Anticoagulation Guidance for Patients with COVID-19

**Thrombosis Mitigation Strategy for ICU Patients with COVID Infection**

Therapeutically anti-coagulate patients with known indications

Consider therapeutic anticoagulation when there is a high clinical suspicion for an acute VTE event

PE in patients with acute pulmonary decompensation

Obtain venous dopplers in the absence of the ability to R/O pulmonary emboli

Provide aggressive dosing for VTE prophylaxis based on BMI and renal function

LMWH (enoxaparin) is the primary agent except ESRD and very low BMI

Utilize a validated bleeding risk assessment tool to assess risk:benefit ratio

Utilize mechanical prophylaxis* in addition to LMWH/UFH or alone if active bleeding/extremely high risk

Post-ICU treatment strategy depends on individual patient thrombotic and bleeding risk

**Background and Rationale**

COVID-19 induced coagulopathy (CIC), the clinical and pathologic hypercoaguable state evident in patients with SARS-CoV-2 infection, has led practitioners to consider institution of therapeutic anticoagulation as standard practice for the most severely ill patients. Laboratory findings consistent with an immunothrombotic state has raised concerns that the coagulopathy is a significant driver of COVID-19 pathophysiology, particularly since increased mortality is associated with the presence of elevated pro-inflammatory markers, especially D-dimer. Contributory to the pro-thrombotic situation include binding of the virus to the angiotensin 2 receptor as well as the elevated thrombotic risk associated with critical illness. Emerging data report an increased incidence of clotting abnormalities, with one series demonstrating thromboembolism in 58% of ICU patients after 21 days.

The optimal intensity of anticoagulation for management of CIC is unknown. In the absence of controlled trials observational data informs our body of knowledge. An early report from a retrospective case series reported a mortality benefit in patients with sepsis-induced coagulopathy receiving VTE prophylaxis (primarily LMWH) compared with no prophylaxis. A subsequent retrospective study evaluating outcomes in therapeutically anticoagulated mechanically-ventilated patients demonstrated reduced mortality compared to those who were not. Despite these encouraging results the inherent risk of confounding with such data requires confirmation of any therapeutic strategy under the conduct of a randomized controlled trial. Given the quality of the data together with the emerging nature of the coagulopathic state there remains no definitive evidence to therapeutically anti-coagulate patients with COVID-19 outside of the usual medical indications or under the conduct of a clinical trial. This conclusion is supported by published guidance from the International Society of Thrombosis and Haemos (ISTH), American College of Cardiology (ACC) and Anticoagulation Forum (AC Forum).

In the absence of therapeutic anticoagulation it is essential to optimize dosing of prophylactic agents. Critically ill patients in general and those with COVID-19 specifically are at the highest risk for the development of VTE. The presence of coagulopathy, concomitant immobility, utilization of neuromuscular blockade and presence of indwelling intravenous catheters significantly increase the risk of a venous thromboembolic event. Additionally many patients with COVID-19 possess comorbid conditions that contribute to baseline VTE risk such as obesity and vascular disease. Therefore, the therapeutic strategy should reflect those utilized in the highest risk subgroups (i.e. spinal cord injury).

Low-molecular weight heparin is the guideline preferred agent for VTE prophylaxis in critically ill patients and is recommended by the aforementioned groups for COVID-19 infected patients where appropriate for renal function. It is important to note that in this population LMWH may have reduced subcutaneous absorption and as such proper dosing is essential to ensure therapeutic efficacy. The highest doses titrated to therapeutic effect (anti-Xa) will provide the best opportunity to administer the amount required to achieve therapeutic targets. To attain the optimal risk benefit ratio a validated bleeding risk assessment tool should be utilized to objectify the risk as well as appreciate the potential drivers of that risk.

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Version 2
Enoxaparin Dosing / VTE prophylaxis in ICU COVID patients

<table>
<thead>
<tr>
<th>BMI &lt; 30 ml/min</th>
<th>BMI ≥ 30 ml/min</th>
<th>ESRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 20</td>
<td>UFH 5000 BID – TID</td>
<td>Below 20</td>
</tr>
<tr>
<td>20 – 25.9</td>
<td>40 mg Daily</td>
<td>30 mg Daily</td>
</tr>
<tr>
<td>26 – 39.9</td>
<td>30 mg BID</td>
<td>40 mg Daily</td>
</tr>
<tr>
<td>40 – 50</td>
<td>40 mg BID</td>
<td>40 mg BID</td>
</tr>
<tr>
<td>Above 50</td>
<td>60 mg BID</td>
<td>60 mg Daily</td>
</tr>
</tbody>
</table>

**Monitoring**

Monitor platelet count daily

Titrated prophylactic anticoagulant to a therapeutic response:

**Enoxaparin (BMI > 40, CrCl < 30, Fluctuating renal function)**

Obtain anti-Xa 4 – 5 hours after 3rd / 4th dose.

