Penn Medicine recommendations for prophylactic/therapeutic anticoagulation in inpatients with COVID-19 - SUMMARY

I. Pharmacologic prophylaxis/treatment recommendations for inpatients with COVID-19

Table 1. Suggestions for pharmacologic prophylaxis/treatment in hospitalized COVID-19 patients.

<table>
<thead>
<tr>
<th>Population (location)</th>
<th>Bleeding risk</th>
<th>Recommended pharmacologic prophylaxis/treatment (see Table 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected or proven VTE (ICU or medical floor)</td>
<td>Low</td>
<td>Therapeutic-intensity</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Unfractionated heparin (UFH) infusion – goal aPTT 60-85 seconds</td>
</tr>
<tr>
<td>Stable (medical floor)</td>
<td>Low</td>
<td>Standard-intensity</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Consider standard-intensity</td>
</tr>
<tr>
<td>Condition deteriorating (medical floor, but high-risk for transfer to ICU)</td>
<td>Low</td>
<td>Intermediate-intensity or therapeutic-intensity</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Standard-intensity or intermediate-intensity</td>
</tr>
<tr>
<td>Critically ill (ICU)</td>
<td>Low</td>
<td>Intermediate-intensity or therapeutic-intensity</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Standard-intensity or intermediate-intensity</td>
</tr>
</tbody>
</table>

- These suggestions are intended to provide guidance to clinicians. They are not intended to substitute for clinical judgment. All decisions require weighing an individual patient’s bleeding and thrombotic risk. In addition to pharmacologic prophylaxis, all ICU patients should receive mechanical prophylaxis (e.g., intermittent pneumatic compression, out of bed/ambulation as feasible).
- Any patients undergoing epidural/spinal anesthesia should receive UFH 5000 Q12H or Q8H as thromboprophylaxis. If these patients require therapeutic-intensity dosing, discuss choice of agent with Anesthesia.

1. No validated criteria exist to define deteriorating condition in this population. Consider supplemental oxygen requirement ≥6L, clinical exam, signs of organ failure (e.g., CNS, renal, liver).
2. No validated criteria exist for defining bleeding risk in this population. Consider bleeding history, clinical exam, platelet count, PT/aPTT, age>65. In general, pharmacologic prophylaxis and treatment should be withheld in patients with active or very recent (within the last 24-48 hours) bleeding.

Table 2. Recommended regimens for pharmacologic prophylaxis/treatment (round enoxaparin to nearest syringe size)

<table>
<thead>
<tr>
<th>Prophylaxis/treatment intensity</th>
<th>Creatinine Clearance (CrCl) ≥ 30 mL/min</th>
<th>15 ≤ CrCl &lt; 30</th>
<th>CrCl &lt; 15 mL/min OR on renal replacement therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard-intensity</td>
<td>Enoxaparin 40mg Q24H</td>
<td>Enoxaparin 30mg Q24H</td>
<td>UFH 5000 Q12H to Q8H</td>
</tr>
<tr>
<td>Intermediate-intensity</td>
<td>Enoxaparin 0.5 mg/kg Q12H</td>
<td>UFH 7500 Q8H</td>
<td>UFH 7500 Q8H</td>
</tr>
<tr>
<td>Therapeutic-intensity</td>
<td>Enoxaparin 1 mg/kg Q12H</td>
<td>Enoxaparin 1 mg/kg Q24H</td>
<td>UFH infusion – goal aPTT 60-85 seconds</td>
</tr>
</tbody>
</table>

II. Management of inpatients with COVID-19 who were previously on anticoagulation

Patients admitted on therapeutic anticoagulation:
- Warfarin: continue warfarin if they are not being admitted to an ICU and are not undergoing any procedures
- Direct oral anticoagulants (DOACs), if CrCl ≥ 30 mL/min: change to enoxaparin 1mg/kg every 12 hours, due to frequent need for ICU, with no upper weight limit to enoxaparin use (can resume DOAC once stable for discharge)

