Health Services
LOS ANGELES COUNTY

DHS Expected Practices

Specialty: Anticoagulation

Subject: Anticoagulation for Hospitalized Patients with COVID-19 Pneumonia

Date: 5/6/2020

Purpose:

To provide guidance regarding selection and dosing of anticoagulants for patients with severe COVID-19 pneumonia.

Target Audience:

Providers participating in the care of hospitalized patients with COVID-19 pneumonia

Abbreviations:

VTE	Venous thromboembolism
UFH	Unfractionated heparin
LMWH	Low molecular weight heparin
DOAC	Direct oral anticoagulant
PT	Prothrombin time
INR	International normalized ratio
aPTT	Activated partial thromboplastin time
DVT	Deep venous thrombosis
PE	Pulmonary embolism
BMI	Body mass index
NC	Nasal cannula
HITT	heparin-induced thrombocytopenia and thrombosis

This *Expected Practice* was developed by a DHS Specialty-Primary Care Work Group to fulfill the DHS mission to ensure access to high-quality, patient-centered, and cost-effective health care. SPC Work Groups, composed of specialist and primary care provider representatives from across LA County DHS, are guided by 1) real-life practice conditions at our facilities, 2) available clinical evidence, and 3) the principle that we must provide equitable care for the entire population that LA County DHS is responsible for, not just those that appear in front of us. It is recognized that in individual situations a provider's clinical judgment may vary from this *Expected Practice*, but in such cases compelling documentation for the exception should be provided in the medical record.

Background:

Although the incidence of venous thromboembolic (VTE) disease in patients with COVID-19 pneumonia is unknown, there is limited evidence that coagulation parameters in these patients are significantly altered compared to healthy people.[1] In a small, retrospective analysis of 81 patients with patients with severe pneumonia due to COVID-19, the incidence of VTE was 25% (20/81).[2]

Published reports suggest that rising D-dimers correlate with poor survival among COVID-infected patients. Autopsy reports suggest a microvascular thrombosis contributes to respiratory dysfunction in infected patients. These and anecdotal reports of overt VTE and significant dialysis-related thrombosis have led some centers to increase to higher or therapeutic dosing of heparins early in the course of moderate-severe COVID infection.[3],[4] Although there is no high quality evidence, it may be reasonable to increase the intensity of anticoagulation (from standard-intensity prophylaxis to intermediate-intensity prophylaxis or from intermediate-intensity prophylaxis to therapeutic anticoagulation) in certain clinical settings.[5]

Any decisions regarding anticoagulation should be made on an individual basis and should consider both the patient's thromboembolic and bleeding risk.

Expected Practice:

<u>General approach and rationale</u>:

1. Heparins (unfractionated or low molecular weight) have anti-inflammatory and anti-complement activity and may bind viral proteins. Therefore, enoxaparin and unfractionated heparin (UFH) are generally the preferred agents for prophylactic and therapeutic anticoagulation.

2. For patients admitted on therapeutic doses of warfarin for a mechanical heart valve, we recommend either continuing warfarin therapy or switching to treatment dose IV unfractionated heparin in consultation with Cardiology.

3. Direct oral anticoagulant (DOAC) medications may have drug-drug interactions with antiviral therapy, steroids, or other investigational treatments for COVID-19. For patients admitted on therapeutic doses of anticoagulation with a DOAC, we recommend reviewing potential drug-drug interactions throughout hospitalization and transitioning to UFH/LMWH if needed. If a patient is taking DOAC for coronary artery disease, consult cardiology before switching.

4. DOAC medications have the potential to increase Anti-Xa levels, PT/INR, and to a lesser extent aPTT. Providers should be aware of this *potential effect* when reviewing patient's

baseline coagulation values. Additionally, if a patient's baseline Anti-Xa value is elevated due to recent DOAC use, it will temporarily affect the ability to monitor either LMWH or UFH with Anti-Xa values.[6],[7] For specific questions about how to dose and monitor IV unfractionated heparin and LMWH for patients recently on DOAC medications, please consult with inpatient pharmacy, hematology, or local anticoagulation experts.

5. Specific guidance regarding selection of DOAC and dosing is summarized in Table 1

6. For patients on antiplatelet therapy, if platelets are >100,000/mL, we recommend continuing antiplatelet therapy and prophylactic doses of anticoagulation (Level 1 and 2). Should patient require full dose anticoagulation consider reducing dual antiplatelet therapy to single agent antiplatelet therapy or stopping antiplatelet therapy in consultation with Cardiology. For patients with platelets 50,000-100,000/mL consider holding antiplatelet therapy. If COVID antiviral or other therapies planned, check for drug interactions such as via CYP3A4 effects.

