Joint Pulmonary Critical Care Medicine, Hematology, Nephrology, Cardiology and Pharmacy
Anticoagulation Guidance for Patients with COVID-19

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COVID-19 may predispose to both venous and arterial thromboembolic disease due to excessive inflammation, hypoxia, immobilization and diffuse intravascular coagulation (DIC), especially in severe cases. Current evidence emphasizes the need to apply pharmacologic thromboprophylaxis in all hospitalized COVID-19 patients and there is insufficient data to recommend for or against the use of higher than prophylactic dose of anticoagulation for VTE prophylaxis outside of a clinical (ref- ASH). However, optimal anticoagulant dosing to reduce thrombotic complications is being actively investigated. For instance, a large National Institutes of Health (NIH) multiplatform, adaptive-design trial that incorporates three global studies/networks (REMAP-CAP, ATTACC, and ACTIV-4A) was set up to address the question of whether more intensive anticoagulation is indicated in critically ill or moderately ill patients. Providers should also be vigilant in monitoring for signs of thromboembolic disease and order appropriate labs and diagnostic tests if clinical suspicion for VTE is high.

Key Hematologic Characteristics in COVID-19:
- COVID-19-associated coagulopathy can result in microvascular thrombosis, venous thromboembolism, and consumption of coagulation factors.
  - Most common pattern: increased fibrinogen and D-dimer levels, degree of aPTT elevation is often less than PT elevation, mild thrombocytopenia (platelet count ~ 100 k/mm$^3$), lack of microangiopathy
  - Severe COVID-19 infection reflected by DIC: thrombocytopenia, prolongation of PT/INR, elevation of D-dimer and fibrin degradation products, and decreased fibrinogen (< 1 g/L). Fibrinogen noted to drop dramatically over 3 days.

Key Recommendations:
- All adult patients (including non-critically ill) who require hospital admission for COVID-19 should receive prophylactic dose low molecular weight heparin (LMWH, e.g., enoxaparin), unless contraindicated.
  - Dosing and selection of medication should take into consideration individual patient factors including weight, BMI, renal function, HIT history, coagulation status, concomitant indications for anticoagulation, & any potential drug-drug interactions.
  - Low-dose unfractionated heparin (LDUH) or reduced-dose LMWH may be considered for patients with substantial renal impairment (i.e., CrCl < 30 mL/min).
  - Contraindications include active bleeding, platelet count less than 25 k/mm$^3$, or fibrinogen less than 0.5 g/L.
  - Mechanical thromboprophylaxis (with sequential compression devices) should be used when pharmacological thromboprophylaxis is contraindicated

- The COVID-19 VTE Prophylaxis and Treatment Algorithm on the next page contains details for recommended VTE prophylaxis and treatment medications and dosing – in general:
  - VTE prophylaxis (including those requiring ICU level of care): Use standard VTE prophylaxis strategies (preferably LMWH) with dosage adjustments for renal function and body weight/BMI
  - VTE treatment for patients with confirmed VTE or high clinical suspicion for VTE: Use standard dosing for treatment of thromboembolism – selection of agent should take into consideration renal function. Treatment with enoxaparin is recommended unless contraindicated.
  - Consider Hematology and Pharmacy consultation for patients with HIT, history of HIT, or heparin/LMWH allergy
  - Consider anti-Xa level monitoring in patients who are on intermediate or therapeutic dose enoxaparin
  - HOLD prophylactic recommendations FOR COVID-19 patients with platelet count less than 25 k/mm$^3$ and fibrinogen less than 0.5 g/L
COVID-19 VTE Prophylaxis and Treatment Algorithm

PUI or COVID-19 Positive
Labs to be monitored at baseline and as needed:
D-dimer, PT, PTT, fibrinogen, CMP, and CBC with differential

VTE Prophylaxis

BMI < 40 kg/m²

ABW 45 kg or more:
• CrCl ≥ 30 ml/min:
  Enoxaparin 40mg SubQ daily
• CrCl < 30 ml/min:
  Enoxaparin 30mg SubQ daily
• HD:
  Heparin 5000 units SubQ Q8h
• Hx HIT:
  Fondaparinux 2.5mg SubQ daily

ABW < 45 kg:
• Enoxaparin 30mg SubQ daily
• HD:
  Heparin 5000 units SubQ Q12h
If contraindicated, PLT < 25,000 or bleeding:
• Mechanical thromboprophylaxis

