**Title: Clinical Update for Physical Therapists: Coagulopathy and COVID-19**

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Physical therapists have a unique role in both prevention of VTE through the promotion of early mobility and physical activity and diagnosis through discovery of signs and symptoms of VTE. This Perspective updates clinicians on the latest information regarding pathophysiology of coagulopathy associated with COVID-19 and applies VTE clinical practice guidelines to COVID-19 in order to provide guidance on physical therapist management.

Physical therapists are increasingly working with individuals who have been diagnosed with coronavirus disease 2019 (COVID-19), including patients in the acute phase while hospitalized and during the recovery phase in the inpatient rehabilitation, skilled care, home health, and outpatient settings.[1] The effect of the virus on the respiratory system appears to range from a simple respiratory tract infection to acute respiratory distress syndrome (ARDS) with multiorgan failure.[1] People with COVID-19 may also develop coagulopathy that can lead to venous thromboembolism (VTE) and microvascular thrombosis throughout the body.[1] Physical therapists have a unique role in both prevention of VTE through the promotion of early mobility and physical activity and diagnosis through discovery of signs and symptoms of VTE. Therefore, it is critical physical therapists are aware of the clinical implications of this unique coagulopathy and the prevalence of VTE in patients diagnosed with and recovering from COVID-19.

**[H1] Pathophysiology of COVID-19 Coagulopathy**

The COVID-19 virus causes an acute inflammatory response throughout the entire body upon entering via the angiotensin-converting enzyme 2 (ACE2) receptors,[1,2] which are expressed in multiple organs and endothelial cells.[1-4] In fact, some have referred to COVID-19 as COVID endothelialitis due to the effect the virus has on the endothelium of all tissues in the body and especially on the arterial and venous endothelium.[2,3] The clinical presentation of COVID-19 varies greatly among patients with some expressing only mild symptoms, whereas others have a severe presentation that can progress to critical illness.[4] Patients admitted to the hospital with COVID-19 have an increased risk for VTE and microvascular thrombosis.[4,5,6] Venous thromboembolism includes deep vein thrombosis (DVT), pulmonary embolism, or both. Patients with COVID-19 are thought to be at an increased risk of VTE secondary to a hyperactive

immune response resulting in a cytokine storm that occurs with the profound systemic inflammation.[5,7,8] Zhai[6] reported that approximately 20% of patients with COVID-19 present with severe coagulation abnormalities, but it could be present in all of the cases of severe and critical illness. Due to a lack of awareness of these coagulation issues early on, VTE may have been present in more patients seen across the world with COVID-19 and potentially was the cause of some of the unexplained deaths.[6,9]

The coagulation abnormalities found in COVID-19 appear as a hypercoagulable state, including widespread microvascular thromboses that compromise the blood flow to small blood vessels in multiple organs.[10] Retrospective studies of medical records from hospitalized patients who tested positive for COVID-19 have revealed that COVID-19 coagulopathy presents with profoundly elevated fibrinogen and D-dimer, abnormalities in platelet counts, and (in some cases) mild prolongation in prothrombin time (PT).[11]

Elevations in fibrinogen and D-dimer are common with severe inflammatory disease and are associated with significant clotting and even disseminated intravascular coagulopathy (DIC).[3] Tang et al[10] concluded that 71% of the patients with COVID-19 who died met the International Society on Thrombosis and Haemostasis (ISTH) criteria for DIC compared with only 0.6% of the survivors.

Greatly elevated D-dimer (3.5-fold increase above normal) and elevated fibrinogen (1.9 X normal levels) in patients with COVID-19 were significantly related to an increased risk of mortality.[8,10] Despite the association between elevated D-dimers and poor patient prognosis,[10]

elevated D-dimer is so common in hospitalized patients with COVID-19 that elevated D-dimers alone would be insufficient to warrant further testing for VTE, including a duplex ultrasound. In a meta-analysis of 9 studies including 1779 patients with COVID-19, Lippi et al[12] found the platelet count was significantly lower in patients with severe disease (mean = 31,000/μL), with an even lower platelet count associated with mortality (mean = 22,000/μL).[12] As there are no data on laboratory values from patients who tested positive for COVID-19 but were not hospitalized, identifying less severe patients at increased risk for VTE is more challenging.

