EMORY HEALTHCARE

EMORY CRITICAL CARE CENTER

Guidelines for the Prevention and Treatment of VTE in Critically Ill Patients with COVID-19

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There are increasing reports, both in the literature and from our own providers, of high rates of coagulopathy and venous thromboembolism (VTE) among critically ill patients with COVID-19. This guideline is not intended to be used for patients with incidental, asymptomatic SARS-CoV-2 swabs for other reasons (screening prior to surgery, etc.). Analysis of patients admitted to EHC with COVID-19 indicates that those with a D-dimer above 3,000 at any point during their hospitalization have a 4-fold increase in their risk of VTE. Further analyses indicate that an increase in D-dimer of 2,000 or more within a 24-hour period during the first 10 days of hospitalization is also associated with a 4-fold increase in VTE, with a positive predictive value of 48%. Clinicians caring for patients with COVID-19 should be aware of these increased risks and have a low threshold to evaluate for clot and/or escalate therapy depending on the clinical situation.

If concerned for "refractory hypercoagulability," with the development or progression of blood clots or clinical deterioration concerning for thrombosis (macro or microvascular) despite standard therapeutic anticoagulation, please *consult Hematology at your campus*. They will review cases with a multidisciplinary group to determine additional labs to send and whether additional interventions (e.g., anti-platelet, DTIs, plasma exchange, tPA) should be considered.

Laboratory monitoring:

1. On hospital admission: DIC panel, IL-6 level
2. Daily: DIC panel (*Note: Patients who are clinically stable with a D-dimer that is not increasing can have daily DIC panel discontinued. Institutional data suggest that a D-dimer level of < 1,500 after 7 days of admission has a 95% negative predictive value for development of a new thrombus.)*

Assessing risk of bleeding:

1. Ensure platelet count is > 25K for patients on Levels 1 and 2, and > 50K for patients on Level 3 anticoagulation.
2. Consider risk-benefit ratio of anticoagulation carefully in patients with active or recent bleeding, surgery, coagulopathy, comorbidities or concurrent medications associated with high risk of bleeding.
3. Consult hematology if concerns or questions.

LEVEL 1 (standard prophylaxis): For patients with symptomatic COVID admitted to the floor without known thrombus AND a D-dimer < 3,000*:

Anticoagulation	Notes
LMWH 0.5mg/kg/day (Min 40 mg, Max 80 mg) OR For renal insufficiency: - if stable SCr and CrCl >15-30 ml/min, monitor anti-Xa and dose adjust - if unstable SCr (SCr change by ±0.5 in 24 hours), anuria, or CrCl <15 ml/min, can use UFH 5000 units Q8H†	1. For obese patients with renal insufficiency, can dose adjust UFH for BMI 25-35: 7500 units Q8H†; BMI > 35: 10000 units Q8H†

On discharge: 7 days of continued prophylaxis with LMWH or DOAC (DOAC preferred). See discharge guidance below.
**At EDH, D-dimer threshold = 3.0 FEU/ml (i.e., 6x ULN). †Consider Q12H regimen on the floor*

LEVEL 2 (intermediate dosing): For **ALL patients admitted to the ICU for COVID-related reasons** (who do not have an indication for Level 3) OR for floor patients without known thrombus AND a D-dimer ≥ 3,000*:

Anticoagulation	Notes
LMWH 0.5 mg/kg/Q12h (or 1mg/kg/day) OR	1. LMWH anti-Xa monitoring as below. 2. As able, baseline LE dopplers should be checked (formal vs. POCUS), with repeat for changes in clinical status

For unstable SCr, anuria, or CrCl ≤30 ml/min: Heparin gtt, low-standard without bolus	3. For patients with stable renal function, LMWH preferred over heparin gtt given volume infusion with gtt. 4. For non-ICU patients or patients who are stable in the ICU, consider initiating DOAC (no loading doses) while inpatient if clinically appropriate (see dosing chart) 5. For UFH, use standard dosing algorithms and target anti-Xa levels

On discharge: Continue treatment for 4 weeks with DOAC or LMWH (DOAC preferred). See discharge guidance below.
**At EDH, D-dimer threshold = 3.0 FEU/ml (i.e., 6x ULN).*

LEVEL 3 (therapeutic dosing): For patients with known or suspected VTE, or otherwise unexplained increase in oxygen requirement, dead space, or organ failure (e.g., AKI, MSOF) with concern for microvascular thrombi.

Anticoagulation	Notes
LMWH 1mg/kg/q12h OR Stable renal function and CrCl 15-30 ml/min: LMWH 1 mg/kg/qday (Goal anti-Xa remains 0.6-1) OR Unstable SCr, anuria, or CrCl ≤15 ml/min: Heparin gtt, high-standard with bolus	1. Anti-Xa monitoring as below. 2. If concern for heparin resistance with heparin dose >24 units/kg/hr (or 3-4mg/kg/ 24 hrs of LMWH) and still subtherapeutic (e.g., anti-Xa not at goal), consider switching to a DTI (argatroban/ bivalirudin) as inpatient. 3. In patients with AT level of <50%, start directly with DTI. 4. For non-ICU patients, consider initiating DOAC (with loading doses) while inpatient if clinically appropriate (see dosing chart below). 5. For UFH, use standard dosing algorithms and target anti-Xa levels

On discharge: Continue treatment for 3 months for provoked VTE with treatment-dose LMWH (unless patient was on DTI for concern of heparin resistance), warfarin, or DOAC (DOAC preferred if no contraindications). See Discharge guidance below.