BMI ≥ 40 kg/m²

• CrCl ≥ 30 ml/min:
  Enoxaparin 40mg SubQ Q12h
• CrCl < 30 ml/min:
  Heparin 5000 units SubQ Q8h OR
  Enoxaparin 40mg SubQ daily
• HD:
  Heparin 5000 units SubQ Q8h
• Hx HIT, ABW > 50 kg:
  Fondaparinux 2.5mg SubQ daily
If contraindicated, PLT < 25,000 or bleeding:
• Mechanical thromboprophylaxis

Confirmed VTE or High clinical suspicion of VTE

Treatment Dose Anticoagulation

• CrCl ≥ 30 ml/min:
  Enoxaparin 1mg/kg (ABW) SubQ Q12h
  OR Enoxaparin 1.5mg/kg (ABW) SubQ daily
• CrCl < 30 ml/min:
  Heparin 5000 units SubQ daily OR
  Heparin continuous IV infusion per protocol
• HD:
  Heparin continuous IV infusion per protocol
• Hx HIT:
  Fondaparinux (see dosing below) or Argatroban drip per protocol
  ABW < 50 kg:
  Fondaparinux 5mg SubQ daily
  ABW 50-100 kg:
  Fondaparinux 7.5mg SubQ daily
  ABW > 100 kg:
  Fondaparinux 10mg SubQ daily

HOLD prophylactic anticoagulation for COVID-19 patients with platelet count less than 25 k/mm³ or fibrinogen less than 0.5 g/L (or 50 mg/dL)

NOTE:
• For patients with HIT consider Hematology and Pharmacy consultation (RVAT)
• For patients with up trending D-dimer levels along with clinical deterioration – consider LE Doppler and POC echo. If patient unable to get US or echo due clinical status and clinical suspicion for PE remains high, consider treating with full dose anticoagulation (unless contraindicated) over obtaining any diagnostics testing
• Providers may consider monitoring anti factor Xa levels in certain patient populations, including those patients <45 kg, BMI ≥ 40 kg/m², or with impaired renal function.
• When necessary, the anti Xa level should be drawn ~3-4 hours after enoxaparin administration.

<table>
<thead>
<tr>
<th>Goal anti-Xa level (should be obtained ~3-4 hrs after dose administered)</th>
<th>Prophylaxis - Enoxaparin 1 mg/kg SubQ twice daily</th>
<th>Treatment – based on Enoxaparin 1 mg/kg SubQ twice daily</th>
<th>Treatment – based on Enoxaparin 1.5 mg/kg SubQ daily</th>
</tr>
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<tbody>
<tr>
<td>0.2-0.5 units/mL</td>
<td>0.5-1 units/mL</td>
<td>1-2 units/mL</td>
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</tbody>
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• Based on lab values, doses can be adjusted empirically and then the assay should be repeated.
Lab Monitoring:
- All patients admitted for COVID-19 should have the following tests obtained at baseline and follow up testing based on clinical course: D-dimer, PT, PTT, fibrinogen, CMP and CBC with differential.
- For patients with up trending D-dimer levels along with clinical deterioration:
  - Consider CTA, LE Doppler and POC echo
  - If patient unable to get CTA, US or echo due to clinical status and clinical suspicion for PE remains high, consider treating with full dose anticoagulation (unless contraindicated) over obtaining any diagnostics testing
  - PLEASE NOTE: Changes in D-dimer levels from normal to abnormal, or a rapid increase on serial monitoring, alone is not diagnostic of PE/DVT – other clinical signs or further deterioration should accompany the decision to initiate therapeutic anticoagulation if VTE cannot be confirmed.

Patients with Renal Failure Requiring Kidney Replacement Therapy
- Patients with COVID-19 and renal failure requiring kidney replacement therapy (ie dialysis/hemofiltration) have been noted to have increased risk of circuit clotting.
- Recommended regional anticoagulation with heparin (bolus 5000 units, followed by 1000 units/hr) OR regional citrate anticoagulation if established protocol.
- Strongly consider systemic anticoagulation (targeting PTT equivalent to VTE/PE protocol) if ongoing circuit clotting (e.g. circuit clots 2 times within one shift).

