THE SOCIETY FOR POST-ACUTE AND LONG-TERM CARE MEDICINE
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Anticoagulation of Patients with COVID 19 in PALTC

May 28, 2020

Background:

Hypercoagulability is well known to be associated with severe infections, such as sepsis and pneumonia (Violi F, 2014) (Zhai, 2020) (Clayton TC, 2011). High rates of thrombosis and thromboembolic events have been observed during the COVID 19 pandemic, and indicate a poor prognosis (Wang, 2020) (Guan, 2020).

In January 2020, the World Health Organization (WHO) issued interim guidance recommending prophylactic daily low-molecular weight heparins (LMWHs) for patients hospitalized with COVID-19. (Clinical management of severe acute respiratory infection when novel coronavirus infection is suspected, 2020), and interim guidance from the International Society of Thrombosis and Haemostasis (ISTH) was released on March 20, 2020 that echoed this recommendation. (Thachil, 2020).

This interim guidance recommendation has yet to be validated, and in another published study, better prognosis appears to be limited to the subpopulation of severe COVID-19 infections that meet sepsis-induced coagulopathy (SIC) criteria with a score ≥ 4 and/or have markedly elevated D-dimer (>3 microgram/mL). In a population of patients with severe COVID-19, 20% met the SIC criteria, and 35.9% met the elevated D-dimer criteria alone; in these patients, there was a 20% reduction in mortality for those who were treated with LMWH. (Tang, 2020)

This limited evidence about which patients are likely to benefit is particularly relevant to providers in the PALTC setting. On the one hand, recognized risk factors for thrombosis include advanced age, history of cardiovascular disease, malignancy, and immobility. On the other hand, the PALTC population is very vulnerable to polypharmacy adverse events, and these are exacerbated by the addition of drugs that are being used to treat COVID-19 and anticoagulant/antiplatelet therapy. The risks are also exacerbated by immobility, now that patients in most facilities are isolated to their rooms and are unable to ambulate to the dining room, activities, outside, or within the facility.

Specifically, the authors of an article in the Journal of the American College of Cardiology authors recommended caution about drug-drug interactions between investigational drugs for COVID-19 (Lopinavir/ritonavir) and anticoagulants and antiplatelet therapies, which are either contraindicated and/or need dosing adjustments. The same document also counsels that in the absence of high-quality data, anticoagulation prophylaxis of patients with mild COVID-19 should be reserved for those who are at highest risk of thrombosis. (Bikdeli B. , 2020)

This guidance addresses two populations of PALTC residents: (1) residents who become infected and are treated in place and (2) residents and community members who were hospitalized with moderate or severe COVID-19 and discharged to PALTC to continue their recovery. This document is intended to provide interim guidance based on current understanding of the disease to frontline PALTC providers.

Significant distinctions between the PALTC setting and the hospital that must be considered include:

1. Limited access to diagnostic testing
2. Limited access to personal protective equipment (PPE)
3. Limited staffing: i.e., an already challenged workforce that is experiencing significant illness and increased workloads
4. Patient population with many comorbidities and medications resulting in increased susceptibility to significant drug-drug interactions

Sample Facility Policy on Anticoagulation for PALTC Residents Who Have Covid-19

Purpose:

To decrease the risk of thrombosis in individuals with a clinically significant COVID-19 infection

Background:

The incidence of thrombotic events in PALTC residents with COVID-19 infection has not been established. The PALTC population has experienced high mortality from COVID-19. In patients hospitalized with severe COVID-19, a markedly elevated D-Dimer (6 X higher that upper normal limit), appears to increase mortality risk, and in this subset, improve survival in those who were treated prophylactically with anticoagulants (Tang N e. a., 2020). Like most decisions in PALTC patients, the decision to use anticoagulation therapy must balance the risks and benefits of the medications.

Policy:

Residents with COVID-19 will be considered for anticoagulation based on balancing the possible benefits in reducing risks of thrombosis against the risk of complications such as clinically significant bleeding.

Procedure:

1. In residents with an active Covid-19 infection, assess risks for thrombosis and for bleeding complications (see Appendices for examples of options for risk calculation approaches for both thrombosis and for bleeding).

2. Determine possible anticoagulation interventions and discuss with the resident and family members to guide decision making.