Table 1: DHS Anticoagulation Guidelines for COVID-19 patients[1]

EXCLUSION CRITERIA: known bleeding diathesis, active bleeding, pre-existing coagulopathy, ascites (elevates baseline d-dimer), thrombocytopenia <50,000/mL[2]

<table>
<tr><th colspan="3">CLINICAL CATEGORY</th><th colspan="2">CONSIDER THE FOLLOWING</th></tr>
<tr><td colspan="5">LEVEL 1:</td></tr>
<tr><td colspan="3" rowspan="2">NO VTE and D-dimer < 6.0 mcg/ml FEU</td><td>CrCl≥ 30 ml/min</td><td>CrCl<30ml/min:</td></tr>
<tr><td><u>BMI ≤ 30</u>:
Enoxaparin 40 mg subcutaneous Qday
<u>BMI > 30</u>:
Enoxaparin 40mg subcutaneous Q12hr</td><td>Enoxaparin 30 mg subcutaneous Qday
or
UFH 5,000 units subcutaneous Q8hrs</td></tr>
<tr><td colspan="5">LEVEL 2:</td></tr>
<tr><td rowspan="2">NO VTE</td><td>and <u>any</u> of the following:</td><td>• D-dimer <u>≥</u> 6.0 mcg/ml FEU
• D-dimer increased by <u>≥</u> 2.0 mcg/ml FEU despite 48hr of prophylactic LMWH or UFH
• Inability to dialyze due to clotting in line, filter, or machine</td><td>CrCl≥ 30 ml/min</td><td>CrCl<30ml/min:</td></tr>
<tr><td>Enoxaparin 0.5 mg/kg subcutaneous Q12hr
(pharmacy may to round to nearest vial)</td><td>Low Dose IV Unfractionated Heparin Protocol
(use approved order set)</td></tr>
<tr><td colspan="5">LEVEL 3:</td></tr>
<tr><td rowspan="2">KNOWN or SUSPECTED VTE</td><td>or</td><td>Inability to dialyze due to clotting in line, filter, or machine despite Level 2 anticoagulation</td><td>CrCl≥ 30 ml/min</td><td>CrCl<30ml/min:</td></tr>
<tr><td colspan="2"><u>Consider if</u>: Patient requires FiO2 > 50% or O2 flow <u>≥</u> 6L/min (mask or NC) for >4 hrs while on Level 1 or 2 anticoagulation</td><td>Enoxaparin 1 mg/kg subcutaneous Q12hr
(pharmacy may round to nearest vial)</td><td>DVT/PE IV Unfractionated Heparin Protocol
-Use approved order set
-Consider eliminating bolus if recent Anti-Xa at/near goal or LMWH recently dosed</td></tr>
<tr><td colspan="5">LEVEL 4:</td></tr>
<tr><td colspan="3" rowspan="2">Patient develops any of the following while therapeutic on <u>treatment dose</u> of unfractionated heparin or enoxaparin:
(1) VTE
(2) Suspected HITT
(3) D-dimer persistently >20 mcg/ml FEU
(4) Inability to dialyze due to clotting in line, filter, or machine despite Level 3 anticoagulation</td><td colspan="2"><u>Check</u>: -Cardiolipin Ab Panel -Antithrombin III activity
-HITT screen (if indicated) -Beta-2 Glycoprotein Ab Panel</td></tr>
<tr><td colspan="2"><u>Options</u>: -Consider using Anti-Xa for LMWH dosing
-If patient has breakthrough clotting while on therapeutic LMWH (and HIT is not suspected), consider increasing LMWH dose by 25%
-If HIT is suspected, consider switching to argatroban or fondaparinux (fondaparinux requires less nurse/phlebotomy contact with patient)
-If emboli are suspected, consider thrombolysis</td></tr>
</table>

[1]Guideline may be updated as new data become available regarding anticoagulation for COVID-infected patients.

[2]For patients with platelets <50,000/mL we recommend workup other etiologies and consulting hematology.

Table 2: Recommended anticoagulation studies for COVID-19 patients

Recommended studies at baseline: D-Dimer PT/INR aPTT Fibrinogen CBC w/ diff CMP
Repeat every 24-48 hours: D-dimer CBC CMP Fibrinogen
Consider Doppler US of extremities: For patients with rising d-dimer despite Level 1-3 prophylaxis **or** if other usual clinical indication is present

References:

[1] Han H, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clin Chem Lab Med*. https://doi.org/10.1515/cclm-2020-0188. Published online: 16 Mar 2020

[2] Cui, S., Chen, S., Li, X., Liu, S. and Wang, F. (2020), Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost*. Accepted Author Manuscript. doi:10.1111/jth.14830

[3] Tang, N., Bai, H., Chen, X., Gong, J., Li, D. and Sun, Z. (2020), Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. Accepted Author Manuscript. doi:10.1111/jth.14817

[4] Yin, S., Huang, M., Li, D. *et al.* Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. *J Thromb Thrombolysis* (2020). https://doi.org/10.1007/s11239-020-02105-8

[5] COVID-19 and VTE/Anticoagulation: Frequently Asked Questions. American Society of Hematology. https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation. Accessed April 24 2020.

[6] Hillarp A, et al. Effects of the oral, direct factor Xa inhibitor rivaroxaban on commonly used anticoagulation assays. *J Thromb Haemost*, 9: 133-139.

[7] Samama et al.: Laboratory assessment of rivaroxaban:a review. Thrombosis Journal 2013 11:11.