Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editors-in-Chief

Managing suspected venous thromboembolism when a pandemic limits diagnostic testing

Venous thromboembolism (VTE), consisting of deep vein thrombosis (DVT) and/or pulmonary embolism (PE), often presents with nonspecific history and physical exam findings. As a result, we rely on a combination of clinical prediction rules, biomarkers, and imaging studies to confirm or exclude the diagnosis. To reduce the volume of imaging testing and potential radiation exposure, a negative d-dimer testing is often used in conjunction with clinical prediction rules to rule out VTE in patients with a low pre-test probability. Unfortunately, for patients affected by the coronavirus 2019 (COVID-19) pandemic, they have a high risk of VTE and the d-dimer is often quite elevated, limiting its utility to adequately rule out VTE. Additionally, some patients with COVID-19 may not be able to undergo VTE imaging, either due to critical illness status making it unsafe to transport to a radiology suite or because of limited test availability due to contagion concerns and limited personal protective equipment availability associated with COVID-19. This has resulted in patients being treated empirically with anticoagulants for a suspected, but unconfirmed, VTE event. Empiric therapeutic anticoagulation is currently controversial. In the absence of contraindications to anticoagulation, it has been considered for patients with suspected VTE based on clinical, radiographic, and/or laboratory abnormalities, when confirmatory testing is not available [1,2].

While the majority of hospitalized patients with COVID are considered for prophylactic anticoagulation, the use of empiric therapeutic anticoagulation is now resulting in an under-explored clinical question: how to manage patients that were started on empiric anticoagulation with a presumed, but unconfirmed, VTE event upon hospital discharge?

A 40-year-old male with obesity was admitted with acute respiratory distress syndrome (ARDS) from COVID-19 and a superimposed bacterial pneumonia. His disease was complicated by respiratory failure requiring intubation, precluding diagnostic imaging for VTE. D-dimer was > 35.0 mg/L at admission and pulmonary embolism was suspected on clinical grounds. The patient was treated with therapeutic intravenous unfractionated heparin and later transitioned to subcutaneous low molecular weight heparin at 1 mg/kg twice daily. Anticoagulation was complicated by minor gastrointestinal bleeding that was not hemodynamically significant. After 28 days of hospitalization, the patient tested negative for COVID-19 and clinically eligible for additional diagnostic testing. Computer tomography pulmonary angiogram (CTPA) scan was negative for PE and bilateral whole leg venous ultrasound was negative for lower extremity DVT. D-dimer had decreased to 6.0 mg/L after one week on anticoagulation. There was no evidence to suggest disseminated intravascular coagulation or another coagulopathy associated with COVID-19.

As the team was preparing for hospital discharge, they wondered if anticoagulation should be stopped, reduced to prophylactic dosing, or continued considering the “negative” imaging testing.

To best answer this clinical question, it is important to consider two key aspects of VTE management: 1) the reason why anticoagulation is typically given for at least three months and 2) the time course for clot resolution on radiographic studies.

Extensive previous randomized trial evidence has demonstrated superiority of a 3–6 month anticoagulation course over a shorter (often 4–6 weeks) duration of anticoagulation for patients with acute VTE [3]. This is particularly true given the high burden and potential consequence of recurrent PE associated with shorter courses of anticoagulation. For many patients with critical illness and VTE (including the above patient), reduced physical activity status at discharge and poor pulmonary reserve are factors that favor continuing therapeutic anticoagulation.

Relying on delayed imaging testing to identify a VTE event is problematic. While there is some heterogeneity in the literature, retrospective studies show that approximately 80% of patients with acute PE have complete resolution of their clots on follow-up imaging after approximately 28 days [4,5]. Specifically, complete resolution has been reported in up to 38% patients at 1–7 [4] days and up to 57% of patients up to 14 days after the initial diagnosis of acute PE [5]. While it is important to recognize the limitations of retrospective studies, these data highlight the limited utility of delayed imaging to determine if a VTE event previously occurred. It is equally reasonable to suspect that our patient's thrombus burden had resolved by the time imaging was performed as it is to suspect that no VTE event had ever occurred.

