 inpatient SARS-CoV-2 + patients demonstrated a VTE rate of approximately 50% when formal duplex ultrasound was ordered with clinical suspicion.

Risk factors for VTE:
Immobility (due to limited PPE resources for routine ambulation), Obesity, Advanced age (≥ 50 years), Recent surgery or trauma, Sepsis, Pregnancy, Cancer, SARS-CoV 2 +

Pharmacologic VTE Prophylaxis	
CrCl >30	**CrCl <30**
Enoxaparin 40mg q12hr	Enoxaparin 30mg q12hr

Recommended clinical parameters to potentially guide necessity for advanced diagnostic procedures and treatment if confirmed positive:

- Recurrent fever after initial resolution, abrupt declination in oxygen status.

Pharmacologic VTE Treatment After Confirmation of a DVT or PE		
Critically Ill (Unable to take PO/ concern for poor absorption)	**Enteral route available** (Not tolerating diet or renal dysfunction)	**Enteral route available** (Tolerating full diet and CrCl >15mL/min)
Enoxaparin 1mg/kg q12hr	Apixaban 10mg PO q12hr x7 days then Apixaban 5mg PO q12hr	Rivaroxaban 15mg PO q12hr then Rivaroxaban 20mg q24hr *Take with food to increase absorption
CrCl <30: Enoxaparin 1mg/kg q24hr	Hemodialysis: Apixaban 5mg PO q12hr x7 days then Apixaban 2.5mg PO q12hr	CrCl <15: Do not use

*Consider monitoring anti-Xa levels in obesity (>150kg) and/or renal impairment (CrCl <30mL/min). Link to guidance on anti-Xa monitoring listed below.
https://fparchives.com/ololrmc/documents/Anti-Xa%20Monitoring%20Protocol%20(July%202015).pdf

Link to printable COVID-19 Anticoagulation Recommendation Flowsheet listed below:
https://fparchives.com/ololrmc/documents/Anticoagulation%20Guidance.pdf

References

COVID-19 Literature:

1. Rawson T, Moore L, et al. Bacterial and fungal co-infection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing. CID. 2 May 2020. ciaa530
2. Horby, P, Lim W, Emberson JR, et al. Dexamethasone in Hospitalized Patients with Covid-19—Preliminary Report. NEJM. 17 July 2020. DOI: 10.1056/NEJMoa2021436
3. Tomazini BM ,Maia IS, Cavalcanti AB, et al; COALITION COVID-19 Brazil III Investigators. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. *JAMA*.2 September 2020. doi:10.1001/jama.2020. 17021
4. Dequin PF, Heming N,Meziani F ,et al; CAPE COVID Trial Group and the CRICS-TriGGERS ep Network. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: a randomized clinical trial. *JAMA*. 2 September 2020. doi:10. 1001/jama.2020.16761
5. The Writing Committee for REMAP-CAP Investigators. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 Corticosteroid Domain randomized clinical trial. *JAMA*. 2 September 2020. doi:10. 1001/jama.2020.17022
6. The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA*. Published online September 2, 2020. doi:10.1001/ jama.2020.17023
7. Prescott HC, Rice TW. Corticosteroids in COVID-19 ARDS: Evidence and Hope During the Pandemic. *JAMA.* 2 September 2020. doi:10.1001/jama.2020.16747
8. Zhou Y, Qin Y, Lu Y, et al. Effectiveness of glucocorticoid therapy in patients with severe novel coronavirus pneumonia: protocol of a randomized controlled trial. *Chin Med J (Engl).* March 2020.
9. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19–Final report. *N Engl J Med*. 2020.
10. Pan H, Peto R, Karim QA, et al. Repurposed antiviral drugs for COVID-19-interim WHO SOLIDARITY trial results. 15 October 2020. medRxiv preprint. doi.org/10.1101/2020.10.15.20209817.
11. Goldman JD, Lye DC, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. NEJM. 27 May 2020. DOI: 10.1056/NEJMoa2015301
12. Spinner CD, Gottlieb RL, Criner RL, et al. Effect of Remdesivir vs Standard of Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. *JAMA.* 21 August 2020. doi:10.1001/jama.2020.16349
13. National Institutes of Health. COVID 19 Treatment guidelines. 30 July 2020. https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/remdesivir/
14. Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med*. March 2020.
15. Kalil, AC, Patterson TF, Mehta AK, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. *N Eng J Med.* 11 December 2020. DOI: 10.1056/NEJMoa2031994.
16. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. *BMJ*. 2020;369:m1849.
17. Cavalcanti, AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. *N Eng J Med.* 23 Jul 2020. DOI: 10.1056/NEJMoa2019014
18. Skipper CP, Pastick KA, Engen NW, et al. Hydroxychloroquine in Nonhospitalized Adults with Early COVID-19: A Randomized Trial. *Ann Intern Med.* 16 July 2020. doi:10.7326/M20-4207
19. Self WH, Semler MW, Leither LM, et al. Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients With COVID-19: A Randomized Clinical Trial. *JAMA*. 9 November 2020. doi:10.1001/jama.2020.22240
20. Saleh M, Gabriels J, et al. The effect of chloroquine, hydroxychloroquine and azithromycin on the corrected QT interval in patients with SARS-CoV-2 infection. Circulation. 29 Apr 2020.
21. Mercuro N, Yen C, et al. Risk of QT prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19). JAMA Cardiol. 1 May 2020.
22. Xu X, Han M, Li T et al. Effective Treatment of Severe COVID-19 Patients with Tocilizumab. *Proc Natl Acad Sci USA.* 29 April 2020. doi: 10.1073/pnas.2005615117
23. Rosas IO, Brau N, Waters M et al. Tocilizumab in Hospitalized Patients with COVID-19 Pneumonia. medRxiv preprint. 1 September 2020. doi:10.1101/2020.08.27.20183442
24. Salvarani C, Dolci G, Massari M, et al. Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized with COVID-19 Pneumonia. *JAMA Intern Med.* 20 October 2020. doi: 10.1001/jamainternmed.2020.6615
25. Hermine O, Mariette X, Tharaux P, et al. Effect of Tocilizumab vs Usual Care in Adults Hospitalized with COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. *JAMA Intern Med.* 20 October 2020. doi: 10.1001/jamainternmed.2020.6820
26. Stone JH, Frigault MJ, Serling-Boyd NG, et al. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. *N Eng J Med.* 21 October 2020. doi: 10.1056/NEJMoa2028836
27. Kimming LM, Wu D, Gold M, et al. IL6 Inhibition in critically ill COVID-19 patients is associated with increased secondary infections. (preprint). 6 July 2020. doi.org/10.1101/2020.05.15.20103531
28. Regeneron Pharmaceuticals webpage 2020. https://www.regeneron.com/covid19
29. Regeneron Pharmaceuticals Press Release. 29 September 2020. https://www.prnewswire.com/news-releases/regenerons-regn-cov2-antibody-cocktail-reduced-viral-levels-and-improved-symptoms-in-non-hospitalized-covid-19-patients-301140336.html
30. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. NEJM. 28 Oct 2020. DOI: 10.1056/NEJMoa2029849
31. Eli Lilly and Company. Fact sheet for health care providers Emergency Use Authorization (EUA) of bamlanivimab. Nov 2020. https://www.fda.gov/media/143604/download
32. A Neutralizing Monoclonal Antibody for Hospitalized Patients with Covid-19. NEJM. 22 Dec 2020. DOI: 10.1056/NEJMoa2033130.
33. Ishima T, Fujita Y, Hashimoto K. Interaction of new antidepressants with sigma-1 receptor chaperones and their potentiation of neurite outgrowth in PC12 cells. Eur J Pharmacol. 2014 Mar 15;727:167-73. doi: 10.1016/j.ejphar.2014.01.064. Epub 2014 Feb 5. PMID: 24508523.
34. Lenze EJ, Mattar C, Zorumski CF, et al. Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19: A Randomized Clinical Trial. *JAMA.* 12 November 2020. Doi: 10.1001/jama.2020.22760
35. Caly L, Druce JD, Catton MG, et al. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res*. 2020 Jun;178:104787.
36. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N,, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Muller MA, Drosten C, Pohlmann S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020.
37. Kreutz R, Algharably E, et al. Hypertension, the renin–angiotensin system, and the risk of lower respiratory tract infections and lung injury: implications for COVID-19: European Society of Hypertension COVID-19 Task Force Review of Evidence. *Cardiovascular Research*, cvaa097.
38. Reynolds H, Adhikari S, et al. Renin–Angiotensin–Aldosterone System Inhibitors and Risk of Covid-19. NEJM. 1 May 2020. DOI: 10.1056/NEJMoa2008975
39. Lam, KW, Chow, KW, et al. Continued in-hospital ACE inhibitor and ARB Use in Hypertensive COVID-19 Patient is Associated with Positive Clinical Outcomes. *The Journal of Infectious Diseases.* 23 July 2020. doi.org/10.1093/infdis/jiaa447

