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Hematology Issues during COVID-19

Page 1-3:	Recommendations
Page 4:	Dosing Guidelines
Page 5:	References

Note: **Research on COVID 19 is emerging rapidly. As such, this document is fluid and will be updated regularly.**

I. Recommendations

- a. Diagnostics: For all patients presenting to MGH for COVID-19:
 - i. Obtain baseline: **D-dimer, PT, PTT, fibrinogen, ferritin, LDH, troponin, CPK, CK and CBC with differential**
- b. Monitoring
 - i. Trend D-dimer daily (or whenever labs are being drawn if less frequent) if baseline or subsequent >1000 ng/mL. (A,B) [1,2,3,4,5]
 - ii. For patients in the ICU, trend CBC, PT, PTT and fibrinogen daily (or whenever labs are being drawn if less frequent)
- c. Management
 - i. All patients admitted to MGH for COVID-19 (including non-critically ill) should receive **standard prophylactic anticoagulation with LMWH** (see Dosing Guidelines) in the absence of any contraindications (active bleeding or platelet count less than 25,000); monitoring advised in severe renal impairment; abnormal PT or APTT is not a contraindication (C) [1,3,6,9]
 1. If CrCl >30mL/min – use Lovenox 40mg sc qd
 2. If CrCl <30mL/min) – use UFH (see Dosing Guidelines).



MASSACHUSETTS GENERAL HOSPITAL

3. In obese patients, the recommended dose is 40 mg bid (for renal failure, see Dosing Guidelines)
 4. If history of HIT or HITT, use non heparin alternative.
 5. If anticoagulation is contraindicated, patients should have mechanical prophylaxis (eg: pneumoboots).
- ii. Patients admitted to MGH who are on a direct oral anticoagulant or warfarin as an outpatient (eg. for atrial fibrillation, h/o VTE, prosthetic valves) should be switched to therapeutic dose of LMWH (preferred over UFH to decrease blood draws to monitor PTT) due to possible interactions with COVID 19 treatments). [9]
 - iii. If patient has a confirmed acute DVT or PE or was on therapeutic anticoagulation prior to hospitalization and now changed to parenteral, the following guidelines are recommended:
 1. LMWH is preferred, to minimize blood draws and has superior efficacy in critical care population [10]. (See Dosing Guidelines for special populations and alternatives for renal failure)
 2. Patients who need to be on Unfractionated Heparin (instead of LMWH) should be monitored with antiXa levels (as opposed to PTT given that the latter increases in severely ill COVID-19 patients and may render the PTT unreliable.)
 - iv. Page the inpatient Hematology Consult attending at any time to discuss specific guidance if a patient's coagulopathy appears to be worsening or to discuss enhanced or changed treatment approach [11]
 - v. Whether or not COVID-19 infected patients have a unique increased risk of VTE compared to other critical infections/processes is not currently known, and is an area of active research. At this time, we do not suggest escalating prophylactic dose of anticoagulation. A randomized controlled trial addressing this question will be available shortly.
 - vi. We suggest *limiting* therapeutic anticoagulation to the following COVID-19 patients:
 1. Documented acute DVT/PE (see next section)
 2. Pre-hospitalization management with therapeutic anticoagulation (as for Afib, certain mechanical heart valves, recurrent VTE, etc)

Note: Please contact renal for CVVH related clotting protocol
 - vii. Currently, there is insufficient data to suggest using more advanced therapies (such as TPA) in critically ill COVID-19 patients and we do not recommend it at this time.
- d. Evaluation for suspected VTE
- i. Concern for DVT: Obtain venous Doppler study, if possible, to evaluate asymmetric limb pain or edema. If DVT is present, start full dose anticoagulation (LMWH preferred, see Dosing Guidelines). If patient is unable to get US due to concern of staff exposure to



COVID-19, and clinical suspicion for DVT is high, we **would suggest treating with full dose anticoagulation (unless contraindicated) over obtaining any diagnostics testing** (see Dosing Guidelines). Feel free to page the inpatient Hematology Consult attending for any guidance.