The patient was discharged on twice daily enoxaparin dosed at 1 mg/kg with a plan to complete at least three months of anticoagulation. Overall, when VTE is suspected for patients with COVID-19, appropriate diagnostic testing should be pursued when possible (Fig. 1). Considering the risks of exposing a patient to anticoagulation, every effort should be made to confirm the diagnosis in a conventional fashion rather than pursing empiric anticoagulation as was done in the above case. As for patients without COVID-19, such testing will often be pursued prior to the initiation of anticoagulation. In situations where imaging cannot be performed and empiric anticoagulation is initiated for a presumed VTE, management must be individualized. In general, at least three months of therapeutic anticoagulation should be considered if there was a strong clinical suspicion for VTE in the absence of bleeding risk factors. Managing patients in this scenario (Fig. 1) with a high bleeding risk would be particularly challenging. If no radiographic testing or conventional angiogram is possible, care would need to be individualized.

If diagnostic testing becomes available at a later time, it is reasonable to complete this testing as it may confirm the diagnosis, help risk-stratify the patient, and guide management if bleeding complications arise. Imaging may show the location of the suspected clot(s), the degree of thrombotic burden, and assess for evidence of right heart strain. If the patient has a bleeding complication or clinical deterioration, the presence or absence of clot on imaging may influence decisions regarding anticoagulation or intervention (e.g., thrombectomy). Furthermore, imaging may identify a competing differential diagnosis like pulmonary parenchymal changes related to COVID-19 and/or a

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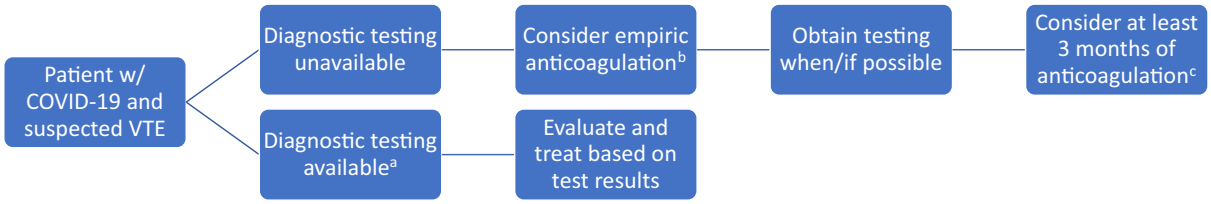

Fig. 1. Possible algorithm for the management of patients with COVID-19 and suspected VTE.

superimposed infection.

Negative imaging tests after a period of therapeutic anticoagulation (even just one week) do not exclude the possibility that the patient had a VTE that was treated and no longer evident on imaging. Patients in this scenario should still be considered for at least three months of anticoagulation, as this would be associated with a reduced risk of recurrent events. Extended VTE prophylaxis may be an intermediate option for when uncertainty in VTE risk exists.

While we anticipate that the aforementioned clinical scenario is much more common in hospitalized patients with COVID-19 (who have a higher pre-test probability of having VTE), the proposed management strategy (Fig. 1) could be applied to outpatients unable to access diagnostic testing as well. Again, considering the risks of anticoagulation and that the long-term management of patients can be more challenging after empiric anticoagulation is initiated, appropriate diagnostic testing should be completed whenever possible. This may require referral to another healthcare facility, so providers should be aware of the resources in their area. In general, we would expect that an outpatient with suspected pulmonary embolism that is unable to be confirmed would be referred to the emergency department or hospitalized. If empiric anticoagulation is administered, it would seem appropriate to monitor them and ensure that there is no competing differential diagnosis mimicking VTE. An outpatient with COVID-19 and suspected DVT that cannot be tested is likely a very rare scenario. If ultrasound or other diagnostic is not available (due to the pandemic and not for convenience), it may be reasonable to check a d-dimer to confirm it is elevated. The patient could then be managed as outlined in Fig. 1 with close outpatient follow-up.

Future research is needed to better understand the rate of resolution of clotting events on imaging for patients with VTE and the risk of recurrent VTE based on how the patient is managed.

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Declaration of competing interest

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