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References

MRSA Nasal Swabs:

1. Carr AL, Daley MJ, Givens Merkel K, et al. Clinical Utility of Methicillin-Resistant Staphylococcus aureus Nasal Screening for Antimicrobial Stewardship: A Review of Current Literature. Pharmacotherapy. 2018 Dec;38(12):1216-1228.
2. Giancola SE, Nguyen AT, Le B, et al. Clinical utility of a nasal swab methicillin-resistant Staphylococcus aureus polymerase chain reaction test in intensive and intermediate care unit patients with pneumonia. Diagn Microbiol Infect Dis. 2016 Nov;86(3):307-310.
3. Parente DM, Cunha CB, Mylonakis E, Timbrook TT. The Clinical Utility of Methicillin Resistant Staphylococcus aureus (MRSA) Nasal Screening to Rule Out MRSA Pneumonia: A Diagnostic Meta-analysis with Antimicrobial Stewardship Implications. Clin Infect Dis. 2018;67(1):1-7.

Anticoagulation References:

1. Ludwig KP, Simons, HJ et al. Implementation of an Enoxaparin Protocol for Venous Thromboembolism Prophylaxis in Obese Surgical Intensive Care Unit Patients. Annals of Pharmacotherapy. November 2011 (45) 1356-62.
2. Bickford, A, Majercik, S et al. Weight-based enoxaparin dosing for venous thromboembolism prophylaxis in the obese trauma patient. The American Journal of Surgery. 2013 (206); 847-852.
3. Mavrakanas, Thomas A., et al. “Apixaban Pharmacokinetics at Steady State in Hemodialysis Patients.” Journal of the American Society of Nephrology, vol. 28, no. 7, 2017, pp. 2241–2248., doi:10.1681/asn.2016090980.
4. Siontis, Konstantinos C., et al. “Outcomes Associated With Apixaban Use in Patients With End-Stage Kidney Disease and Atrial Fibrillation in the United States.” Circulation, vol. 138, no. 15, Sept. 2018, pp. 1519–1529., doi:10.1161/circulationaha.118.035418.
5. Schafer, Joseph H., et al. “Safety and Efficacy of Apixaban Versus Warfarin in Patients With Advanced Chronic Kidney Disease.” Annals of Pharmacotherapy, vol. 52, no. 11, May 2018, pp. 1078–1084., doi:10.1177/1060028018781853.
6. https://www.medpagetoday.com/infectiousdisease/covid19/90351