Cooper University Health Care
COVID-19 Anticoagulation Recommendations

Last updated: 4/23/2020

I. Laboratory monitoring recommendations
   A. Baseline D-dimer, PT, aPTT, fibrinogen, ferritin, LDH, troponin, CPK, CK and CBC w/ diff
   B. Trend D-dimer, CBC, PT, aPTT and fibrinogen daily
   C. Marked elevations in D-dimer may be useful in determining prognosis and need for escalation of care. D-dimer can be elevated in older individuals and hepatic dysfunction

II. Imaging recommendations
   A. Concern for DVT: Obtain ultrasound duplexes to evaluate asymmetric limb, pain, edema or suspected limbs. If DVT is present therapeutic intensity anticoagulation is indicated.
   B. Concern for PE: If unable to obtain standard diagnostic evaluation (CTA, echo) consider: 1.) Ultrasound duplexes to evaluate for DVT 2.) Point of care echo to evaluate otherwise unexplained right heart strain, intracardiac thrombus. If either present, we suggest therapeutic intensity anticoagulation.

III. Prophylactic anticoagulation (**Table 1**)
   A. In the absence of contraindications (active bleeding or platelet count <30 $x10^3$ cells/µ) all patients admitted for COVID-19 should receive VTE prophylaxis. Enoxaparin is the preferred agent, with subcutaneous heparin reserved for patients with CrCl <30 mL/min.
   B. In addition to pharmacologic prophylaxis, all ICU patients should receive mechanical prophylaxis (e.g. intermittent pneumatic compression, out of bed/ambulation as feasible)

IV. Therapeutic anticoagulation (**Table 2**)
   A. Evaluation of bleeding risk: consider bleeding history, clinical exam, platelet count less than 30 $x10^3$ cells/µL, PT/aPTT, fibrinogen <100 mg/dL, age >65, history of head trauma or ICH, history of recent surgery
   B. Low Bleeding risk
      1. Therapeutic anticoagulation is recommended for patients with documented VTE (DVT or PE) ***or*** a HIGH clinical suspicion of VTE if confirmatory imaging is not possible (e.g. exposure concerns or prone positioning). High clinical suspicion of VTE may include but is not limited to:
         a) Marked increase or rising D-dimer (D-dimer >3 µg [FEU]/mL)
         b) Acute worsening of oxygenation, blood pressure, tachycardia without a clear explanation for example worsening pneumonia
         c) High dead space ventilation physiology
         d) Asymmetric limb pain and swelling
   C. High bleeding risk
      1. Intermittent pneumatic compression and strong consideration of chemical thromboprophylaxis. Therapeutic intensity anticoagulation should not be used unless there is a confirmed indication, and perceived benefits exceed the risks. Recommend to assess the risk of bleeding daily

V. Discharge Guidelines

A. For patients receiving therapeutic anticoagulation (confirmed or highly suspected VTE), we suggest completing **at least 3 months** of anticoagulation upon discharge. We recommend a DOAC, or if not feasible, therapeutic LMWH.

1. If determined to be too high risk for continued therapeutic anticoagulation upon discharge consider extended out-of-hospital prophylaxis. Follow up appointment with hematology should be arranged prior to discharge.

B. Extended out-of-hospital prophylaxis is recommended for patients with COVID who did not have a confirmed or highly suspected VTE:

1. Rivaroxaban 10mg daily for 45 days
   a) Do not use if CrCl <30 mL/min
2. Enoxaparin 40mg daily for 45 days
   a) CrCl 15-30 mL/min dose reduce 30 mg once daily
3. If CrCl <15mL/min, consult to hematology recommended for individualized discharge prophylaxis recommendations

