Anticoagulation Dosing Guideline for Adult COVID-19 Patients

Enoxaparin is the preferred first line anticoagulant for patients diagnosed with COVID-19. The incidence of HIT with enoxaparin is less than 1%.

**VTE Prophylaxis:**
VTE prophylaxis will be considered for COVID-19 patients who are low risk.

**Low risk COVID-19 patient**
1. Not receiving mechanical ventilation
2. D-Dimer ≤ 6 mg/L
3. ESRD on iHD without clotting

<table>
<thead>
<tr>
<th>Kidney Function</th>
<th>BMI (kg/m²)</th>
<th>Dosing of Enoxaparin</th>
<th>Concern for HIT or LMWH Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCL ≥ 30 mL/min</td>
<td>18.5-39.9</td>
<td>30mg SUBQ Q12H</td>
<td>Consult Hematology</td>
</tr>
<tr>
<td></td>
<td>40-49.9</td>
<td>40mg SUBQ Q12H</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 50</td>
<td>60mg SUBQ Q12H</td>
<td></td>
</tr>
<tr>
<td>CrCL &lt; 30 mL/min</td>
<td>18.5-39.9</td>
<td>30mg SUBQ Q24H</td>
<td>Consult Hematology</td>
</tr>
<tr>
<td>OR ESRD/AKI on RRT</td>
<td>≥ 40</td>
<td>40mg SUBQ Q24H</td>
<td></td>
</tr>
</tbody>
</table>

**Special Population:** < 18.5 (or weight < 50kg) Heparin 2500 SUBQ Q8H Consult Hematology

*Contraindications: Platelets < 25 K/uL or Fibrinogen < 50 mg/dL or active bleeding

**Therapeutic anticoagulation**
Therapeutic anticoagulation will be considered for COVID-19 patients who are considered high risk or diagnosed with an acute VTE.

**High risk COVID-19 patient (for all hospitalized patients):**
- Receiving mechanical ventilation AND D-dimer ≥ 6 mg/L OR
- Acute kidney injury (Scr increase > 0.3 mg/dL above baseline) +/- CVVHD/AVVHD/SLED or IHD with clotting

**Anti-Xa level goals for enoxaparin therapy (when indicated):**
1. Therapeutic peak LMWH level (Drawn 4 hours after 3rd dose): 0.6-1 anti-Xa units/mL
2. Therapeutic trough LMWH level (Drawn 1 hour prior to 3rd dose): < 0.5 anti-Xa units/mL

<table>
<thead>
<tr>
<th>Kidney Function</th>
<th>BMI (kg/m²)</th>
<th>Dosing of Enoxaparin</th>
<th>Concern for HIT or LMWH Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCL ≥ 30 mL/min</td>
<td>12-49.9</td>
<td>1 mg/kg SUBQ Q12H</td>
<td>Bivalirudin infusion (see Anticoagulation COVID-19 guidelines for dosing)</td>
</tr>
<tr>
<td></td>
<td>≥ 50</td>
<td>0.8 mg/kg SUBQ Q12H</td>
<td>Consult pharmacist to assist with obtaining anti-Xa level and dose adjustment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*monitor peak anti-Xa level with 3rd dose</td>
<td></td>
</tr>
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<td>CrCL &lt; 30 mL/min</td>
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<td></td>
<td></td>
<td>*monitor peak anti-Xa level with 3rd dose</td>
<td></td>
</tr>
<tr>
<td>ESRD or AKI on RRT</td>
<td></td>
<td>0.8 mg/kg SUBQ Q24H (MAX dose 1mg/kg Q24H)</td>
<td>Bivalirudin infusion (see Anticoagulation COVID-19 guidelines for dosing)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*monitor peak and trough anti-Xa level with 3rd dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consult pharmacist to assist with obtaining anti-Xa level and dose adjustment</td>
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</tr>
</tbody>
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*Contraindications: Platelets < 50 K/uL or fibrinogen < 100 mg/dL or active bleeding

**Intra-dialytic anticoagulation for renal replacement therapy**
Nephrology service will determine the need for a booster dose of IV enoxaparin when ordering renal replacement therapy
- Renal replacement therapy (IHD/SLED/CRRT)
  - Enoxaparin 30 mg IV x 1 preferably prior to or within an hour of starting dialysis
  - If HIT positive or enoxaparin failure, recommend switching to bivalirudin

This guideline/pathway is not intended to be a substitute for clinical judgement. The risk of bleeding must be weighed against the risk of thrombosis and its consequences.
Anticoagulation in Pregnant Patients: Antenatal and Postpartum

Management of anticoagulation therapy during labor and delivery requires specialized care and planning and should be managed similarly in pregnant patients with COVID-19 as other conditions that require anticoagulation in pregnancy.