III. Post-discharge recommendations for inpatients with COVID-19

Post-discharge considerations:
- **Indication for therapeutic anticoagulation**: continue anticoagulation as per usual recommendations.
- **Received empiric therapeutic anticoagulation**: complete a 90-day course of anticoagulation for presumed VTE if bleeding risk permits. If bleeding risk does not permit this, consider extended prophylaxis as below.
- **Received prophylaxis dosing**: Given the risk of VTE in COVID patients, extended out-of-hospital prophylaxis should be strongly considered in patients with low bleeding risk and CrCl ≥ 15. Duration can be limited to 30 days if required by insurance for coverage. Options include:
  - Betrixaban 160mg x 1, then 80mg daily for 35-42 days (including hospital stay) – reduce dose if CrCl < 30
  - Rivaroxaban 10mg daily for 31-39 days (including hospital stay)
  - Enoxaparin 40mg daily for 28 days from discharge (not FDA-approved)

Drafted by Steve Pugliese, Adam Cuker, Chris Domenico, and Todd Hecht
Venous thromboembolism (VTE) prophylaxis/treatment recommendations

- D-dimer levels should not be used to influence use of therapeutic anticoagulation in the absence of clinical suspicion for acute arterial or venous thromboembolism
- Recent data (Klok FA, et al. Thrombosis Research 2020) suggest a 31% rate of thromboembolic events (majority of which were PE) in ICU patients with COVID despite use of prophylactic-intensity LMWH.
  - However, it is important to note that 9.2% of patients in this case series arrived in the hospital on therapeutic anticoagulation, suggesting this may be a higher risk population than most
- Laboratory studies of COVID inpatients have consistently demonstrated a profile favoring hypercoagulability: extremely elevated D-dimer, relatively preserved PT/aPTT, elevated fibrinogen, and normal platelets (Zhou F, et al. Lancet 2020).
- In view of these studies, pharmacologic prophylaxis or therapeutic anticoagulation is recommended for all non-bleeding inpatients with COVID
- Recommendations for intensive care unit (ICU) patients (see “Choice of therapeutic anticoagulation” and “Choice of pharmacologic prophylaxis” sections below for specific medication recommendations):
  - In ICU patients at low risk for bleeding, we recommend use of intermediate-intensity OR therapeutic-intensity anticoagulation
  - In ICU patients at high risk for bleeding, we recommend:
    - Use of intermittent pneumatic compression for all patients PLUS
    - Strong consideration of use of standard-intensity or intermediate-intensity pharmacologic prophylaxis as well
      - Pharmacologic prophylaxis should be withheld if patient is actively bleeding, but should be restarted within 24-48 hours of cessation of bleeding
- Recommendations for medical floor patients (see “Choice of therapeutic anticoagulation” and “Choice of pharmacologic prophylaxis” sections below for specific medication recommendations):
  - Medical floor patients should be assessed for risk for escalation to ICU setting but no precise criteria exist. Consider ≥6L NC, clinical exam, or other organ failure.
  - Medical patients at high risk for ICU and low risk for bleeding should receive intermediate-intensity OR therapeutic-intensity anticoagulation
  - Medical floor patients at high risk for ICU and high risk for bleeding should receive:
    - Use of intermittent pneumatic compression for all patients PLUS
    - Strong consideration of use of standard-intensity or intermediate-intensity pharmacologic prophylaxis as well
      - Pharmacologic prophylaxis should be withheld if patient is actively bleeding, but should be restarted within 24-48 hours of cessation of bleeding
  - Medical floor patients at low risk for ICU and low risk for bleeding should receive standard-intensity pharmacologic prophylaxis
  - Medical floor patients at low risk for ICU and high risk for bleeding should receive
    - Use of intermittent pneumatic compression for all patients PLUS
    - Consideration of use of standard-intensity pharmacologic prophylaxis
      - Pharmacologic prophylaxis should be withheld if patient is actively bleeding, but should be restarted within 24-48 hours of cessation of bleeding
- Post-discharge VTE prophylaxis/treatment recommendations
  - Patient who received prophylactic anticoagulation during hospital stay
    - Given the risk of VTE in COVID patients, extended out-of-hospital prophylaxis should be strongly considered in patients with low bleeding risk and CrCl ≥ 15 (no conventional post-discharge prophylaxis options exist for patients with CrCl<15).
    - Options include (duration can be limited to 30 days if required by insurance for coverage):
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- Betrixaban 160mg x 1, followed by 80mg daily for 35-42 days inclusive of hospital stay (Cohen AT, et al. NEJM 2016)
  - If CrCl < 30 but ≥ 15, Betrixaban is 80mg x 1, followed by 40mg daily for 35-42 days inclusive of hospital stay
- Enoxaparin 40mg daily for 28 days from discharge (Hull RD, et al. NEJM 2010) – not FDA-approved
  - Patients who received therapeutic-intensity anticoagulation during hospital stay
    - Patients who were on anticoagulation prior to hospitalization should continue anticoagulation for at least 3 months following discharge or longer if indication persists
    - Patients with acute VTE, suspected VTE, or empirically treated with full dose anticoagulation based on high risk criteria should complete 3 months of anticoagulation depending on estimation of bleeding risk. If bleeding risk does not permit use of therapeutic-intensity anticoagulation, extended VTE prophylaxis (see above) should be considered.

