COVID-19 and VTE: What We Know and What We Don't Know

A review of what is currently known about the role of inflammation, markers of disease in coagulation studies, pathologic and clinical evidence of thrombosis, and the approach to anticoagulation of COVID-positive hospitalized patients.

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In December 2019, an outbreak of novel coronavirus SARS-CoV-2, subsequently termed COVID-19, led to a global pandemic. At the time of this writing, more than 7.2 million cases and 411,000 deaths have been reported worldwide, with nearly 2 million cases and over 110,000 deaths in the United States.[1] Reports in the United States suggest a high intensive care unit (ICU) mortality and a stressed health care system.[2,3] It was soon recognized that the virus can manifest with high levels of inflammation, abnormal coagulation studies, pathologic evidence of microvascular thrombosis, and clinical evidence of large vessel thrombosis.

ROLE OF INFLAMMATION

SARS-CoV-2 infection is characterized by a high inflammatory state associated with elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, and interleukin (IL)-6 levels.[4] The inflammation plays an integral role in the pathology of the virus, and many anti-inflammatory and immunomodulatory treatments including IL-6 inhibitors, hydroxychloroquine, and JAK inhibitors have been used. In fact, higher levels of proinflammatory cytokines have been associated with worse disease.[5] Inflammation and coagulation are intricately linked at an evolutionary level, and disseminated intravascular coagulation, sepsis-induced coagulopathy, and deep vein thrombosis (DVT) are common in the highly inflamed states of severe infection.[6] Inflammation and its subsequent effects on coagulation are therefore not unique to COVID-19, but there is evidence that the degree of hypercoagulability in COVID-19 may warrant a different therapeutic approach. It is likely that the unique phenotype of inflammatory storm with COVID-19 will lead to a similarly unique coagulation profile.

LABORATORY CLOTTING STUDIES

The coagulation profile in COVID-19 typically reveals a normal prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time (PTT), platelet count, and elevated fibrinogen and D-dimer levels. A classic disseminated intravascular coagulopathy pattern is rare. There is a link between elevated D-dimer and mortality. In a large study of 1,099 COVID-19 patients from > 550 hospitals in China, D-dimer was found to predict severe illness and mortality.[7] In response, many have advocated for serially trending D-dimer as a marker of disease and even to guide clinical decisions about anticoagulation or anti-inflammatory treatment.

Thrombocytopenia is less common with COVID-19, although one large meta-analysis of nine studies found that it was more common in patients with severe disease.[8] Elevated von Willebrand factor and factor VIII levels have also been described. The presence of antiphospholipid (APL) antibodies may be common, with one multicenter trial finding positive results in 50 of 57 patients who were tested.[9] However, the clinical implications of APL antibodies are not clear, as their presence can be seen in active infections, and the diagnosis of APL syndrome requires repeated positive results over time.

Thromboelastography (TEG) has been increasingly used in various clinical scenarios and may be a better tool to characterize clotting activity than traditional laboratory assays. TEG also allows separation of heparin effect with the use of heparinase assays. In a small cohort study of 20 critically ill COVID-19 patients, 19 of 20 had hypercoagulable TEG results, and elevated maximal amplitude (MA) on TEG conferred 100% sensitivity for thrombotic results. The MA on TEG was a better predictor of thrombosis than PT, INR, PTT, or platelet levels.[10] In a study of critically ill patients with COVID-19, Yuriditsky et al found a large proportion to have hypercoagulable TEG profiles. Parameters related both to coagulation factors, as well as fibrinogen and platelet function (MA) were commonly deranged.[11]

PATHOLOGIC EVIDENCE OF CLOT

Despite the high worldwide death rate with COVID-19, there are relatively few autopsy studies. Examining the