- **Prophylactic anticoagulation**
  - All low risk pregnant women with suspected or confirmed COVID-19 infection should receive prophylactic unfractionated heparin upon admission to reduce risk of venous thromboembolism

<table>
<thead>
<tr>
<th>Trimester</th>
<th>Dosing of Heparin</th>
<th>Concern for HIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>5000-7500 units SUBQ Q12H</td>
<td>Consult Hematology</td>
</tr>
<tr>
<td>2nd</td>
<td>7500-10000 units SUBQ Q12H</td>
<td></td>
</tr>
<tr>
<td>3rd</td>
<td>10000 units SUBQ Q12H</td>
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</tr>
</tbody>
</table>

- **Therapeutic anticoagulation**
  - For a high risk critically ill pregnant patient less than 22 weeks gestation or post-partum, enoxaparin should be considered

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>Kidney Function</th>
<th>BMI (kg/m²)</th>
<th>Dosing of Enoxaparin</th>
<th>Concern for HIT or LMWH Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 22</td>
<td>CrCL ≥ 30 mL/min</td>
<td>12-49.9</td>
<td>1 mg/kg SUBQ Q12H <strong>monitor peak anti-Xa level with 3rd dose</strong> • Consult pharmacist to assist with obtaining anti-Xa level and dose adjustment</td>
<td>Consult Hematology</td>
</tr>
<tr>
<td>≥ 50</td>
<td></td>
<td>0.8 mg/kg SUBQ Q12H <strong>monitor peak anti-Xa level with 3rd dose</strong> • Consult pharmacist to assist with obtaining anti-Xa level and dose adjustment</td>
<td>Consult Hematology</td>
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<td>12-49.9</td>
<td>1 mg/kg SUBQ 24H <strong>monitor peak anti-Xa level with 3rd dose</strong> • Consult pharmacist to assist with obtaining anti-Xa level and dose adjustment</td>
<td>Consult Hematology</td>
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<tr>
<td>≥ 50</td>
<td></td>
<td>0.8 mg/kg SUBQ 24H <strong>monitor peak anti-Xa level with 3rd dose</strong> • Consult pharmacist to assist with obtaining anti-Xa level and dose adjustment</td>
<td>Consult Hematology</td>
<td></td>
</tr>
<tr>
<td>ESRD or AKI on</td>
<td></td>
<td>0.8 mg/kg SUBQ 24H (MAX dose 1 mg/kg Q24H) <strong>monitor peak and trough anti-Xa level with 3rd dose</strong> • Consult pharmacist to assist with obtaining anti-Xa level and dose adjustment</td>
<td>Consult Hematology</td>
<td></td>
</tr>
<tr>
<td>RRT</td>
<td></td>
<td>If minor bleeding prior to obtaining steady state anti-Xa levels • Decrease dose to 0.5 mg/kg and monitor anti-Xa peak and trough with 1st dose of new regimen • Consult pharmacist to assist with obtaining anti-Xa levels and dose adjustment</td>
<td>Consult Hematology</td>
<td></td>
</tr>
</tbody>
</table>

*Contraindications: Platelets < 50 K/µL or fibrinogen < 100 mg/dL or active bleeding

  - For a high risk critically ill pregnant patient greater than 22 weeks gestation, unfractionated heparin should be considered due to its short half-life and reversibility
    - aPTTs should be monitored according to institutional protocol
  - Unfractionated heparin, low molecular weight heparin, and warfarin do not accumulate in breast milk and do not induce an anticoagulant effect in the newborn; therefore, they can be used in breastfeeding women with or without COVID-19 who require VTE prophylaxis or treatment
    - Direct-acting oral anticoagulants are not routinely recommended due to lack of safety data
    - Direct thrombin inhibitors should be used as a last line option with an assessment of benefit versus risk in patients who require anticoagulation and are unable to receive heparin products (e.g., heparin-induced thrombocytopenia) due to limited data available

This guideline/pathway is not intended to be a substitute for clinical judgement. The risk of bleeding must be weighed against the risk of thrombosis and its consequences.
Bivalirudin: therapeutic anticoagulation
Due to the liver injury that may be seen in patients with COVID-19, bivalirudin is the preferred direct thrombin inhibitor for the treatment of HIT, enoxaparin failure, or patients receiving extracorporeal membrane oxygenation (ECMO).

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Bivalirudin Initial dose (mg/kg/hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>0.15 +/- 0.1</td>
</tr>
<tr>
<td>30-60</td>
<td>0.08 +/- 0.04</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>0.05 +/- 0.02</td>
</tr>
<tr>
<td>IHD (25% clearance by HD filters) or CRRT</td>
<td>0.07 +/- 0.03</td>
</tr>
</tbody>
</table>

IHD - intermittent hemodialysis, CRRT – continuous renal replacement therapy

Dose adjustments:

<table>
<thead>
<tr>
<th>aPTT (seconds)</th>
<th>Dose adjustment</th>
<th>Monitoring recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>Increase infusion rate by 20%</td>
<td>Re-check aPTT 4 hours after rate change</td>
</tr>
<tr>
<td>50-80</td>
<td>No change</td>
<td>Re-check aPTT at 4 hours; if 2 consecutive aPTTs are at goal, check aPTT q 24 hours</td>
</tr>
<tr>
<td>&gt;80*</td>
<td>Decrease infusion rate by 20%</td>
<td>Re-check aPTT 4 hours after rate change</td>
</tr>
</tbody>
</table>

