St. Joseph's Health

Policies and Procedures

COVID-19 ANTICOAGULATION GUIDELINE

Department: Interdisciplinary

***** THIS IS A GUIDELINE. PROVIDER DISCRETION ON THE USE OF ANTICOAGULANTS SHOULD NOT SOLELY BE DETERMINED BY D-DIMER LEVELS*****

BACKGROUND

This guideline should be considered as an interim guidance since the clinical experience of managing this pandemic is increasing. The aim of this guidance document is to provide a risk stratification at admission for a COVID-19 patient and management of coagulopathy which may develop in some of these patients, based on easily available laboratory parameters.

Patients with severe COVID-19 infection can develop a coagulopathy which mimics disseminated intravascular coagulopathy (DIC) per International Society on Thrombosis and Haemostasis (ISTH) criteria, with fulminant activation of coagulation, resulting in widespread microvascular thrombosis and consumption of coagulation factors. This risk for thrombosis is further propagated by the cytokine storm.

- This is reflected by thrombocytopenia (possible), prolongation of the PT/INR, PTT, elevation of D-dimer, and decreased fibrinogen levels (end stages of COVID-19).
- Patients may develop microvascular thrombosis in which conventional means of diagnosis for suspected VTE may have minimal utility.
- The coagulopathic presentation is more prothrombotic than hemorrhagic.

***Rationale for early anticoagulation*:**

- Pathophysiology of COVID-19 associated respiratory disease is consistent with pulmonary vascular thromboemboli with increased dead space ventilation.
    - Autopsy studies have demonstrated venous thromboembolism in deceased coronavirus patients.[1]
    - Early anticoagulation is necessary to prevent propagation of microthrombi at disease presentation and may be associated with decreased mortality.[2]

***Rationale for choice of anticoagulant*:**

- Heparins bind tightly to COVID-19 spike proteins, downregulate IL-6 and directly dampen immune activation.[3-5]
- Direct Oral Anticoagulants (DOAC) do not appear to have these anti-inflammatory properties.
    - Use inpatient is not recommended; consideration for use should be made at discharge.
- Agents such as fondaparinux (Arixtra®) are not recommended except in those with a history of heparin-induced thrombocytopenia (HIT).

Anticoagulation EXCLUSION criteria AND when to HOLD anticoagulation:

- Hgb drop > 2g/L in 24-hour period
- History of Hemorrhagic Stroke within the past 3 months
- Observed bleeding during past 24 hours
- Recent gastrointestinal bleed
- Planned invasive procedures (per physician discretion)
- Platelet count < 25 x 109/Ls
- Fibrinogen < 0.5 g/L

ANTICOAGULANT DOSING

The following recommendations for anticoagulant therapy, prophylactic and therapeutic dosing, in patient under investigation (PUI) for COVID-19 or those with confirmed COVID-19 is found below. Additional guidance on the use of anticoagulants can be found in Appendix 1. Considerations for intermediate or therapeutic dosing strategies should not be solely determined based off d-dimer alone. The clinical status of the patient must be considered when weighing the risk-benefit of anticoagulant strategies. Please refer to the COVID-19 Anticoagulation Flowsheet for additional dosing guidance.

PUI for COVID-19 or those with confirmed COVID-19

- **Prophylactic dose** enoxaparin (30 mg BID or 40 mg daily SC) should be given to all hospitalized patients
  Refer to VTE PROPHYLAXIS IN ADULT GUIDELINE FOR DOSING RECOMMENDATIONS IN SPECIAL POPULATIONS

Drug	Renal function	Dose Recommendation
Enoxaparin	CrCl ≥ 30 mL/min	40 mg daily ++
	CrCl < 30 mL/min, AKI or ESRD	30 mg daily
	≥ 100 kg and BMI ≥ 40*	40 mg BID*
Heparin	N/A	5,000 units Q8H
	≥ 100 kg and BMI ≥ 40	7,500 units Q8H

* if CrCl < 30 mL/min , AKI or ESRD enoxaparin is not the preferred agent. If enoxaparin is used, consider 40 mg daily.++Enoxaparin once daily should be used, in most circumstances, in COVID patients. Enoxaparin 30mg BID dosing may be considered at physician discretion.

- **Enoxaparin is preferred over unfractionated heparin (reduced frequency of administration).**
- If heparin 5,000 units SC is used, Q8H dosing should be used over Q12H dosing.
- For patients with history of HIT, fondaparinux may be considered. (Appendix 2)

For critically ill (severe) PUI for COVID-19 or those with confirmed COVID-19 with a d-dimer > 5 mcg/mL:

- **Intermediate prophylactic doses** of may be considered for management of hypercoaguable state.
- Risk of bleeding using VTE-BLEED score should be assessed in all patients prior to starting intermediate prophylactic dosing (Appendix 3).