TABLE 1. ANTICOAGULATION RECOMMENDATIONS FOR PATIENTS WITH COVID-19

Anticoagulation Forum[25]	ISTH[26]	NIH[27]
▪ Recommend use of anti-Xa rather than aPTT to monitor UFH dosing ▪ Recommend standard dose of prophylaxis for noncritically ill patients ▪ For critically ill patients, increase dose of enoxaparin to 40 mg or 0.5 mg/kg subcutaneously twice daily or heparin to 7,500 units three times a day based on expert opinion ▪ Recommend against using biomarker thresholds (ie, D-dimer) as the sole reason to trigger escalations in anticoagulant dosing outside the setting of a clinical trial ▪ Recommend against extended routine VTE prophylaxis to discharged patients ▪ Recommend an evaluation at discharge for ongoing VTE risk factors balanced with bleeding risks to identify a population of patients similar to those in the rivaroxaban and betrixaban trials who may benefit from extended prophylaxis	▪ Recommend trending platelet count, PT, D-dimer, and fibrinogen, and if these parameters worsen, consider more aggressive critical care support and/or "experimental therapies" ▪ Use prophylactic "low-dose" LMWH in all patients in the absence of contraindications (bleeding and platelet count < 25 X 10^9/L) ▪ Note that bleeding is rare in the setting of COVID-19	▪ Insufficient data to suggest continuous monitoring of clotting parameters to guide management decisions ▪ Hospitalized patients should receive VTE prophylaxis per the standard of other hospitalized patients with VTE ▪ Limited data exist to recommend for or against increasing anticoagulant dosing for VTE prophylaxis in hospitalized COVID-19 patients outside the setting of a clinical trial ▪ Evaluate for thromboembolic disease in patients with rapid deterioration of pulmonary cardiac or neurologic function or loss of peripheral perfusion

Abbreviations: aPTT, activated partial thromboplastin time; ISTH, International Society of Thrombosis and Haemostasis; LMWH, low-molecular-weight heparin; NIH, National Institutes of Health; PT, prothrombin time; UFH, unfractionated heparin; VTE, venous thromboembolism.

limited COVID-19 autopsy case series, several found microvascular thrombosis, including fibrinous thrombi in small pulmonary arterioles and an increased amount of megakaryocytes on pulmonary pathology.[12,13] Similarly, a series from Italy found fibrin thrombi in small arterial vessels in 87% of autopsies.[14] Another small series from New York found microvascular thrombosis as well as endothelial injury and complement deposition in lung and skin biopsies.[15] This series was notable in that it demonstrated a vascular tropism of the virus in more than one organ and also raised the possibility that complement deposition may contribute to the vascular injury pattern.

CLINICAL EVIDENCE OF THROMBOSIS

In addition to pathologic evidence of small vessel thrombosis, an even larger number of studies have identified clinically relevant large vessel thrombosis. A single center in Lille, France, noted a higher than expected number of patients with pulmonary embolism (PE) in their first consecutive 107 patients. They compared the COVID-19 patients to a matched cohort of influenza patients from 2019 and found PE was more frequent (20.6% vs 7.5%).[16] A small study of 26 critically ill COVID-19 patients on either prophylactic or therapeutic anticoagulation found a very high rate of thromboembolic events (69%; 18 DVT and 6 PE). They performed systematic screening with ultrasound and CTA for unexplained respiratory failure, which may have impacted the high percentages.[17] A single French center reviewed 34 ICU patients on mechanical ventilation due to COVID-19. They similarly screened all patients for DVT and found 65% had DVT on admission and 79% after 48 hours.[18]

A multicenter cohort study of 184 patients in the Netherlands found a 31% cumulative incidence of thrombosis, including 25 PEs and three arterial thromboses. All patients were receiving prophylaxis. The authors recommended higher doses of anticoagulation prophylaxis based on their findings.[19] Another multicenter prospective study from four French ICUs analyzed 150 COVID-19 patients with acute respiratory distress syndrome, finding 64 clinically relevant thrombotic complications. PE predominated, but ischemic strokes and clotting of renal replacement therapy were also common.[9]

The totality of these aforementioned findings suggests COVID-19 is associated with a high percentage of venous thromboembolism (VTE), but it is important to recognize that VTE is common in critically ill patients in general. Indeed, one study found a 29% rate of PE in critically ill patients sent for CTA.[20] Noncritically ill patients hospitalized with pneumonia also have an elevated risk for VTE related to active infection, immobility, and an elevated inflammatory state. Additional risk factors including age, obesity, cancer, heart failure, and prior history of VTE. Obesity is of interest, as it has been linked to severe disease with COVID-19.[2,21] Irrespective of