**[H1] Risk Factors and Prevalence of Coagulopathy**

Although available data on COVID-19 are still sparse, the evidence in support of this severe COVID-19 coagulopathy continues to emerge. In the study by Helms et al[13] from France, thrombus was found in dialysis catheters and extracorporeal membrane oxygenation (ECMO) catheters. In one autopsy study, 4 out of 21 individuals demonstrated significant pulmonary embolism, 5 of 21 had microthrombi in alveolar capillaries, and 3 had thrombotic microangiopathy in glomerular capillaries.[13,14] In multiple studies and in spite of anticoagulation, VTE occurred in 27% of the population hospitalized with severe COVID-19.[15] Microvascular thrombosis has also been found in small vessels, including the pulmonary capillaries, distal digits in extremities, and other organs.[14,16] Microvascular thrombosis is a potential cause of elevations in cardiac enzymes (troponin and proBNP), need for dialysis due to renal dysfunction or failure, and other organ dysfunctions.[14,16]

The risk of VTE is increased in all individuals who are critically ill but appears to be even higher in those with COVID-19.[14,15] In addition to the systemic inflammation already mentioned,

patients with COVID-19 may have additional risk factors for VTE if certain medical interventions were required, such as mechanical ventilation and central venous catheters. There are reports of nutritional deficiencies and liver dysfunction that can interfere with the production of coagulation factors.[17-20] Furthermore, patients who are older with multiple comorbidities are more likely to experience more severe clinical symptoms of COVID-19, adding additional risk factors for VTE to the clinical picture.[6] Finally, the limited supply of personal protective equipment (PPE) has forced facilities to limit health care workers' interactions with patients who have COVID-19, including those of physical therapists. Concerns regarding emergent needs to access patients who pull out lines and tubes have led the medical team to favor sedation for protection of both patient and worker, leading to increased amount and length of sedation.[21] The culmination of these decisions has ultimately reduced the total mobility of these patients, therefore increasing the risk of VTE.

**[H1]Prevention of Venous Thromboembolism (VTE)**

Clinical practice guidelines currently exist, notably the guideline from the American College of Chest Physicians, to provide direction on the management and prevention of VTE; however, these guidelines do not specifically address the unique concerns of COVID-19 given its novel status.[22] When the disease first emerged in other countries (China, South Korea), routine chemical prophylaxis was not provided.[8,9] However, since learning about the risk of thrombosis and coagulopathy, prophylactic doses of anticoagulation are now a standard part of the protocol on admission for individuals diagnosed with COVID-19, unless there is an absolute contraindication to anticoagulation. If contraindication to anticoagulation is present, then mechanical prophylaxis (intermittent pneumatic compression) is strongly recommended.[4] This

practice was instituted based upon clinical evidence of the risk of thrombotic events described above, as there have not been any randomized clinical trials to substantiate this practice to date. In addition, assessment of VTE risk of all patients with COVID-19 on admission is the current recommendation, as elevated risk may require a therapeutic dose of anticoagulation rather than a prophylactic dose.[3,4] Current studies are reporting the use of the IMPROVE and Padua risk assessment models (RAMs) for patients with COVID-19, and the Caprini Risk Assessment for all patients who have surgery or trauma.[4] These RAMs include additional risk information—such as history of active cancer or heart failure and severe loss of mobility—that contribute to the clinical picture of the patient with COVID-19.

As mentioned above, all patients with COVID-19 admitted to the hospital should be receiving prophylactic anticoagulation;[6] however, there are cases of increased risk or medical team preference where patients are receiving therapeutic doses prophylactically.[6] Unfractionated heparin (UFH) is a common treatment option because of its short half-life and reduced drug-drug interactions with investigational COVID-19 therapies and is the primary drug to be used when the patient has decreased creatinine clearance (renal dysfunction).[3,23,24] The need to reduce exposure to health care providers and use of PPE equipment, however, may present challenges given the frequent blood draws required with UFH. For this reason, if it is deemed unlikely a patient will be requiring a procedure, low molecular weight heparin (LMWH) may be preferable.

As recommended in the *Role of Physical Therapists in the Management of Individuals at Risk for or Diagnosed With Venous Thromboembolism: Evidence-Based Clinical Practice Guideline,*[23] physical therapists should advocate for a culture of mobility and physical activity unless medical

contraindications for mobility exists. This key action statement applies to individuals with COVID-19. Patients with COVID-19 should be encouraged to maintain physical activity. For those managing symptoms at home, performing short bouts of aerobic and body weight resistance training may help prevent losses in function, benefit the immune system,[25] and decrease the risk of VTE.[23] Patients in the hospital who are medically stable should be encouraged to get out of bed, move around their room, and, when appropriate, follow a prescribed exercise program.[23] Supervision by a physical therapist, with monitoring of vital signs, may be appropriate in some cases. Bed rest should be discouraged to maintain physiological function and to lower the risk of VTE.[23]

Although it is outside the scope of this article, it is important to note that the coagulation abnormalities may also be affecting the arterial side of the vascular system, causing stroke, myocardial injury, and peripheral arterial embolisms.[15,26,27] At this time, the prevalence of arterial thrombosis does not appear to be as high as VTE, but there have been some alarming reports of stroke as the presenting sign of COVID-19 in a small group of young patients.[26,27] For these reasons, health care practitioners should consider COVID-19 a risk factor for thrombotic complications and be vigilant in their assessment of patients presenting with risk of or signs/symptoms of cerebral vascular injury or myocardial injury.