3. Encourage general prophylaxis such as mobilization and optimizing overall the medication regimen, recognizing that adequate mobilization may be challenging as many facilities are following strict isolation policies.

4. Institute appropriate anticoagulation, adjusting dosages to minimize possible drug-drug interactions

5. Monitor for signs of thromboembolic disease as in any patient.

6. Monitor periodically for potential adverse side effects of treatment, as in any patient on anticoagulation.

Appendix 1: Clinical Classifications of Coronavirus Disease 2019 Infection

(according to the fifth edition of the diagnosis and treatment plan issued by the National Health Commission)

Classification	*Symptoms*
Mild	Mild clinical symptoms, no signs of pneumonia on imaging
Moderate	Fever and respiratory symptoms, etc., with pneumonia signs on imaging
Severe	Patients with any of the following conditions: respiratory distress with respiratory rate $\geq$ 30 breaths/min; $SPO_2 \leq 93\%$ at rest; $PaO_2/FiO_2 \leq$ 300mm Hg (1mm Hg. 0.133 kPa)
Critically Ill	Patients with any of the following conditions: respiratory failure requiring mechanical ventilation; shock; other organ failure requiring admission to Intensive Care Unit (ICU).

Appendix 2: Risk Stratification Tools for Venous Thromboembolism Risk Assessment

Caprini Risk Assessment Score (most established for post-surgical) (Pannucci CJ, 2017) (Grant PJ, 2016)	
Risk Factors	***Points***
Stroke	5
Acute spinal cord injury/paralysis in last month	5
Hip/Pelvis/leg fracture in last month	5
Multiple trauma in last month	5
Age ≥ 75 years	3
History of DVT/PE	3
Family history of VTE	3
History of thrombophilia (e.g. +Factor V Leiden or other congenial or acquired thrombophilia)	3
Heparin-induced thrombocytopenia	3
Age 61-74 years	2
Positive history of cancer	2
Immobilizing plaster cast	2
Patient confined to bed ≥ 72 hours	2
Age 41-60 years	1
Congestive Heart Failure	1
COPD or abnormal pulmonary function	1
Inflammatory bowel disease	1
Severe lung disease (including pneumonia)	1
Acute myocardial infarction	1
Sepsis in last month	1
Surgery in last month	1
Varicose veins	1
Obesity (BMI >25)	1
Swollen legs (current)	1
Central venous catheter present	1
Immobile/not ambulating for >72 hours prior to hospitalization	1
Hormone replacement therapy	1
A linear association is found between the total risk score and incidence of VTE. There is not a clear threshold that has been established for when there is a clear benefit of administering prophylaxis in the PALTC COVID-19 patient. In surgical patients, the threshold to treat is a total score of 7 or higher.	

IMPROVE (non-surgical medical patient) (Gibson CM, 2017; Tapson VF, 2007)	
Risk Factor	**Points**
Previous VTE	3
Malignancy within previous 6 months	1
Thrombophilia	3
Age ≥ 60 years	1
Scoring	
0-1	Low: observed VTE risk <1%
2-3	Moderate
4	High: observed VTE risk >5.7%
If D-Dimer added to the risk assessment, get additional 2 points for a D-Dimer more than twice the upper limit of normal (UNL)	

Padua Prediction Score (Barbar S, 2010) (https://www.mdcalc.com/padua-prediction-score-risk-vte, 2020)	
Risk Factor	**Points**
Active cancer	3
Previous VTE	3
Reduced mobility	3
Known thrombophilic condition	3
Trauma or surgery in last month	2
Age ≥ 70	1
Heart and/or respiratory failure	1
Acute MI and/or ischemic stroke	1
Acute infection and/or rheumatologic disorder	1
Obesity (BMI>30)	1
Ongoing hormonal treatment	1
Scoring	
< 4	Low risk of VTE
=/> 4	High risk of VTE
In one study, use of the Padua Prediction Score for patients hospitalized for COVID-19 revealed that 40% were scored at high risk for VTE (Wang T, 2020) Thromboprophylaxis should be considered for those at high risk without contraindications	