AUTHORS' PROPOSED VTE THROMBOPROPHYLAXIS RECOMMENDATIONS FOR HOSPITALIZED COVID-19 PATIENTS

- All hospitalized COVID-19–positive patients should receive standard VTE thromboprophylaxis
- Enoxaparin 40 mg twice daily should be used for obese patients
- Accelerated thromboprophylaxis (enoxaparin 40 mg subcutaneously twice daily or 0.5 mg/kg subcutaneously twice daily) should be used in critically ill patients
- Empiric therapeutic anticoagulation for a short duration should be considered on an individual patient basis
  - High-risk features include critically ill, highly elevated (two- to threefold higher) D-dimer levels, acute kidney injury, elevated dead space fraction on mechanical ventilation, rising inflammatory markers
- Follow anti-Xa levels for unfractionated heparin dosing as the prevalence of antiphospholipid antibodies may render the partial thromboplastin time unreliable
- Consider extended postdischarge prophylaxis with either rivaroxaban or betrixaban in selected patients after weighing risks of clotting versus thrombosis. Patients should be considered based on the populations who benefited in the MAGELLAN and APEX trials, respectively[28,29]
- Ongoing review of the literature is a must. Randomized controlled trials for anticoagulation are enrolling and have the potential to be practice-changing

COVID-19, a dose of enoxaparin 40 mg subcutaneously twice daily has been shown to be superior to standard dosing in morbidly obese patients.[22] Whether COVID-19 infection is truly associated with a greater occurrence of thrombosis than other severe viral illnesses is an area of active investigation.

TREATMENT

Unless there are contraindications, all hospitalized COVID-19 patients should receive VTE prophylaxis. However, there is debate as to whether COVID-19 patients should receive accelerated prophylaxis or therapeutic anticoagulation in the absence of diagnosed thrombosis. Some suggest full-dose anticoagulation not only to prevent large vessel clot but to mitigate microvascular thrombosis and capillary injury. However, prior trials of anticoagulation in sepsis have not shown a benefit. It is also unclear whether clinicians should follow D-dimer and other markers to guide decisions over anticoagulant intensity. Although there are ongoing randomized trials to help answer these questions, all data are currently retrospective. A retrospective analysis of 449 patients with severe COVID-19 (respiratory rate > 30 breaths/min; PaO_2/FiO_2 < 300 mm Hg) found that those with an elevated sepsis-induced coagulopathy score and those with elevated D-dimer (> 3 µg/mL) had lower mortality when treated with heparin prophylaxis.[23] Another larger retrospective study of 2,773 patients from a single center in New York City found an in-hospital mortality rate of 22.5% in patients receiving therapeutic anticoagulation and 22.8% in those who did not receive anticoagulation. In a subset of 395 mechanically ventilated patients, 29% who received anticoagulation and 62.7% who did not receive anticoagulation died.[24]

Societies including the International Society on Thrombosis and Haemostasis (ISTH), American Society of Hematology, National Institutes of Health (NIH), and the Anticoagulation Forum have published guidelines about anticoagulation for COVID-19–positive patients (Table 1),[25-27] and the authors' proposed recommendations are noted in the Sidebar.[28,29] The ISTH and NIH recommend standard prophylactic doses of low-molecular-weight heparin only.[26,27] The Anticoagulation Forum recommends a standard dose for noncritically ill patients and an accelerated dose of enoxaparin 0.5 mg/kg subcutaneously twice daily or heparin 7,500 units three times a day for critically ill patients.[25]

SUMMARY

COVID-19 infection appears to be associated with a high rate of venous thromboembolic disease. There is pathologic evidence of small vessel thrombosis, and observational clinical studies have shown high rates of DVT and PE. Many clinicians have begun to employ higher doses of thrombosis prophylaxis and even therapeutic anticoagulation for more severe cases of COVID-19, although data regarding benefit are sparse. The community is eagerly awaiting more data, especially results of randomized trials of full versus prophylactic doses of anticoagulation. Until then, several societies have published recommended anticoagulation guidelines for COVID-positive patients, and we have provided our recommendations. ■

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