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Thromboinflammation and the hypercoagulability of COVID-19

Invited Commentary

Running head: COVID-19 Rannuci commentary

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The pathogenic coronavirus has been wreaking havoc worldwide since January. Infection with SARS-CoV-2 is problematic as no one has prior immunity, and no specific antiviral treatments are available. While many people with COVID-19 develop mild to moderate symptoms, some develop profound seemingly unchecked inflammatory responses leading to acute lung injury and hypoxemic respiratory failure, the most common cause for death. The interplay between inflammation and coagulation—thromboinflammation--has been well described, and recently reviewed. [1, 2] COVID-19 infection is associated with coagulation abnormalities characterized by increases in procoagulant factor levels including fibrinogen, and increases in D-dimers that have been associated with higher mortality. [3, 4] While sepsis -

induced coagulopathy (SIC) and disseminated intravascular coagulopathy (DIC) have been documented with severe disease, especially in non-survivors, a hyperfibrinolytic consumptive DIC with a bleeding diathesis has not been reported. [5, 6] The findings of Tang et al suggested that routine prophylactic dose heparin can decrease mortality in those with the most severe coagulation disturbances, defined as a SIC score >4 or D-dimer > 3.0 mg/l. [6,7]

Recent published and other reports note what appears to be an increased incidence of venous thromboembolic events (VTE) in critically ill patients admitted to the ICU with COVID-19. Klok reported a 27% (95% CI 17-37) VTE incidence and 3.7% arterial vascular events despite the use of standard weight based VTE prophylaxis with low molecular weight heparin (LMWH). [8] Of note, the failure rate for standard VTE prophylaxis in an ICU setting is 7.7%. [9] Cui et al report a similar 25% incidence of VTE in China, but VTE prophylaxis was not given as the incidence of VTE in Asian population is very low therefore VTE prophylaxis not routinely used. [10,11] In addition to increased VTE incidence, published pathology reports and verbal communications have identified both microvascular thrombosis and pulmonary emboli at autopsy in the small number of patients currently reported. The microvascular thrombosis is seen in an environment of marked inflammatory changes including mononuclear cell infiltrates, virally infected cells, and diffuse alveolar damage. (https://www.medrxiv.org/content/10.1101/2020.04.06.20050575v1, accessed April 12, 2020)

In this issue of JTH, **Rannuci** and colleagues report on coagulation parameters in COVID-19 patients including interleukin 6 levels, fibrinogen, d-dimers, and viscoelastic testing in critically ill patients with acute respiratory distress syndrome (ARDS). [12] Baseline testing on admission in 16 patients receiving 4000 IU nadroparin twice daily included PT,PTT, fibrinogen, D-dimer, and viscoelastic measurements. Initial results were similar to other reports, with the median fibrinogen level elevated above the upper limit of normal. Despite normal clotting times on viscoelastic testing, other indices demonstrated increased clot firmness with above normal values for contributions from fibrinogen (94%) and platelets (62%), after which time nadroparin dosing was empirically increased to 6000 IU or 8000 IU

BID if BMI > 35 kg/m2. Two patients were treated with antithrombin concentrates for levels < 70% and one patient was treated with clopidogrel 75 mg/day for a platelet count > 400,000/ul. Follow up standard coagulation test results were available for 10 patients over 7 days of the increased dose, and 9 had a second viscoelastic test after 2 weeks of increased LMWH.

The use of an increased prophylactic dose of nadroparin resulted in a significant decrease in D-dimer levels although all patients still had values above the normal range. Similarly, viscoelastic testing suggested decreased hypercoagulability after increasing LMWH as they show in figure 2, and decreases in clot firmness as a result of a decreased contribution from fibrinogen and platelets to varying degrees. One important finding from this report is the correlation of Il-6 and fibrinogen levels, demonstrating and confirming the link between inflammation and pro-coagulant changes. All patients had IL-6 levels far above the upper limit of normal at admission.