- ii. Concern for PE: This is a challenge given the inherent hypoxia and perturbed coagulation profile of COVID-19 infected patients.
 1. Consider PE in the case of:
 - a. Marked increase/rising Ddimer from priors
 - b. Acute worsening of oxygenation, blood pressure, tachycardia with imaging findings not consistent with worsening COVID-19 PNA
 2. During the COVID pandemic, standard diagnostic evaluation (CTA, ECHO) may not be possible.
 - a. if possible, obtain US and if + DVT, treat with full dose anticoagulation or
 - b. if possible, obtain point of care ECHO and if evidence of acute, otherwise unexplained right heart strain, or intra-cardiac thrombus, treat with full dose anticoagulation.
 - c. If patient unable to get US or ECHO due to concern of staff exposure to COVID-19 and clinical suspicion for PE remains high, we **would suggest treating with full dose anticoagulation (unless contraindicated) over obtaining any diagnostics testing** (see Dosing Guidelines).

e. Bleeding concerns

Currently, there is limited data available regarding bleeding issues in the setting of COVID-19. If bleeding does develop, similar principles to septic coagulopathy as per the ISTH guidelines with respect to blood transfusions may be followed. [5]

II. Heme Contact

Please contact the Hematology Consult Attending for any coagulation-related COVID-19 issues or questions.

Notes:

(A) It is already well-established that older individuals and those who have co-morbidities (both groups tend to have higher D-dimer) are more likely to die from COVID-19 infection. [1]

Studies specifically looking at abnormal coagulation parameters have identified markedly elevated D-dimers as one of the predictors of mortality. [2,4]

Huang and colleagues showed that D-dimer levels on admission were higher in patients needing critical care support (median [range] D-dimer level 2400 ng/mL[600–14,400]) than those patients who did not require it (median [range] D-dimer level 0.5 ng/mL [300–800], $p=0.0042$). [3]

Comments regarding D-dimer: When thrombin is activated, it cleaves fibrinogen into fibrin. The fibrin then polymerizes and is cross-linked by Factor XIII. When such a fibrin clot is generated in any disorder, microvascular or macrovascular, the fibrinolytic system is activated, and plasmin cleaves the cross-linked fibrin into smaller pieces which are the D-dimers. Therefore, the **D-dimer reflects the production of cross-linked fibrin** and is also affected by hepatic function; D-dimers are cleared by a normal liver but rise with liver dysfunction.



(B) Tang et al noted development of DIC on day 4 in 71.4% of patients who didn't survive the infection compared to just 1 patient (0.6%) who survived. Researchers also noted a statistically significant increase in D-dimer levels, and PT with a decrease in fibrinogen levels in non-survivors at days 10 and 14. [2,5]

(C) LMWH protects critically ill patients against venous thromboembolism. In addition, LMWH has been shown to have anti-inflammatory properties which may be an added benefit in COVID infection where proinflammatory cytokines are markedly raised. [1,3,6,9]. **See dosing instructions below.**

(D) Multi-organ failure is more likely in patients with sepsis if they develop coagulopathy and inhibiting thrombin generation may have benefit in reducing mortality. [7,8,9]. As noted in (B), this evidence suggests that monitoring PT, D-dimer, platelet count and fibrinogen can be helpful in determining prognosis in COVID-19 patients and if there is worsening of these parameters, more aggressive critical care support is warranted and consideration should be given for more 'experimental' therapies in and blood product support as appropriate [2,5,9]

(E) Subgroup analysis comparing patients by survival noted lower platelet count correlated with mortality. Thrombocytopenia was also associated with over five-fold increased risk of severe COVID-19 illness (OR, 5.1; 95% CI, 1.8-14.6). This suggests thrombocytopenia at presentation may be prognosticator.[10]



Dosing Guidelines (see attached charts) [11]