Appendix 3: Risk Stratification Tool for Risk of Bleeding

VTE Bleed Score		
Factor	Score	Classification: <2 Low bleeding risk ≥2 High bleeding risk
Active cancer (newly diagnosed or treated within 6 months, excluding skin BCC or SCC)	2	
Male with uncontrolled arterial hypertension (systolic baseline ≥ 140)	1	
Anemia (< 13 g/dl men, <12 g/dl women)	1	
History of Bleeding (rectal bleeding, frequent nose bleeding, hematuria)	1	
Age >60 years	1	
Renal Dysfunction	1	
Other factors that contribute to bleeding: Thrombocytopenia, Cirrhosis, Other anti-thrombotic use, eGFR <60 ml/min		
Absolute contraindications: intracranial bleeding, severe active bleeding, recent brain/eye/spinal cord surgery, malignant hypotension		
Adapted from (Flok FA, 2017)		

IMPROVE Bleeding Risk Score (IMPROVE In-hospital Risk Model Bleeding Risk Factors, 2020)			
Risk Factor	Points	Risk Score	Observed rates of bleeding
Gastro-duodenal ulcer		1	1.6%
Bleeding in prior 3 months		4	4.1%
Admission platelets <50 x 109		7	14%
Hepatic Failure		15	0.5%
ICU/CCU stay		Model is still being validated for use in predicting post-discharge bleeding	
CV catheter			
Rheumatic diseases			
Current cancer			
Sex, Age, GFR			

Combined IMPROVE Bleeding and VTE Risk Models: online Risk Model calculator (beta version) https://www.outcomes-umassmed.org/IMPROVE/risk_score/index.html (Center for Outcomes Research , 2020)

VTE Risk Factors	Bleeding Risk Factors
Previous VTE	Gastro-duodenal ulcer
Thrombophilia	Bleeding in the prior 3 months
Lower Limb paralysis	Admission platelets <50 x 109
Current cancer	Hepatic failure
Immobilization ≥ 7 days	ICU/CCU stay
ICU/CCU stay	CV catheter
Age >60 years	Rheumatic diseases
	Current Cancer
Sex, Age, GFR	

Appendix 4: Interim Guidance for Dosing of LMWH and Direct Oral Anticoagulants for Prophylaxis and Treatment of VTE in COVID-19 (Lexicomp, Inc, 2020)

Anticoagulant	Prophylactic Dose for COVID-19	Therapeutic Dose to consider if D-Dimer ≥ 6x UNL	Notes
Optimal Duration of anticoagulation unknown; for high risk, consider 45 days			
Direct Oral Anticoagulants			
Dabigatran (Pradaxa)	110 mg for first day, then 220 mg QD This medication is not FDA approved for VTE prophylaxis in medical patients; it is approved for prophylaxis post-orthopedic surgery	150 mg BID after 5-10 days of parenteral anticoagulation	Many drug-drug interactions exist, as well as adjustments for renal function & obesity; carefully review with consultant pharmacist to make appropriate dose adjustments May be difficult to reverse if clinically significant bleeding occurs
Apixaban (Eliquis)	2.5 mg BID This medication is not FDA approved for VTE prophylaxis in medical patients; it is approved for prophylaxis post-surgery	10 mg BID for first week, then 5 mg BID	
Rivaroxaban (Xarelto)	10 mg QD	15 mg BID with food for 3 weeks then 20 mg once daily with food	
Betrixaban (Bevyxxa)	160 mg day 1, then 80 mg daily	Not indicated	
If CrCl is <30mL/min, apixaban at a modified dose is the safest of the DOACs			
LMWH			
Enoxaparin	40 mg SQ QD		Dose adjustment may be needed for renal insufficiency and extremes of weight (high and low)
Dalteparin	5000 units SQ QD		
Tinzaparin	4500 anti-Xa SQ QD		
If CrCl is <30mL/min, consider using unfractionated heparin instead If major bleeding develops, can reverse urgently with protamine sulfate			