**Goal 0.2 – 0.4 units/ml**

Repeat based on clinical response and renal function.

**UFH (BMI > 50)**

Obtain mid-point aPTT or anti-Xa after 4th dose.

**Goal aPTT 35 – 45 sec or anti-Xa 0.1 – 0.25 units/ml**

**Assess Bleeding Risk** (IMPROVE bleeding risk; increased Risk with score ≥ 7)

Review risk drivers such as actual bleeding / history vs. age/gender/moderate RF before considering less aggressive prophylaxis strategies (UFH 5000 units BID or mechanical prophylaxis* alone)

**Therapeutic Anticoagulation**

Unfractionated heparin is the preferred agent for therapeutic anticoagulation in ICU patients due to its short duration of action and the lack of accumulation in renal dysfunction. Therapeutic LMWH (enoxaparin) may also be considered in patients with stable renal function who are unlikely to require invasive procedures and who are not at high risk for bleeding.

**Monitoring:**

Standard heparin protocol or the low-intensity protocol use aPTT to adjust doses.

Anti-Xa# should be utilized to monitor heparin when the aPTT is elevated at baseline.

**Goal Range:**

- **Full Intensity 0.3 – 0.7 units/ml**
- **Low Intensity 0.3 – 0.5 units/ml** (may adjust if significant bleeding risk)

**Consult your ICU pharmacist for assistance in utilizing anti-Xas for UFH monitoring**

#In patients on LMWH, fondaparinux or DOACs within the previous 72 hours obtain a baseline anti-Xa to evaluate for residual effect. If detectable, use of the anti-Xa to titrate the UFH must be delayed.

*Mechanical Prophylaxis = Intermittent Pneumatic Compression Device
**Post ICU Considerations**

Once a patient is transferred out of the ICU it is unclear if a high thrombotic risk persists. Each patient must be considered individually with regard to risk of both thrombosis as well as bleeding.

**Consult an anticoagulation management service pharmacist for assistance in selecting post-ICU and post discharge treatment plans.**

**Continuation of VTE prophylaxis with maximum (ICU) doses:**

- If ICU doses are tolerated from a bleeding standpoint and risk remains high (weakness or immobility, elevated inflammatory markers, BMI > 40) it is reasonable to continue maximum doses.
  - Assumes stable renal function as significant change will alter the dose and bleeding risk
- In the absence of above it is reasonable to de-escalate to standard dosing

**Continuation of therapeutic anticoagulation**

- In patients with a proven thrombus the standard treatment recommendations for a provoked VTE would apply (3 months)
- In the absence of a proven thrombosis (i.e., initiated in the ICU because of high clinical suspicion without objective evidence of a thrombus) continuation of therapeutic anticoagulation should be carefully considered. Objective information utilized to initiate anticoagulation such as abrupt change in respiratory status vs. lack of clinical improvement are relevant.
- Utilization of a risk assessment tools for bleeding may be useful to guide therapy. (see below)

**Post Discharge VTE Prophylaxis**

Previous trials conducted in the acute medically ill hospitalized population have showed varying degrees of VTE risk reduction, with benefits in part offset by an increased risk of bleeding. Assessment of individual bleeding and thrombotic risk is warranted in order to limit prophylaxis to patients with optimized risk-benefit profiles. To maintain equipoise, the decision to continue thromboprophylaxis post-discharge should be considered on a case-by-case basis.

**COVID + patients who may be reasonable for evaluation include:**

- High risk patients identified by the ICU team due to a prolonged stay or significant deconditioning
  - Transfer summary / ICU pharmacist communicates risk assessment
- Those with ongoing risk factors at time of discharge
  - Significantly reduced mobility, weakness, or history of VTE
- Those with risk factors and persistent significant elevation in d-dimer near time of discharge
  - Could consider obtaining repeat d-dimer to assess trend in a high risk patient
- Application of the Modified IMPROVE VTE / IMPROVEDD RAM (see below)

**All patients considered must have low bleeding risk.** May take into consideration risk factors such as those outlined in the IMPROVE Bleeding RAM as well as the criteria below.