Drug	Renal function	Dose Recommendation
Enoxaparin	CrCl ≥ 30 mL/min	0.5 mg/kg BID*
	CrCl < 30 mL/min, AKI or ESRD	UFH recommended
Heparin	N/A	7,500 units Q8H

* Round to nearest syringe size (within 10% of recommended dose)

For critically ill (severe) PUI COVID-19 or those with confirmed COVID-19 with d-dimers > 10 mcg/mL or persistent hypoxia despite aggressive ventilation strategies or those showing other signs of hypercoagulable state:

- Consider **therapeutic dose** enoxaparin.
- In those with high suspicion for VTE, consider use of the Modified Wells Score for Assessment of Clinical Likelihood (Appendix 4) and VTE-BLEED Score (Appendix 3).
  - The decision to provide therapeutic dosing should patient specific.
  - Utilization of thromboelastography may be considered, although is utility is unclear.

Drug	Renal function	Dose Recommendation
Enoxaparin	CrCl ≥ 30 mL/min	1 mg/kg BID or 1.5 mg/kg daily*
	CrCl < 30 mL/min^{++}	0.5 mg/kg BID or 1 mg/kg mg daily*
Heparin^{++}	N/A	Anti-Xa driven Heparin Continuous Infusion

* Round to nearest syringe size (within 10% of recommended dose)

++ Heparin continuous infusion preferred in AKI, CKD or RRT

- **Heparin monitoring of anti-Xa levels instead of aPPT should be considered as COVID-19 can cause elevations in aPTT levels.** Please refer to ANTI-XA DRIVEN HEPARIN GUIDELINE.
- For patients with history of HIT, fondaparinux may be considered. (Appendix 2)
- Alteplase is currently NOT recommended for COVID-19 coagulopathy (outside of a clinical trial)

- Thrombolysis may be considered if confirmed or high suspicion of indications specific to lytic therapy (e.g. acute ischemic stroke, PE, acute myocardial infarction).

*****D-dimers should be monitored throughout hospitalization as guidance for anticoagulation prophylaxis and treatment. Considerations for intermediate dosing or therapeutic dosing strategies should not be solely determined based off d-dimer alone. The clinical status of the patient must be considered when weighing the risk-benefit of anticoagulant strategies. *****

Patients on anticoagulation prior to hospitalization:

- Consider switching to treatment dose enoxaparin (1 mg/kg BID or 1.5 mg/kg daily; *requires dose adjustment for CrCl < 30 mL/min, AKI or ESRD) or heparin continuous infusion in severe illness.
- Mechanical valve or LVAD patients on warfarin should be transitioned to enoxaparin (or heparin if indicated) until COVID-19 is ruled out.

Duration of anticoagulation

- In patients with presumed or confirmed VTE, duration of therapy should be a minimum of 3 months
  - Patients may be transitioned to DOAC agents when clinically appropriate
- In critically ill (severe) disease with d-dimer $\geq$ 5 mcg/mL, intermediate dosing anticoagulation should be continued until resolution of severe disease/critical illness.
  - Trend in d-dimer can be used to guide de-escalation from intermediate dosing to standard prophylactic dosing, also considering the clinical status of the patient.
- In patients who do not meet criteria for intermediate or full dose anticoagulation, or those de-escalated from intermediate dose, should be continued on standard prophylactic dosing for remainder of hospitalization.
- In patients at high risk for VTE following hospital discharge, post-discharge prophylaxis may be considered for a duration of 30 days.
  - Continuation of therapy should only be considered in patients with a low bleed risk (IMPROVE bleed score < 7) **AND** one of the following:
    - Moderate – significant immobility, prior VTE, cancer, ongoing respiratory compromise (shortness of breath), were admitted to an intensive care unit with prolonged intubation, sedation or paralysis.
  - Prophylactic dose enoxaparin (30 mg BID or 40 mg daily)* or DOACs (rivaroxaban 10 mg daily or apixaban 2.5 mg BID) may be considered. Therapy should be determined on a patient specific basis.
    - **Enoxaparin adjustments for obesity or renal dysfunction are required*

References

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Appendix 1. Journal of the American College of Cardiology Antithrombotic Therapy in COVID Summary

