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. Development of coagulopathy, particularly an elevated D-dimer, has been associated with greater risk of death among patients with COVID-19 infection.

Preliminary 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, MOCHA panel, IL-6 level
2. Daily: DIC panel (*Note: Patients who are clinically stable with a D-dimer that is not increasing can likely have daily DIC panel discontinued. Preliminary 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, coagulopathy, comorbidities or concurrent medications associated with high risk of bleeding.
3. Consult hematology if concerns or questions.

LMWH Considerations

1. Round doses to nearest 10 mg (or syringe, depending on hospital practice), do not cap doses, unless otherwise stated
2. LMWH Anti-Xa Monitoring: Draw peak level 3-6 hours after administration of 2nd or 3rd dose (steady state) on initiation or when dose is changed
    a. Dose adjust using proportions to achieve goal levels

Risk Level	Anti-Xa Goal
Level 1	0.1-0.3
Level 2	0.3-0.6
Level 3	0.6-1

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

LEVEL 1 (standard prophylaxis): for patients 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. No need to routinely monitor anti-Xa levels if CrCl >30 ml/min and stable 2. 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 patients without known thrombus AND a D-dimer ≥ 3,000*:

Anticoagulation	Notes
LMWH 0.5 mg/kg/Q12h (or 1mg/kg/day) OR For unstable SCr, anuria, or CrCl ≤30 ml/min: Heparin gtt, low-standard without bolus	1. Where able, monitor anti-Xa for LMWH for all patients at initiation of therapy and with changes in renal function; do not recommend repeat testing if within range 2. As able, baseline LE dopplers should be checked (formal vs. POCUS) in these patients, with repeat for changes in clinical status 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)

On discharge: Continue treatment for 4-6 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. Where able, monitor anti-Xa levels for LMWH for all patients at initiation of therapy and with changes in renal function; do not recommend repeat testing if within range 2. If concern for heparin resistance when dose of heparin exceeds 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) while 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).

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.

- 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.

General Guidance: Once a patient meets criteria for a particular level, they should remain at that level for the duration of their admission and follow-up period, unless there are bleeding concerns which may be addressed on a case-by-case basis in consultation with hematology. In addition, personal and/or family history of VTE should also be elicited and documented, as this will aid with risk stratification.

CRRT: CRRT clotting should be managed in accordance with the CRRT protocol. This VTE protocol does not apply to CRRT clotting without other known or suspected VTE or thrombi. For patients on CRRT who would otherwise qualify for anticoagulation according to this VTE protocol (i.e., D-dimer ≥ 3,000 or known or suspected VTE), anticoagulation should be done at the highest level according to either the CRRT or VTE protocols with close communication with renal and pharmacy 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 > 14 day supply unless in the setting of malignancy
- If discharging on Lovenox, consider rounding to nearest syringe size (Syringes available: 30 mg, 40 mg, 60 mg, 80 mg, 100 mg, 120 mg, 150 mg)

DOAC Dosing

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