STONY BROOK ANTICOAGULATION PROTOCOL FOR COVID-19 PATIENTS

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A novel coronavirus disease (COVID-19) that is caused by SARS-CoV-2 caused a pandemic infecting over 1.6 million humans globally and caused over 100,000 deaths by early April of 2020. Up to 20% of all COVID-19 patients require hospitalization and approximately 10% require admission to the intensive care unit and mechanical ventilation. Many of the patients remain hospitalized for a prolonged time period, sometimes exceeding 3 weeks.

It has become increasingly clear that a large percentage of patients with COVID-19, particularly those that become critically ill, develop a pro-thrombotic state which places them at a significantly increased risk of thrombosis. Thrombotic events include autopsy-proven micro-vascular thrombosis in a variety of vascular beds (pulmonary, hepatic, renal)[1] likely contributing to end organ function deterioration, as well as large vessel thrombosis such as extensive DVTs or, more impressively, life and/or limb threatening arterial thromboses in otherwise low risk patients (Fig 1).

Interestingly, a wide range of increase in D-dimer levels has been documented in hospitalized COVID-19 patients and there are early reports that have linked higher D-dimer levels to worse outcomes.[2] Whether the increase in D-dimer level reflects a more severe pro-thrombotic state or is the result of a more intense inflammatory response (likely both), is not clear at this point.

Despite a multitude of communications based on early observations supporting the pro-thrombotic state in COVID-19patients, a consensus on if and when patients should receive anticoagulation, what type and for how long, has not been reached. It is not surprising, therefore, that across geographical areas and institutions a wide spectrum of approaches to this issue are reported, ranging from prophylactic DVT regimens for all hospital admitted COVID-19 patients to therapeutic anticoagulation for all.

At Stony Brook University Medical Center, we assimilated published reports from Chinese and Italian centers, information obtained through personal contact of colleagues in Italy, Spain and France, and some early observations in our institution as the number of treated patients with COVID-19 started to increase. Based upon this information, we developed a protocol for escalation of anticoagulation on the basis of D-dimer levels. Our inpatient anticoagulation protocol is outlined in Fig 2. Every COVID-19 positive patient or patient under investigation (PUI) admitted has a D-dimer level drawn and based on this initial result the patient is placed on the appropriate regimen. D-dimers are trended daily and the anticoagulation level is appropriately adjusted (escalation only).

In the past 2 weeks four COVID-19 patients discharged after hospitalization returned to our ED with symptomatic lower extremity DVT. Another COVID 19 patient returned to the ED 10 days after discharge with acute onset of abdominal pain and was diagnosed with superior mesenteric artery thrombosis which required operative thrombectomy. There were no other comorbid conditions predisposing to thrombosis other than COVID-19 infection in any of these patients. This has led to a modification of the anticoagulation protocol to include the post-hospitalization period. The key points in our protocol are outlined below:

1- Anticoagulation regimen:
    a. All admitted COVID-19 diagnosed patients or PUIs are placed on Lovenox 40mg/Qday if their initial D-dimer is lower than 500.
    b. For D-dimer values between 500 and 3,000, Lovenox 40mg/bid is given.
    c. If the D-dimer level exceeds 3,000, the patient is placed on therapeutic anticoagulation
2- Therapeutic anticoagulation is established either with Lovenox 1mg/kg bid (mainly used for patients with normal renal function and low bleeding risk) or with unfractionated IV heparin (target PTT range 60-90) and is based on ICU physician decision/preference.
3- If patients are on oral anticoagulation or dual antiplatelet therapy on admission, the anti-thrombotic regimen is individualized
4- Therapeutic anticoagulation continues until discharge.
5- All COVID-19 patients who are placed on therapeutic anticoagulation during their hospitalization on the basis of D-dimer levels >3000, are discharged home with a 2-week course of therapeutic Lovenox. An outpatient upper and lower extremity duplex ultrasound is scheduled for these patients within 2 weeks after discharge to rule out DVT.
6- If DVT is not detected on the outpatient duplex, Lovenox is discontinued after the completion of the 2-week post discharge course. If a DVT is identified, the patient is transitioned to oral anticoagulation for a total of 3 months (standard treatment protocol for provoked DVT)
7- All COVID-19 patients diagnosed with an acute DVT during their hospitalization are also placed on oral therapeutic anticoagulation for 3 months.

Since out institution started treating COVID-19 patients, a total of 65 patients (all admitted to ICU) were treated on the basis of the anticoagulation protocol above. In those 65 patients there were

- No large DVTs or clinically significant PEs
- No clinically significant peripheral arterial thromboses
- No MIs or strokes
- No significant liver dysfunction
- Five patients developed acute renal failure and required hemodialysis
- Two patients developed clinically significant but controllable bleeding: one had gross hematuria and moderate size access site neck hematoma following insertion of a Quinton catheter for hemodialysis and the other a minor GI bleed. Both required transfusion of 1unit RBCs and holding of heparin anticoagulation for 24 hours.
- There were 5 mortalities in this group (none from bleeding complications) and 10 patients whose care was downgraded.