General Guidance: Once a patient meets criteria for a particular level, they should typically remain at that level for the duration of their admission and follow-up period. However, patients who were empirically escalated to Level 3 while in the ICU (i.e., without documented thrombus), may be returned to Level 2 after leaving the ICU at the discretion of the treating team. In addition, if there are bleeding concerns on discharge, these may be addressed on a case-by-case basis in consultation with hematology. Personal and/or family history of VTE should also be elicited and documented, as this will aid with risk stratification.

LMWH Considerations

1. Round doses to nearest 10 mg (or syringe, per hospital practice), do not cap doses, unless otherwise stated
2. LMWH Anti-Xa Monitoring:
    a. Daily anti-Xa monitoring is not required. The following groups can have a peak level drawn 3-6 hours after administration of 2nd or 3rd dose (steady state) on initiation or when dose is changed:
        i. BMI > 40
        ii. CrCl < 50 ml/min and/or age > 75 years old
        iii. If D-dimer increases by > 10,000 in < 48 hours
        iv. Every 4 days in ICU patients as a proxy for AT3 levels
        v. At discretion of team if concern for clinical deterioration or anticoagulation failure (e.g., based upon AT3 levels, D-dimer increases by > 10,000 in < 48 hours, or other)
    b. Dose adjust using proportions to achieve goal levels:

Risk Level	Anti-Xa Goal for LMWH*

Level 1	0.1-0.3
Level 2	0.3-0.6
Level 3	0.6-1
*For UFH use standard dose algorithm and anti-Xa goals not the LMWH anti-Xa goal listed above.	

Consults: Pharmacotherapy consult for discharge DOAC education. Include Level (1, 2, or 3), drug, dose, frequency, duration.

- If patient is started on a DOAC prior to discharge, pharmacy is required by CMS to provide counseling to the patient. Please alert pharmacy if a patient is started on a DOAC with the intent to discharge within the same day.

At this time, pharmacists will not order anti-Xa levels or adjust LMWH doses without the approval of the provider.

For pharmacists: Where applicable, open "Pharmacy Clinical Intervention" linked to the anticoagulation therapy and monitor daily for adjustments required by renal function and/or Anti-Xa monitoring. All recommendations are to be addressed with the provider prior to changing doses or ordering levels.

CRRT: CRRT clotting should be managed in accordance with the COVID-19 CRRT Anticoagulation protocol. By definition, according to this above VTE protocol, as all patients receiving CRRT are in the ICU, all CRRT patients should already be receiving at a minimum LEVEL 2 VTE anticoagulation as above. For patients on CRRT, anticoagulation should be done at the highest level called for by either the CRRT or VTE protocols with close communication with nephrology and clinical pharmacists if any questions or concerns.

tPA: While there are many reports circulating about the utilization of tPA for various indications in the context of COVID-19, at this time we feel there is insufficient evidence to support its use outside of the traditional indications of cardiac arrest or hemodynamic instability due to thrombus. If there is concern for impaired fibrinolysis or other refractory hypercoagulability, please consult hematology as above.

Discharge Considerations

- All Level 3 patients should follow-up in clinic 6 weeks after discharge:
  - Stroke → Neurology clinic: Send EEMR communication message to Dr. Fadi Nahab, Neurology
  - Myocardial infarction → Cardiology clinic with EEMR message to Dr. Bryan Wells
  - Other known or suspected VTE → Joint thrombosis clinic run by Hematology and Pulmonary: Send EEMR communication message to Dr. Manila Gaddh (Hematology), Dr. Charles Grodzin (Pulmonology) and Tracy Middlebrooks (clinic coordinator)
- Send discharge prescriptions to The Pharmacy at Emory Midtown or The Pharmacy at Emory, if able, for patients without insurance or needing financial assistance with prescription drug coverage
- If not using an Emory Pharmacy, print and provide patient with Free 30-day Trial Card (does not work for 7 day supply)
  - Apixaban: https://mprsetrial.mckesson.com/6822/landingPage.html?src=Emory#
  - Rivaroxaban: https://sservices.trialcard.com/Coupon/xareltotrialoffer (does NOT cover 10 mg daily dosing)
- Most insurances will require PA for Lovenox (enoxaparin) > 14 day supply unless in the setting of malignancy
- If discharging on Lovenox (enoxaparin), consider rounding to nearest syringe size (Syringes available: 30 mg, 40 mg, 60 mg, 80 mg, 100 mg, 120 mg, 150 mg)

DOAC Dosing: *Level 1 = 1 week, Level 2 = 4 weeks, Level 3 = 3 months*

Risk Level	Xarelto (Rivaroxaban) dosing	Eliquis (Apixaban) dosing	Pradaxa (Dabigatran) dosing

Level 1 or Level 2 at high risk of bleed	10 mg daily	2.5 mg BID	110 mg BID
Level 2 (no loading doses)	20 mg daily	5 mg BID	150 mg BID
Level 3	15 mg BID x21 days (subtract the number of days of therapeutic anticoagulation already received) followed by 20 mg daily to complete 3 months of AC post discharge	10 mg BID x 7 days (subtract the number of days of therapeutic anticoagulation already received) followed by 5 mg BID to complete 3 months of AC post discharge	After at least 5 days of parenteral anticoagulation, transition to 150 mg BID