Table 6. Summary of Consensus Recommendation on Antithrombotic Therapy During the COVID-19 Pandemic	
	Patients with Mild COVID-19 (outpatient)
	For outpatients with mild COVID-19, increased mobility should be encouraged. Although indiscriminate use of pharmacological VTE prophylaxis should not be pursued, assessment for the risk of VTE and of bleeding is reasonable. Pharmacologic prophylaxis could be considered after risk assessment on an individual case basis for patients who have elevated risk VTE, without high bleeding risk.*
	There is no known risk of developing severe COVD-19 due to taking antithrombotic agents (i.e. antiplatelet agents or anticoagulants). If patients have been taking antithrombotic agents for prior known thrombotic disease, they should continue their antithrombotic agents as recommended.
	For outpatients on vitamin K antagonists who do not have recent stable INRs, and are unable to undergo home or drive-through INR testing, it is reasonable to transition the treatment DOACs if there are no contraindications and no problems with drug availability and affordability. If DOACs are not approved or available, low-molecular weight heparin can be considered as alternative.*
	Patients with Moderate or Severe COVID-19 without DIC (hospitalized)
	Hospitalized patients with COVID-19 should undergo risk stratification for VTE prophylaxis.
	For hospitalized patients with COVID-19 and not in DIC, prophylactic doses of anticoagulation can be administered to prevent VTE.*¥† If pharmacological prophylaxis is contraindicated, it is reasonable to consider intermittent pneumatic compression.
	For hospitalized patients with COVID-19 and not in DIC, there is insufficient data to consider routine therapeutic or intermediate-dose parenteral anticoagulation with UFH or LMWH.*‡
	Routine screening for VTE (e.g. bilateral lower extremity ultrasound) for hospitalized patients with COVID-19 with elevated D-Dimer (>1,500 ng/mL) cannot be recommended at this point&
	Patients with Moderate or Severe COVID-19 and suspected or confirmed DIC (hospitalized)
	For patients with moderate or severe COVID-19 and in DIC but without overt bleeding, prophylactic anticoagulation should be administered.*¥§
	For hospitalized patients with COVID-19 with suspected or confirmed DIC, but no overt bleeding, there is insufficient data to consider routine therapeutic or intermediate-dose parenteral anticoagulation with UFH or LMWH.*β
	For patients with moderate or severe COVID-19 on chronic therapeutic anticoagulation, who develop suspected or confirmed DIC without overt bleeding, it is reasonable to consider the indication for anticoagulation and weigh with risk of bleeding when making clinical decisions regarding dose adjustments or discontinuation. The majority of authors of this manuscript recommended reducing the intensity of anticoagulation in this clinical circumstance, unless the risk of thrombosis considered to be exceedingly high. ‖
	For patients with moderate or severe COVID-19 and an indication for dual antiplatelet therapy (e.g. percutaneous coronary intervention within the past 3 months or recent myocardial infarction) and with suspected or confirmed DIC without overt bleeding, in the absence of evidence, decisions for antiplatelet therapy need to be individualized. In general, it is reasonable to continue dual antiplatelet therapy if platelet count >50,000, reduce to single antiplatelet therapy if 25,000<platelet count<50,000; and discontinue if platelets <25,000. However, these guidelines may be revised upward or downward depending on the individualized relative risk of thrombotic complications vs. bleeding.
	For patients who were admitted and are now being discharged for COVID-19, routine screening for VTE risk is reasonable for consideration of pharmacological prophylaxis for up to 45 days post-discharge. Pharmacological prophylaxis should be considered if there is elevated risk for thrombotic events, without high bleeding risk. *# Ambulation and physical activity should be encouraged.
	Patients with COVID-19 presenting with ACS
	For presentations concerning for STEMI and COVID-19, clinicians should weigh the risks and severity of STEMI presentation with that of potential COVID-19 severity in the patient, as well as risk of COVID-19 to the individual clinicians and to the healthcare system at large. Decisions for primary percutaneous coronary intervention or fibrinolytic therapy should be informed by this assessment.*
	Patients without COVID-19 who have previously-known thrombotic disease
	There is no known risk of developing severe COVD-19 due to taking antithrombotic agents. Patients should continue their antithrombotic agents as recommended.
	To minimize risks associated with healthcare worker and patient in-person interactions, follow-up with e-visits and telemedicine is preferable in most cases.
	Patients without COVID-19 who develop new thrombotic disease
	To minimize risks associated with healthcare worker and patient in-person interactions, in-home treatment or early discharge should be prioritized.
	To minimize risks associated with healthcare worker and patient in-person interactions, follow-up with e-visits and telemedicine is preferable in most cases.
	Patients without COVID-19 but with co-morbid conditions (e.g. prior VTE, active cancer, major cardiopulmonary disease), who are homebound during the pandemic
	Recommendations include increased mobility, and risk assessment for the risk of VTE and risk of bleeding is reasonable. Administration of pharmacologic prophylaxis could be considered after risk assessment on an individual case basis for patients who have elevated risk for thrombotic events, without high bleeding risk.
*Indicates recommendations as reached by consensus of at least 66% of authors determined via Delphi method. ¥Although high-quality data are lacking, some panel members (55%) considered it reasonable to use intermittent pneumatic compression in patients with severe COVID-19, in addition to pharmacological prophylaxis. Specific areas of concern included limited data on use in the prone position as well as potential high incidence of preexisting asymptomatic DVT. †If VTE prophylaxis is considered, enoxaparin 40mg daily or similar LMWH regimen (e.g. dalteparin 5000U daily) can be administered. Subcutaneous heparin (5000U twice to three times per day) can be considered for patients with renal dysfunction (i.e. creatinine clearance <30 mL/min). ‡While the majority of the writing group did make this recommendation, 31.6% of the group were in favor of intermediate-dose anticoagulation [e.g. enoxaparin 1mg/kg/day, or enoxaparin 40mg BID, or UFH with target aPTT of 50-70] and 5.2% considered therapeutic anticoagulation. &The majority of the investigators recommended against routine VTE screening (68%); however, the remaining members of the group (32%) recommended to consider such testing. §The majority of the investigators recommended prophylactic anticoagulation (54%). A minority of investigators (29.7%) voted for intermediate-dose parenteral anticoagulation in this setting, and 16.2% considered therapeutic anticoagulation. ‖While the majority of investigators voted to reduce the intensity of anticoagulation if the indication were not acute (62%), this survey question did not meet prespecified cut-off of 66%. #The majority of the writing group recommended prophylaxis with DOACs (51%) and minority (24%) recommended LMWH, if available and appropriate. ACS: acute coronary syndrome; DOAC: direct oral anticoagulant, LMWH, low-molecular weight heparin; STEMI, ST-segment elevation myocardial infarction; UFH, unfractionated heparin; VTE, venous thromboembolism.	