Choice of therapeutic anticoagulation

- All admitted COVID patients who are on warfarin at time of admission should remain on warfarin if they are not being admitted to an intensive care unit (ICU) and are not undergoing any procedures
- All admitted COVID patients who are on a therapeutic-intensity dose of a direct oral anticoagulant (DOAC, including dabigatran, rivaroxaban, apixaban, or edoxaban) at time of admission and have a CrCl ≥ 30 mL/min should be transitioned to enoxaparin 1mg/kg every 12 hours (with no upper weight limit to enoxaparin use)
  - This strategy is being pursued due to the frequency with which inpatients with COVID need to transition to an ICU setting and/or undergo procedures
  - DOACs have more drug-drug interactions and generally have longer half-lives than enoxaparin
  - Once an inpatient with COVID is stable for discharge home or is in the recovering phase on a medical floor, DOAC therapy can be resumed provided no drug-drug interactions from COVID treatments preclude their use
- When parenteral therapeutic-intensity anticoagulation is indicated in a patient with no prior h/o HIT, **enoxaparin is preferred to an UFH infusion** when renal function and/or use of epidural/spinal anesthesia permits use, with preferred agent and dosing as follows:
  - CrCl ≥ 30 mL/min: enoxaparin 1mg/kg Q12h (with no upper weight limit to enoxaparin use)
  - 15 ≤ CrCl < 30 mL/min: enoxaparin 1mg/kg Q24h (with no upper weight limit to enoxaparin use) – check anti-Xa level 4 hours after 3rd dose – contact Hematology fellow for approval of testing
  - CrCl < 15 mL/min or on any form of renal replacement therapy: UFH infusion
    - If the baseline aPTT is above the upper limit of normal, consult Hematology to explore reason for APTT prolongation and using anti-Xa levels to adjust dosing
  - History of or newly-diagnosed heparin-induced thrombocytopenia (HIT): consult Hematology and see Heparin-Induced Thrombocytopenia Diagnostic and Treatment Guidelines in Penn Pathways and online formulary

Choice of pharmacologic prophylaxis

- **Standard-intensity prophylaxis:**
  - CrCl ≥ 30 mL/min AND not undergoing epidural/spinal anesthesia: Enoxaparin 40mg daily
  - CrCl ≥ 30 mL/min AND history of HIT: **Fondaparinux 2.5mg daily**
  - 15 ≤ CrCl < 30 mL/min: enoxaparin 30mg daily
  - CrCl < 15 OR undergoing epidural/spinal anesthesia: **UFH 5000 Q12H or Q8H**
  - CrCl < 30 AND h/o HIT: consult Hematology for pharmacologic prophylaxis recommendations
  - Higher doses may be required due to the thrombotic risk associated with COVID as well as for patients with elevated body weight
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- **Intermediate-intensity prophylaxis (not to be used if undergoing epidural/spinal anesthesia)**
  - CrCl $\geq$ 30 mL/min: Enoxaparin 0.5mg/kg twice daily, rounded to nearest syringe size
  - CrCl < 30: UFH 7500 Q8H
- **Therapeutic-intensity prophylaxis/treatment:** see “Choice of therapeutic anticoagulation” section above
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References