Special Considerations During Pregnancy and Lactation
- Pregnancy itself is a hypercoagulable state, however, it is not yet known whether COVID-19 increases this risk. In several cohort COVID-19 studies, VTE was not reported as a complication however use of anticoagulants in either prophylactic or treatment dosing varied.
- For pregnant patients hospitalized for severe COVID-19, prophylactic anticoagulation is recommended unless contraindicated.
  - The American College of Obstetricians and Gynecologists (ACOG) advises that VTE prophylaxis can reasonably be considered for hospitalized pregnant COVID-19 patients (especially those with severe disease) despite there being no data for or against thromboprophylaxis in this population.
  - LMWH is the preferred anticoagulant during pregnancy for VTE prophylaxis in COVID-19 patients.
- VTE prophylaxis after hospital discharge is not recommended for pregnant patients – decisions to continue VTE prophylaxis in pregnancy should be individualized, considering concomitant VTE risk factors.

Anticoagulation on Quarantined Patients at Home (NOT Post-discharge)
- The role of thromboprophylaxis for quarantined patients with mild COVID-19 but significant co-morbidities, or for patients without COVID-19 who are less active because of quarantine is uncertain. These patients should be advised to stay active at home.
- In the absence of high-quality data, pharmacological prophylaxis should be reserved for those at highest risk patients, including those with limited mobility and history of prior VTE or active malignancy.

Anticoagulation on Patient Discharge
- After hospital discharge from acute medical illness, extended thromboprophylaxis can reduce the risk of VTE, at the cost of increase in bleeding events, including major bleeding. As part of discharge planning for COVID-19 patients, chronic disease states, the prior-to-admission medication list, and
thrombotic/bleeding risk should be considered. The COVID-19 Post-discharge Anticoagulation Recommendations on the next page details recommendations for discharge planning – in general:

- Patients who were on long-term anticoagulation prior to admission for another treatment indication should continue the previously prescribed medication unless contraindicated. The anticoagulation plan should be evaluated for potential need for “bridging” therapy and/or follow-up monitoring to achieve an adequate level of therapeutic anticoagulation.
- Patients with a newly diagnosed VTE during hospital admission should follow standard of care with therapeutic anticoagulation for 3 months. Longer duration (or chronic therapy) may be warranted based on other prothrombotic conditions and/or previous thrombotic history.
- While no data specific to COVID-19 exist, it is reasonable to employ individualized risk stratification for thrombotic and hemorrhagic risk, followed by consideration of extended prophylaxis (for up to 45 days) for patients with elevated risk of VTE (e.g., reduced mobility, active cancer, h/o VTE) who have low risk of bleeding.

COVID-19 Post-discharge Anticoagulation Recommendations

**COVID-19 Positive Patient Ready for Discharge**

- Prior-to-Admission indication for chronic anticoagulation
  - Continue previously prescribed anticoagulant unless contraindicated
  - Assess need for “bridging” therapy and follow-up monitoring
- Newly diagnosed VTE during hospitalization
  - Therapeutic anticoagulation for 3 months (LMWH, DOAC, or Warfarin with INR goal 2-3)
  - Longer duration (or chronic therapy) may be warranted based on other prothrombotic conditions and/or previous thrombotic history
- No other specific diagnosis for long-term anticoagulation

**Anticoagulation based on Thrombotic Risk Stratification**

- **Low Risk**
  - No risk factors
  - No long-term prophylaxis recommended
  - Aspirin 81mg PO daily can be considered upon discharge
  - Advise to stay active at home and monitor

- **High Risk**
  - Co-morbidities, immobility, prior VTE history, cancer, and no bleeding risks, etc.
  - Post-discharge thromboprophylaxis with either LMWH, DOAC, or warfarin for 45 days with follow-up
    - Enoxaparin 40mg SubQ daily (preferred)
    - Apixaban (Eliquis) 2.5mg PO twice daily,
    - Rivaroxaban (Xarelto) 10mg PO daily
    - OR
    - Warfarin dose-adjusted to goal INR 2-3
  - Selection of agent and dosing should factor in renal function, age, body weight, insurance coverage, and patient’s ability to administer (e.g. for subcutaneous injections)
  - At the physician’s discretion, patient should follow-up at either 2 or 4 weeks post discharge to assess mobility, assess for presence of VTE, assess need for outpatient diagnostic imaging, and need for continuation of VTE prophylaxis