**[H1]Indicators of Coagulopathy and Likelihood Assessment**

For physical therapists treating this patient population who encounter physical signs suggestive of lower extremity (LE) DVT (ie, pain, unilateral swelling, warmth, tenderness below knee), the clinical practice guidelines (CPG) on VTE should be following, and the Wells criteria should be

used to determine the likelihood of LE DVT.[23] If an upper extremity DVT is suspected (Tab. 1), the Constans criteria should be utilized.[28] Although all providers should remain vigilant in looking for these common DVT signs, the increased risk of VTE in patients with COVID-19 most often presents as pulmonary embolism rather than DVT.[29,30] If there are signs and symptoms consistent with pulmonary embolism—including dyspnea, tachycardia, chest pain, presyncope or syncope, or hemoptysis—the physical therapist should use a clinical prediction rule (eg, Geneva score)[31,32] pulmonary embolism or the Wells criteria for pulmonary embolism) to determine likelihood of pulmonary embolism.[31] It is important to note that, although the clinical manifestations of pulmonary embolism can be variable, other common signs may warrant the use of a clinical prediction rule, such as hemodynamic instability, hypoxemia, hypocapnia, electrocardiographic evidence of right ventricular strain, or sinus tachycardia.[31]

When applying clinical judgment in the presence of patients with COVID-19, it may be helpful to discern the overall risk profile. In addition to using the insights gained from clinical imaging—such as echocardiography (to assess right ventricular strain) and computed tomographic pulmonary angiography, laboratory biomarkers including D-dimers, markers of myocardial injury (ie, troponin) and right ventricular dysfunction (ie, B-type natriuretic peptide (BNP) and N-terminal (NT)-proBNP)—physical therapists can perform a clinical risk assessment screen to determine pulmonary embolism severity and risk of early death. The 2019 European Society of Cardiology Guidelines recommend the use of the Pulmonary Embolism Severity Index (PESI) or simplified PESI (sPESI) for risk stratification, which can be used by physical therapists to help direct clinical decision making.[31]

At the earliest possible stage, it is critical to identify patients that may be presenting with massive pulmonary embolism. Any patient that has hemodynamic instability should be immediately considered to have a high-risk pulmonary embolism and referred to emergency care.[30] Patients that present with right ventricular dysfunction on transthoracic echocardiogram or computed tomographic pulmonary angiography, elevated cardiac biomarkers, and/or PESI > III (sPESI ≥ 1) should be considered low intermediate risk for early death (in-hospital or 30-day).[31] If patients present with the aforementioned findings and elevated cardiac troponin levels, this would increase the patient's risk of early death to high intermediate risk.[31] If the patient is hemodynamically stable, lacks evidence of right ventricular dysfunction, has normal cardiac troponins, and has PESI I or II (sPESI = 0), the patient is at a low risk of early death.[31]

**[H1]Long-Term Management**

Finally, recommendations for length of medical treatment for VTE post–COVID-19 have been presented in 3 guidelines recommending up to 45 days of extended prophylaxis after hospitalization for those with severe or critical cases.[3,4,6] Individuals who had a documented VTE during hospitalization are recommended to continue the therapeutic dosage of the prescribed anticoagulant for 3 months and reassessed after that time.[3,4,6] Table 2 lists current anticoagulation doses regularly reported in the treatment of COVID-19 patients. Dosages may be adjusted posthospitalization based upon presence of VTE during hospitalization, but direct oral anticoagulants (DOACs) often have been prescribed posthospitalization due to lack of need to be followed for blood therapeutic levels and due to inability of patients to have caregivers to administer shots.[22]