* If aPTT >3x baseline, consider holding infusion for 1 hour and re-starting at 50% lower rate

- Monitoring:
  - aPTT q 4 hours following initiation of infusion and following dosing adjustment – target aPTT 50-80
  - If 2 consecutive aPTTs are at goal, check aPTT q 24 hours
  - CBC as appropriate based upon clinical status of patient

Bivalirudin for renal replacement therapy
- CVVH: no loading dose, bivalirudin 2 mg/hour one hour prior to RRT until completion
  - If doses of 2 mg/hour are ineffective, increase bivalirudin dose by 20%

Transition from therapeutic enoxaparin to an oral anticoagulant
- Prior to discharge:
  - All high-risk patients previously on therapeutic anticoagulation without a confirmed VTE may transition to a DOAC at prophylactic doses
    - Rivaroxaban 10 mg daily (for patients with a CrCl > 30 ml/min) OR apixaban 2.5 mg bid x 4 weeks
      - In patients who do not have insurance coverage for a DOAC or in whom a DOAC may be contraindicated, prophylactic doses of enoxaparin may be used for the time frame listed above
      - Warfarin may be considered in patients who have confirmed HIT
  - All high-risk patients on therapeutic anticoagulation for a confirmed VTE may transition to a DOAC at treatment doses
    - Rivaroxaban 15 mg bid x 21 days followed by 20 mg daily thereafter OR apixaban 10 mg bid x 7 days followed by 5 mg bid thereafter
      - In patients who do not have insurance coverage for a DOAC or in whom a DOAC may be contraindicated, treatment doses of enoxaparin may be continued for the time frame listed above
      - Warfarin may be considered in patients who have confirmed HIT
**Determine COVID risk status**

**Low risk:**
- Not receiving mechanical ventilation
- D-dimer < 6 mg/L
- ESRD on iHD without clotting

**High risk:**
- Receiving mechanical ventilation AND D-dimer ≥ 6 mg/L
- Acute kidney injury (Scr increase 0.3 mg/dL above baseline) +/- CVVHD/AVVHD/SLED or IHD with clotting

- **Recommend Prophylactic Dose Enoxaparin**
  - **BMI 18.5 – 39.9 kg/m²**
    - CrCl ≥ 30 ml/min: Enoxaparin 30 mg SUBQ q 12 hours
    - CrCl < 30 ml/min: Enoxaparin 30 mg SUBQ q 24 hours
  - **BMI > 40 kg/m²**
    - CrCl ≥ 30 ml/min: Enoxaparin 40 mg SUBQ q 12 hours
    - CrCl < 30 ml/min: Enoxaparin 40 mg SUBQ q 24 hours
  - **BMI > 50 kg/m²**
    - CrCl ≥ 30 ml/min: Enoxaparin 60 mg SUBQ q 12 hours
    - CrCl < 30 ml/min or ESRD on iHD: Enoxaparin 40 mg SUBQ q 24 hours

- **Concern for HIT/LMWH failure**

- **Recommend Therapeutic Dose Enoxaparin**
  - **BMI 12 – 49.9 kg/m²**
    - CrCl ≥ 30 ml/min: Enoxaparin 0.8 mg/kg SUBQ q 12 hours
    - CrCl < 30 ml/min: Enoxaparin 0.8 mg/kg SUBQ q 24 hours
  - **BMI > 50 kg/m²**
    - CrCl > 30 ml/min: Enoxaparin 0.8 mg/kg SUBQ q 24 hours
    - CrCl < 30 ml/min: Enoxaparin 0.8 mg/kg SUBQ q 24 hours
  - **ESRD/AKI on RRT**
    - Enoxaparin 0.8 mg/kg SUBQ q 24 hours

**Concern for HIT, LMWH failure, or patients receiving ECMO**
- Recommend bivalirudin infusion

**Anti-Xa goals (when indicated)**
- **Therapeutic peak LMWH level** (drawn 4 hours after the 3rd dose): 0.6-1 anti-Xa units/mL
- **Treatment trough LMWH level** (drawn one hour prior to 3rd dose): < 0.5 anti-Xa units/mL

- **If patients transition from low-risk to high risk based upon criteria or develop a VTE on prophylaxis, full-dose anticoagulation is warranted**
- **If BMI ≤ 18.5 kg/m² or weight ≤ 50 kg, recommend Heparin SQ 2500 units q 8 hours**
- **If BMI ≥ 50 kg/m² or AKI/ESRD, recommend anti-Xa monitoring (consult pharmacy for assistance)**
- **Bivalirudin is preferred to argatroban given likelihood of elevated transaminases (e.g., secondary to medications, ischemia, among other causes) in the COVID patient**
- **Upon discharge, apixaban 2.5 mg bid x 4-6 weeks should be continued in patients without a confirmed VTE and normal renal function and 2 weeks for patients with AKI/ESRD. Warfarin may be considered in cases of confirmed HIT. Patients with a confirmed VTE should be discharged on therapeutic anticoagulation.**
References

1. Rush Anticoagulation Guidelines. Rush University Medical Center. May 2019