Table 1: Pharmacologic VTE Prophylaxis for COVID-19 patients

BMI	**BMI <35 kg/m^2**		**BMI >35 and <50 kg/m^2**		**BMI ≥50 kg/m^2**	
CrCl	**CrCl > 30 mL/min**	**CrCl ≤ 30 mL/min**	**CrCl > 30 mL/min**	**CrCl < 30 mL/min**	**CrCl > 30 mL/min**	**CrCl < 30 mL/min**
Chemical VTE prophylaxis*	Enoxaparin 40 mg SC q24h	Heparin 5000 units SC q8h	Enoxaparin 40 mg SC q12h	Heparin 7500 units SC q8h	Enoxaparin 60 mg SC q12h$^{\$}$	Heparin 7500 units SC q8h

*In the absence of contraindications (active bleeding or platelet count <30,000) all patients admitted for COVID-19 (including non-critically ill) with low bleeding risk should receive chemical VTE prophylaxis. Patients with a high-bleeding risk should receive intermittent pneumatic compression and consideration of chemical VTE prophylaxis

$^{\$}$Consider LMWH anti-Xa monitoring when BMI >50 kg/m^2. Anti-Xa levels should be checked 4 hours after the 3rd dose of enoxaparin and several days later (after 6-8 doses) to ensure anti-Xa levels do not increase with persistent use.The target anti-Xa range for prophylaxis is 0.2-0.4 units/mL.

Table 2: Therapeutic Anticoagulation for COVID-19 patients

BMI	**<150 kg**		**≥150 kg**	
CrCl	**CrCl > 30 mL/min**	**CrCl ≤ 30 mL/min**	**CrCl > 30 mL/min**	**CrCl < 30 mL/min**
Therapeutic anticoagulation*	Enoxaparin 1 mg/kg SC q12h	Enoxaparin 1 mg/kg q24h OR IV UFH$^{\wedge}$	Enoxaparin 0.8 mg/kg SC q12h$^{\$}$	IV UFH$^{\wedge}$

*Therapeutic anticoagulation is recommended for patients with a high clinical suspicion of VTE and low bleeding risk. See guidelines for evaluation of VTE and bleeding risk. In addition, all patients with a confirmed VTE should receive therapeutic intensity anticoagulation per standard guidelines.

$^{\wedge}$IV unfractionated heparin (UFH), order CUH VTE Heparin Protocol

$^{\$}$Consider LMWH anti-Xa monitoring when weight ≥150 kg. Anti-Xa levels should be checked 4 hours after the 3rd dose of enoxaparin and several days later (after 6-8 doses) to ensure anti-Xa levels do not increase with persistent use.The target anti-Xa range for therapeutic anticoagulation is 0.5-1 units/mL.

Detailed COVID-19 Anticoagulation Recommendations

I. Hypercoagulability
   A. A recent study from Klok et al.[1] (4/10/20) showed a **31% incidence of thromboembolic events** (primarily PE) among 184 ICU patients with COVID-19 despite the use of LMWH for prophylaxis, although 2 of 3 centers underdosed patients.
   B. Cui et al.[2] found a **25% incidence of VTE** among 84 patients in the ICU, none of which received prophylactic anticoagulation.
   C. Multiple studies have shown significantly elevated D-dimers among COVID-19 patients.[3-5] **Elevated D-dimer levels on admission and rising levels during hospitalization are associated with an increased risk of severe disease (ARDS, DIC) and death.[5,6]** A retrospective study by Tang et al showed 16 of 181 (8.8%) patients with COVID-19 developed DIC. 71.4% of non-survivors versus 0.6% of survivors fulfilled the clinical criteria for disseminated intravascular coagulation (DIC) during the disease course.[6]
   D. Thrombocytopenia is significantly associated with the severity of disease based on a meta-analysis of 9 studies, and a more sizable drop is seen in non-survivors.[7]

II. Mechanism
   A. Systemic inflammatory response as seen in sepsis
   B. Stasis/critical illness
   C. Endothelial dysfunction from direct viral invasion may induce a pro-thrombotic state and could explain the systemic organ dysfunction seen in many patients
      1. A recent study by Varga et al[12] showed the presence of SARS-CoV2 viral elements in endothelial cells on post-mortem analysis
      2. Luo et al.[6] reported finding microthrombi in the vasculature of one COVID-19 patient on autopsy and thrombotic complications on autopsy were also described by Fox et al.[16]