Supplemental Table S1: Chemoprophylaxis Dosing Recommendations

	UFH	Enoxaparin ¹	Fondaparinux ²	Apixaban ³	Rivaroxaban ⁴	Dabigatran ⁵
Standard Dose	5000 units SQ q12h	40 mg SQ q24h Trauma: 30 mg SQ q12h	2.5 mg SQ q24h	2.5 mg PO q12h	10 mg PO q24h	110 mg x 1 on post-op day 0 followed by 220 mg q24h
Renal Adjustment	No dose adjustment required	CrCl 15 - 29 mL/min: 30 mg SQ q24h CrCl < 15 mL/min or renal replacement therapy: Consult Pharmacy Avoid use if fluctuating renal function	CrCl 30 – 50 mL/min: 1.25 mg SQ q24h CrCl < 30 mL/min: Consult Pharmacy Avoid use if fluctuating renal function	CrCl < 15 mL/min or on renal replacement therapy: 2.5 mg PO q12h No dose adjustment required	Avoid use if CrCl < 30 mL/min Avoid use if fluctuating renal function	Avoid use if CrCl < 30 mL/min Avoid use if fluctuating renal function
Obesity (BMI > 40 kg/m ² , weight > 120 kg)	120 – 150 kg: 5000 units q8h > 150 kg: 7,500 SQ units q8h	CrCl ≥ 30 mL/min: 40 mg SQ q12h CrCl < 30 mL/min or on renal replacement therapy: 40 mg SQ q24h + Consult Pharmacy	Limited Data, Consult Pharmacy	Limited Data, Consult Pharmacy	Limited Data, Consult Pharmacy	Limited Data, Avoid Use
Low Body Weight (< 50 kg)	5,000 units SQ q12h or 2,500 units SQ q12h	30 mg SQ q24h	Limited Data, Avoid Use	Limited Data, Avoid Use	Limited Data, Avoid Use	Limited Data, Avoid Use
Drug-Drug Interactions	N/A	N/A	N/A	Major DDI Consult Pharmacy	Major DDI Consult Pharmacy	Major DDI Consult Pharmacy
Monitoring	Consult pharmacy or hematology in patients with organ dysfunction, extremes of weight or close monitoring warranted (e.g., high bleed risk, failure to thrive); consider drug-specific anti-Xa monitoring					N/A

Abbreviations: AKI – acute kidney injury; BMI – body mass index; DDI – drug drug interactions; PO – per os (oral route); SQ – subcutaneous route

Supplemental Table S2: Therapeutic Parenteral Anticoagulation Recommendations

	Unfractionated Heparin	Enoxaparin ¹	Fondaparinux ²	Bivalirudin ⁶	Argatroban ⁷
Standard Dose	ACS: 60 unit/kg bolus + 12 units/kg/hr infusion VTE/Afib: 80 unit/kg bolus + 18 units/kg/hr infusion	1 mg/kg SQ q12h (for normal renal function)	Weight-based: < 50 kg: 5 mg SQ q24h 50 – 100 kg: 7.5 mg q24h > 100 kg: 10 mg q24h	See Protocol - Standard Starting Dose: 0.15 mg/kg/hr	See Protocol – Usual Starting Dose: Medically ill: 0.5 - 1 mcg/kg/min Critically ill: 0.25 mcg/kg/min ⁸
Renal Adjustment	No Dose Adjustment Necessary	CrCl 15 – 29 mL/min: 1 mg/kg SQ q24h CrCl <15 mL/min: Consult Pharmacy	CrCl < 30 mL/min: Avoid use	CrCl 30 – 60 mL/min: 0.05 mg/kg/hr CrCl < 30 mL/min or on Renal Replacement Therapy: 0.025 mg/kg/hr	No Dose Adjustment Necessary
Hepatic Adjustment	No Dose Adjustment Necessary	No Dose Adjustment Necessary	No Dose Adjustment Necessary	No Dose Adjustment Necessary	Moderate (Child-Pugh B) Hepatic Insufficiency: 0.5 mcg/kg/min Severe (Child-Pugh C) Hepatic Insufficiency: Use bivalirudin
Obesity (BMI > 40 kg/m ² , weight > 120 kg)	Consult Pharmacy	CrCl ≥30 mL/min: 0.75 mg/kg q12h ^{9,10} CrCl < 30 mL/min: 0.75 mg/kg q24h > 150 kg: Avoid Use	> 100 kg: 10 mg SQ q24h	Limited data, Consult Pharmacy	Limited data, Consult Pharmacy

Abbreviations: ACS – acute coronary syndrome; Afib – atrial fibrillation; BMI – body mass index; SQ – subcutaneous route; VTE – venothromboembolism



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