For mild-to-moderate COVID-19, patients should be instructed on the importance of hydration and mobility for prevention of VTE and to watch for new signs of VTE. Therapists can use the *Physical Activity Guidelines for Americans* as a reference for activity guidelines.[31] In individuals who were considered to be at increased risk for VTE with mild-to-moderate COVID-19, continuation of some dosage of anticoagulation is recommended, as well as instruction in how to avoid sedentary behavior and appropriate exercise prescription to keep these individuals active. [6] Anticoagulation may be necessary for up to 3 months post–COVID-19;[6] therefore, health care professionals treating patients post–COVID-19 should assess presence of and compliance with medications to decrease risk of VTE. Physical therapists should acknowledge the elevated risk of VTE in this population due to the coagulopathy associated with COVID-19 and the fact that even with anticoagulation, some individuals will still experience a VTE.[15]

**[H1]Application to Clinical Practice**

Physical therapists should be aware of coagulopathy and elevated VTE risk in patients diagnosed with and recovering from COVID-19, particularly those patients who were hospitalized with severe or critical illness. For this reason, all patients who test positive for COVID-19 should be screened regularly for signs and symptoms of VTE (Tab. 1), and immediate action should be taken if the physical therapist suspects new VTE.[23,30,33] A clinical decision algorithm to help guide physical therapists as they encounter patients with COVID-19 who present with suspected VTE is found in the Figure. As shown in the Figure, mobility is encouraged once the individual is stable and medically managed, in most cases with anticoagulants.

Once the patient's VTE has been medically managed and the individual is medically stable, the patient can return to physical activity. As addressed by Hillegass et al,[23] once therapeutic dosages of medications have been reached, mobility should be encouraged. Physical therapists should advocate for these individuals to begin an exercise program or adjust their previous program given their current medical state.[23]

In those individuals who are currently being treated for VTE, the current medical management should be identified on the initial visit, including anticoagulation, length of treatment, or the need for mechanical intervention.[22] Practitioners need to remember that even with prophylaxis medications, the risk of VTE is still present.[15] Patients need to be educated on the risk for bleeding with anticoagulants and how to take precautions, especially when they cut themselves or fall.

Knowing the risks for VTE and the appropriate treatment are essential parts of physical therapist assessment and intervention because this knowledge could save lives. As movement specialists, physical therapists need to encourage mobilization to help prevent the initial VTE and to help decrease the risk of a recurrent VTE. The unique nature of COVID-19 may force us to deliver physical therapy services within a confined space due to isolation protocols, or we may have to provide education instead of hands-on treatment to keep ourselves safe. However, it is the role of physical therapists to promote a culture of mobility to help patients with COVID-19 maintain function and possibly decrease their risk of VTE.[23]

We are learning more information on this critical illness daily that may provide better information on the mechanisms involved and possible markers for screening those patients more likely to present with coagulopathies. Until more is known, our best course of action is to use previously published clinical practice guidelines on the prevention, screening, and management of those with VTE combined with our clinical expertise.[22,23,31] Physical therapists need to stay current with the literature as more is published and information is shared about COVID-19 and coagulopathy.

## Author Contributions

Concept/idea/research design: K. Lukaszewicz, E. Hillegass, M.L. Puthoff,
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## Disclosures

The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

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**Table 1.** Signs and Symptoms of Venous Thromboembolism (VTE)[23,30,33]

| Signs and Symptoms | Lower Extremity DVT | Upper Extremity DVT | Pulmonary Embolism |
|---|---|---|---|
| Pain/tenderness | **X** | **X** | |
| Swelling/edema | **X** | **X** | |
| Warmth | **X** | | |
| Discoloration/redness | **X** | | |
| Cyanosis | | **X** | |
| Dilation of superficial veins | **X** | **X** | |
| $HR_{rest}$ >100 bpm | | | **X** |
| Dyspnea | | | **X** |
| Chest pain | | | **X** |
| Presyncope/syncope | | | **X** |
| Hemoptysis | | | **X** |

**Table 2.** Anticoagulation Medications Commonly Used in the Outpatient Setting with COVID-19[34,35]

| Dose | Low Molecular Weight Heparin | Direct Oral Anticoagulants | |
|---|---|---|---|
| | Enoxaparin (Lovenox) | Xarelto | Eliquis |
| Prophylactic dose | 0.5 mg/kg daily, or approximately 40 mg/day | 10 mg once daily | 2.5 mg twice daily |
| Therapeutic dose | 0.75 mg/kg twice daily | 15 mg twice daily for 3 weeks, then 20 mg once daily | 10 mg twice daily for 1 week, then 5 mg twice daily |

**Figure Caption**

**Figure.** Clinical decision algorithm for venous thromboembolism (VTE) screening in patients with COVID-19. LE DVT = deep vein thrombosis of the lower extremity; UE DVT = deep vein thrombosis of the upper extremity.