**Exclusionary criteria may include those at high risk of bleeding features derived from previous RCTs:**

- Dual antiplatelet therapy use
- Active gastroduodenal ulcer
- Bleeding in the past 3 months
- Active cancer
- History of bronchiectasis, pulmonary cavitation, or pulmonary hemorrhage
- ESRD with CrCl < 15ml/min or on dialysis
- Drug Interactions: Concomitant CYP3A4 and/or P-gp inhibitors (rivaroxaban)

Based on available literature and ease of accessibility, either **enoxaparin 40mg SQ daily** or **rivaroxaban 10mg PO daily** are reasonable agents for extended duration prophylaxis

- Assess patient accessibility prior to discharge, in conjunction with the outpatient pharmacy.
- If prescribed, length of therapy will depend on individual assessment such as perceived duration of reduced mobility. These agents have been studied up to ~35-45 days post-discharge.
## VTE Risk Assessment Models

### Thrombosis Risk Assessment Model (RAM)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous VTE</td>
<td>3</td>
</tr>
<tr>
<td>Known thrombophilia(^a)</td>
<td>2</td>
</tr>
<tr>
<td>Current lower limb paralysis or paresis(^b)</td>
<td>2</td>
</tr>
<tr>
<td>History of cancer(^c)</td>
<td>2</td>
</tr>
<tr>
<td>Complete immobilization &gt;1day(^d)</td>
<td>1</td>
</tr>
<tr>
<td>ICU/CCU stay</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt;60</td>
<td>1</td>
</tr>
<tr>
<td>D-dimer &gt;2x ULN</td>
<td>2</td>
</tr>
</tbody>
</table>

### Modified IMPROVE risk score:
- 4 or higher risk
- 2 or 3 plus a plasma D-dimer 2x ULN

- Congenital or acquired condition leading to excess risk of thrombosis\(^a\) (e.g., factor V Leiden, lupus anticoagulant, factor C or factor S deficiency).
- Leg falls to bed by 5 seconds, but has some effort against gravity\(^b\) (taken from NIH stroke scale).
- Cancer (excluding nonmelanoma skin cancer) present at any time in the past 5 years (cancer must be in remission to meet eligibility criteria).\(^c\)
- Immobilization: confined to bed or chair with or without bathroom privileges.\(^d\)

## Bleeding Risk Assessment Tools

### IMPROVE Bleeding Risk Score

**Use for VTE prophylaxis bleeding risk**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR 30-59 mL/min/m(^2)</td>
<td>1</td>
</tr>
<tr>
<td>Male vs female</td>
<td>1</td>
</tr>
<tr>
<td>Age 40-84 y</td>
<td>1.5</td>
</tr>
<tr>
<td>Current cancer</td>
<td>2</td>
</tr>
<tr>
<td>Rheumatic disease</td>
<td>2</td>
</tr>
<tr>
<td>Central venous catheter</td>
<td>2</td>
</tr>
<tr>
<td>ICU/CCU</td>
<td>2.5</td>
</tr>
<tr>
<td>GFR &lt; 30 mL/min/m(^2)</td>
<td>2.5</td>
</tr>
<tr>
<td>Hepatic failure (INR &gt; 1.5)</td>
<td>2.5</td>
</tr>
<tr>
<td>Age &gt; 85 y</td>
<td>3.5</td>
</tr>
<tr>
<td>Platelet count &lt; 50K</td>
<td>4</td>
</tr>
<tr>
<td>Bleeding in 3 months PTA</td>
<td>4</td>
</tr>
<tr>
<td>Active gastroduodenal ulcer</td>
<td>4.5</td>
</tr>
</tbody>
</table>

**Interpretation:**
- Bleeding Risk Increased with score > 7

### Riete Bleeding Score

**Use for VTE treatment bleeding risk**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent Major Bleeding</td>
<td>2</td>
</tr>
<tr>
<td>Creatinine &gt; 1.2 mg/dl</td>
<td>1.5</td>
</tr>
<tr>
<td>Anemia</td>
<td>1.5</td>
</tr>
<tr>
<td>Cancer</td>
<td>1</td>
</tr>
<tr>
<td>Clinically Overt PE</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt; 75 yrs</td>
<td>1</td>
</tr>
</tbody>
</table>

**Interpretation:** (major bleeding events)

<table>
<thead>
<tr>
<th>Points</th>
<th>Risk</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>Low (0.1%)</td>
</tr>
<tr>
<td>1-4</td>
<td>Intermediate (2.8%)</td>
</tr>
<tr>
<td>&gt;4</td>
<td>High (6.2%)</td>
</tr>
</tbody>
</table>
References


Paranjpe I, Fuster V, Lala A et al. Association of Treatment Dose Anticoagulation with In-Hospital Survival Among Hospitalized Patients with COVID-19 J Am Coll Card 2020; doi: https://doi.org/10.1016/j.jacc.2020.05.001