The major cause of mortality in patients with COVID-19, progressive hypoxemic respiratory failure and ARDS, is mediated by lung injury caused by the invading pathogen. Viral infection has been demonstrated in multinucleated cells on autopsy in the alveoli of COVID-19 infected patients. [13] The primary infection initiates alveolar injury and the resulting inflammatory response, including production of inflammatory cytokines, including IL-6 which has been demonstrated to be significantly elevated in COVID-19 patients, as well as activation and recruitment of mononuclear cells and neutrophils causing more tissue damage, including damage to the capillary endothelium. In addition to the procoagulant effectors derived as the result of inflammation (including cytokines, NETS, polyphosphates) the usual thrombo-protective state of the vascular endothelial cells is disrupted; both pathophysiologic changes lead to the development of microvascular thrombosis. Over time the pathology of ARDS progresses to a proliferative and then ultimately a fibrotic state, which is ultimately fatal.

Rannuci's report suggests that an increased prophylactic LMWH dose appears to dampen the downstream thrombotic results of the marked inflammatory response to COVID-19. Although patient improvement with viral clearance and decreased inflammatory effects may have occurred and been responsible for some of the changes, despite the decrease in D-dimers the fibrinogen values were still elevated, and the mortality in this small number of patients with ARDS was high. Whether intervening earlier with anticoagulants before patients develop ARDS would make a difference, or whether preventing the microvascular thrombosis will change outcomes remains to be determined. Certainly, it is possible as suggested by Rannuci et al that using increased dose of LMWH might halt the progression to overt DIC as well as mitigate the contribution of microvascular thrombosis to the hypoxemic respiratory failure.

For clinicians trained in using an evidence-based medicine approach, we find ourselves forced to practice without data. Is an empiric increase in prophylactic anticoagulation dose justified with the limited data we have? Despite the small numbers reported, the use of increased LMWH dose was not associated with increased bleeding. Precedent exists in other clinical situations in which patients are considered at a high risk for VTE, for the use of an off-label increased dose of enoxaparin 40 mg (4000 IU) or 60 mg every 12 hours based on BMI for post-bariatric surgery patients, or in pregnancy where increased doses are advised for prophylaxis with minimal supporting data. [14,15.] Some guidance documents from around the world suggest using standard coagulation test values to determine anticoagulant dosing for Covid-19, as suggested in a French guidance document, which recommends full therapeutic dose anticoagulation for patients with increased fibrinogen > 8 g/l or D-dimer > 3.0 ug/ml.(https://www.fichier-pdf.fr/2020/04/03/covid-19-gihp-gfht-3-avril-final-3/? Accessed April 13, 2020) While Klok and colleagues reported using a standard dose of 2850 IU nadroparin daily, with 5700 IU daily for those weighing over 100kg, the mean weight was 87 kg +/- 16, with few patients weighing more than 100kg. The Netherlands centers changed practice after a month of experience treating COVID-19 patients; nadroparin doses were increased to 5700 IU daily regardless of weight at one

center, and at another center the dose was increased to 5700 IU twice a day, very similar to the escalated dose used by Rannuci et al. [8,12] These increased doses may be required to overcome the dramatic elevation in levels of procoagulant factors such as fibrinogen, FVIII, and others, that are not present in the standard post arthroplasty or hospitalized medically ill patient.

In COVID-19 patients, a risk adapted approach to escalating the dose of anticoagulation despite minimal supporting data should be carefully considered after assessing the bleeding risk for each patient. Monitoring fibrinogen, PT, PTT, and renal function should be performed. However increasing anticoagulant doses alone is likely insufficient to change outcomes in patients with severe COVID-19 acute lung injury. Additional therapy with novel anti-inflammatory agents such as IL-6 and Il-1 antagonists, and other approaches to treating the cytokine storm that appears to be responsible for severe and fatal infections, may be critical to decrease the thromboinflammatory responses and subsequent tissue injury that drive the prothrombotic changes resulting in microvascular thrombosis and overt VTE. Anticoagulation might play a role by preventing the contribution of microvascular thrombosis to the progression of respiratory failure, giving time for anti-inflammatory agents to work to decrease damage and to allow innate immunity to clear the virus. As with anticoagulation dosing, multiple anti-inflammatory agents are being used with similar lack of data to guide care. While randomized controlled trials are the ideal, and are being developed or are underway for both anti-inflammatory therapies and anticoagulants, the exponentially increasing numbers of infected patients and the rapid pace of the disease leave little time for many to participate in well conducted studies. However, the report by Rannuci et al provide important insight into the hypercoagulability and thromboinflammatory response associated with Covid-19 and acute lung injury, and may provide some perspective on additional therapeutic strategies to decrease the morbidity and mortality associated with the disease.

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J.M.Connors and J.H.Levy equally contributed to the writing of this manuscript.

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