APPENDIX 2. Fondaparinux dosing

- For patient under investigation (PUI) for COVID-19 or those with confirmed COVID-19, prophylactic dose:

Drug	Renal function	Dose Recommendation
Fondaparinux	CrCl > 50 mL/min	2.5 mg daily
	CrCl 30 – 50 mL/min	Use caution; consider 50% dose reduction
	CrCl < 30 mL/min	Use not recommended
	< 50 kg	Use not recommended for prophylaxis

- For PUI COVID-19 or those with confirmed COVID-19 with d-dimers $\geq$ 5 mcg/mL or persistent hypoxia despite aggressive ventilation strategies or those showing other signs of hypercoagulable state, consider therapeutic dose:

Drug	Renal function	Dose Recommendation
Fondaparinux	CrCl $\geq$ 30 mL/min and < 50 kg	5 mg daily
	CrCl $\geq$ 30 mL/min and 50 – 100 kg	7.5 mg daily
	CrCl $\geq$ 30 mL/min and > 100 kg	10 mg daily
	CrCl < 30 mL/min	Use not recommended; argatroban continuous infusion preferred

Appendix 3. VTE – BLEED Score

Factor	Score
Active cancer	2
Male with uncontrolled arterial hypertension	1
Anemia	1
History of bleeding	1
Age ≥ 60 years old	1
Renal dysfunction	1
Classification of Patients with VTE-BLEED Score	
Low risk of bleeding	Total score < 2
High risk of bleeding	Total score $\geq$ 2

Other factors that contribute to bleeding:
- Thrombocytopenia
- Cirrhosis
- Other anti-thrombotic use (e.g. aspirin, clopidogrel, ticagrelor)

Appendix 4. Modified Wells Score for Assessment of Clinical Likelihood

Pulmonary Embolism

Criteria	Points
Clinical signs and symptoms of DVT (objectively measured calf swelling and pain with palpation in the deep vein region)	3
An alternative diagnosis is less likely than PE	3
HR > 100 beats per minute	1.5
Immobilization or surgery in the previous 4 weeks	1.5
Previous DVT or PE	1.5
Hemoptysis	1
Malignancy (on treatment, treated in past 6 months or palliative care)	1
Total Score (> 4 = PE—likely; $\leq$ 4 = PE – unlikely)	

Deep Vein Thrombosis

Criteria	Points
Active cancer (patient receiving treatment for cancer within the previous 6 months or currently receiving palliative treatment)	1
Paralysis, paresis, or recent casting or immobilization of the lower extremities	1
Recently bedridden for 3 days or more, or major surgery within the previous 12 weeks requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than that on the asymptomatic side(measured 10 cm below the tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Previously documented DVT	1
Collateral non-varicose superficial veins	1
Alternative diagnosis at least as clinically likely as DVT	- 2
Total Score (> 4 = DVT—likely; ≤ 4 = DVT – unlikely)	