III. Lab monitoring
   A. Obtain baseline: **D-dimer, PT, aPTT, fibrinogen, ferritin, LDH, troponin, CPK, CK and CBC with differential**.
   B. **Trend D-dimer daily for all patients**. Marked elevations in D-dimer may be useful in determining prognosis and need for escalation of care.
      1. It is important to note that D-dimer elevations are naturally seen in older individuals and those with hepatic dysfunction
   C. For patients in the ICU, trend CBC, PT, PTT and fibrinogen daily

IV. Anticoagulation prophylaxis
   A. In the absence of contraindications (active bleeding or platelet count <30,000) **all patients admitted for COVID-19 should receive standard prophylactic LMWH regardless of disease severity.** Abnormal PT/APTT is not a contraindication for thromboprophylaxis.[8]
      a) In a retrospective study of 449 patients with severe COVID-19, the use of thromboprophylaxis (primarily LMWH) resulted in a lower mortality rate only among critically ill patients with an ISTH SIC score >3 and those with D-dimers >3ug/mL.[9]
   B. **Concern for DVT:**
      1. Obtain ultrasound duplexes to evaluate asymmetric limb, pain, edema or suspected limbs. If DVT is present therapeutic anticoagulation is indicated. If unable to obtain ultrasound due to concern for staff exposure, and clinical

suspicion for DVT is high, **we suggest therapeutic anticoagulation unless contraindicated**. Risk of bleeding should be weighed against risk of clotting

C. **Concern for PE**:
    1. COVID-19 infected patients are known to be hypoxic and coagulopathic, however clinical suspicion for PE may include: a. Marked increase or rising D-dimer b. Acute worsening of oxygenation, blood pressure, tachycardia without explanation of worsening PNA c. Dead space ventilation
    2. If unable to obtain standard diagnostic evaluation (CTA, echo) consider: a. Ultrasound duplexes to evaluate for DVT b. Point of care echo to evaluate otherwise unexplained right heart strain, intracardiac thrombus. If either present we suggest therapeutic anticoagulation.
    3. **If unable to obtain any diagnostic imaging due to concern of staff exposure to COVID19, and clinical suspicion for PE is high, we suggest therapeutic anticoagulation unless contraindicated.** Risk of bleeding should be weighed against risk of clotting daily

D. **In addition to pharmacologic prophylaxis, all ICU patients should receive mechanical prophylaxis** (e.g., intermittent pneumatic compression, out of bed/ambulation as feasible)

E. Discharge Guidelines
    1. If there is an indication for therapeutic anticoagulation such as atrial fibrillation, confirmed VTE, etc. continue anticoagulation per current evidence-based guidelines.
    2. If the patient received therapeutic anticoagulation without confirmed VTE we suggest completing at least 3 months of anticoagulation upon discharge for presumed VTE if bleeding risk permits. If bleeding risk does not permit consider extended out-of-hospital prophylaxis. Patients should have a follow up appointment with hematology scheduled prior to discharge
    3. Given the risk of VTE in COVID-19 patients, extended out-of-hospital prophylaxis should be considered in patient with low bleeding risk (ISTH is recommending 45 days):
        a) Rivaroxaban 10mg daily for 45 days
            (1) Do not use if CrCl <30 mL/min
        b) Enoxaparin 40mg daily for 45 days
            (1) CrCl 15-30 mL/min dose reduce 30 mg once daily
            (2) If CrCl <15mL/min we recommend consult to hematology

V. Guidelines for bleeding patients
    1. For patients with a low-bleeding risk we recommend the above guidelines for thromboprophylaxis.
    2. **For patients with a high-bleeding risk we recommend intermittent pneumatic compression and the strong consideration for standard thromboprophylaxis per the guidelines above**.
    3. **Thromboprophylaxis should not be used in patients actively bleeding**, but should be restarted 24-48 hours after bleeding cessation.

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