<NOTE: THIS TABLE IS OPTIONAL TO INCLUDE>

Summary of Consensus Recommendation on Antithrombotic Therapy of PALTC Residents during COVID-19 Pandemic
LTC Resident with mild-moderate disease treating in place
Maintain mobility and hydration status
If already taking antithrombotic agent for pre-existing condition (i.e. antiplatelet/anticoagulant), continue
Consider starting VTE prophylaxis based on assessment of elevated VTE risk/low bleeding risk; optimal agent and duration unknown; LMWH, UFH and DOACs all reasonable considerations for up to 45 days*
LTC Resident with severe disease electing palliative treatment in place
Prophylactic treatment with anticoagulants not recommended
If palliative treatment is not elected, resident should be transferred to hospital due to limited resources at PALTC
Patients hospitalized with moderate or severe COVID-19 who are discharged to PALTC for continued recovery
Prophylactic anticoagulants started in hospital should be continued up to 45 days, depending on the balance of risks and benefits (see tools in appendix to help assess this)
Encourage ambulation and physical activity
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) 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.
Table adapted from (Bikdeli B, COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-up, 2020) *Recommended to choose the clinically appropriate agent/route that will provide the least HCW exposure (i.e. oral or SQ over IV, QD over BID, minimize blood draws.) See Appendices for VTE risk and bleeding risk assessment tools and dosing guidelines

Works Cited

(2020, May 11). Retrieved from Lexicomp, Inc.

Barbar S, e. a. (2010). A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. *Journal of Thrombosis and Haemostasis* , 2450-7.

Bikdeli B, e. a. (2020). COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy and Follow-Up. *Journal of the American College of Cardiology*,59- 61.

Center for Outcomes Research . (2020, 05 11). Retrieved from www://outcomes-umassmed.org/IMPROVE/risk_score/index.html

Clayton TC, e. a. (2011). Recent respiratory infection and risk of venous thromboembolism: case-control study through a general practice database. *International Journal of Epidemiology*, 40:819-27.

Clinical management of severe acute respiratory infection when novel coronavirus infection is suspected. (2020). https://www.who.int/docs/defaultsource/.

Flok FA, e. a. (2017). External validation of the VTE-BLEED score for predicting major bleeding in stable anticoagulated patients with venous thromboembolism. *Journal of Thrombosis and Haemostasis*, 1164-1170.

Gibson CM, e. a. (2017). The IMPROVEDD VTE Risk Score: Incorporation of D-Dimer into the IMPROVE Score to Improve Venous Thromboembolism Risk Stratification. *TH Open*, e56-65.

Grant PJ, e. a. (2016). Assessing the Caprini Score for Risk Assessment of Venous Thromboembolism in Hospitalized Medical Patients. *The American Journal of Medicine*, 528-535.

Guan, W. N. (2020). Clinical Characteristics of Coronavirus Disease 2019 in China. *New England Journal of Medicine*.

https://www.mdcalc.com/padua-prediction-score-risk-vte. (2020, 05 11).

IMPROVE In-hospital Risk Model Bleeding Risk Factors. (2020, 05 11). Retrieved from https://www.outcomes-umassmed.org/IMPROVE/risk_score/bleeding/index.html

Pannucci CJ, e. a. (2017). Individualized Venous Thromboembolism Risk Stratification Using the 2005 Caprini Score to Identify the Benefits and Harms of Chemoprophylaxis in Surgical Patients: A Meta-analysis. *Annals of Surgery*, 1094-1103.

Tang N, B. H. (2020; 18). Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patiients with coagulopathy. *J Thromb Haemost*, 1094-1099.

Tapson VF, e. a. (2007). Venous thromboembolism prophylaxis in acutely ill hospitalized medical patients: findings from the International Medical Prevention Registry on Venous Thromboembolism. *Chest*, 132: 936-45.

Thachil, J. e. (2020). ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *JTH*.

Violi F, e. a. (2014). Pneumonia, thrombosis and vascular disease. *Journal of Thrombosis and Haemostasis*, 12:1391-400.

Wang T, e. a. (2020). Attention should be paid to venous thromboembolism in the management of COVID-19. *Lancet Haemotology*.

Zhai, e. a. (2020). Prevention and Treatment of Venous Thromboembolism Associated with Coronavirus Disease 2019 Infection: A Consensus Statement before Guidelines. *Thrombosis and Haemostasis*, epub .

Zhou H, e. a. (2018). Assessment of the Risk of Venous Thromboembolism in Medical Inpatients using the Padua Prediction Score and Caprini Risk Assessment Model. *Journal of Atherosclerosis and Thrombosis*, 1091-1104.