Conclusion: Despite the absence of control data this early in the experience, our anticoagulation approach appears safe and effective. We have not witnessed any significant thrombotic complications or a high rate of bleeding complications in this group of patients treated under the protocol. As the protocol is now applied institution-wide, we will continue monitoring patients closely and make adjustments if deemed necessary. As our data becomes robust, further reports will follow.

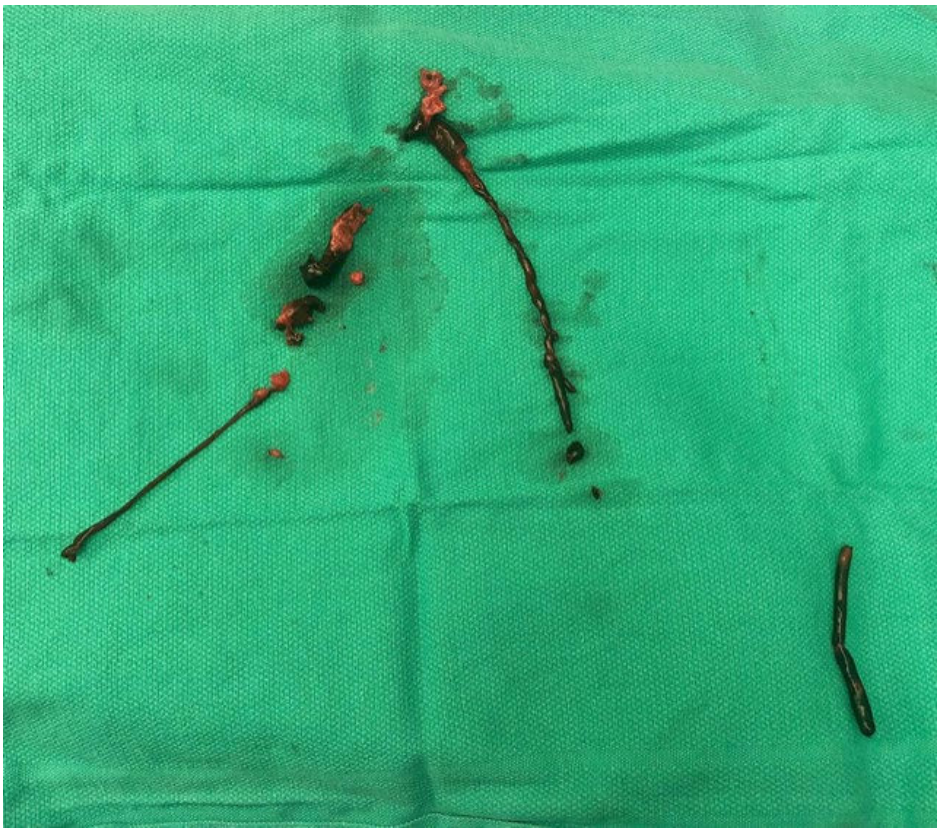

Fig 1. 39 year old Hispanic male without any significant past medical history who presented with acute aortic and bilateral common iliac artery thrombosis and left popliteal artery thrombosis treated with operative thrombectomy. Patient had mild respiratory symptoms and tested positive for COVID-19 infection. Picture courtesy of Dr. Sean Wengerter.

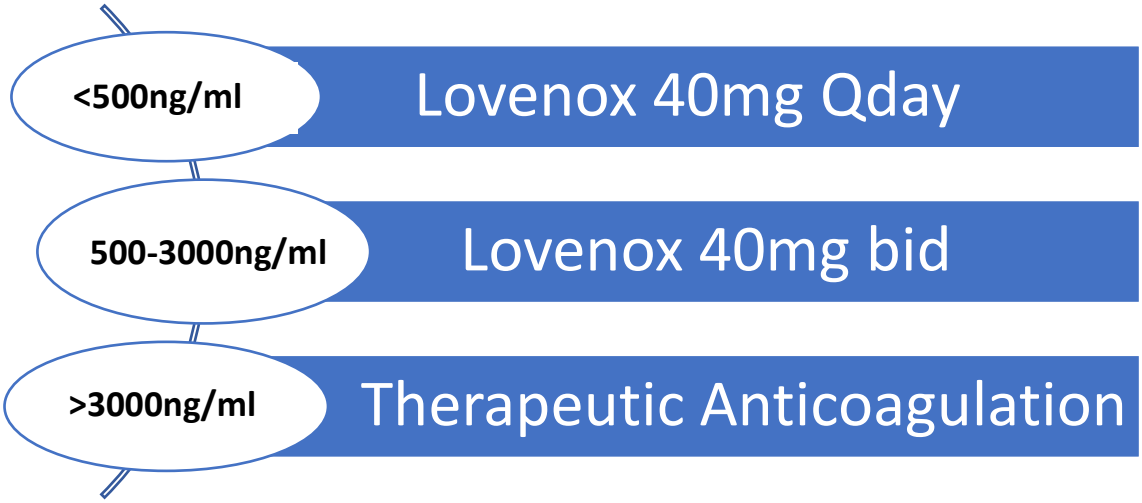

Figure 2. D-dimer-based escalation of anticoagulation protocol in COVID-19 patients

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