Highlights in COVID-19 From the 62nd American Society of Hematology Annual Meeting

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Commentary by Craig M. Kessler, MD, MACP

The high incidence of venous thromboembolism (VTE) and its consequent morbidity and mortality—along with an elevated risk for arterial thrombotic disease—was recognized early on by providers caring for individuals with coronavirus disease 2019 (COVID-19). Many hypotheses have been presented to explain the pathologic hypercoagulability seen in these patients. It has been difficult to determine how each potential risk factor contributes to the development of thrombotic complications, however. Patients hospitalized with COVID-19 typically have underlying medical conditions, and the illness affects multiple organs. The use of various therapeutic modalities to mitigate the systemic effects of the illness can further obscure the direct effects of COVID-19.

At this time, physicians are searching for ways to predict which patients with COVID-19 are most likely to be affected by thrombosis. Identifying them is important because aggressive VTE prophylaxis may increase the rates of major bleeding complications and mortality, even as it reduces thrombogenesis. The concept of individualizing the dosing of low-molecular-weight heparin according to the severity of each patient's COVID-19 clinical status is emerging, and adaptive therapeutic trials are in progress. Until results are available, however, it is important to recognize potential risk factors for thrombosis. The following observational studies from the 62nd American Society of Hematology (ASH) Annual Meeting provide some insights on how to accomplish this.

Study Identifies Factors Associated With VTE in COVID-19 Patients With Cancer

Hospitalized patients with COVID-19 who have ever had a cancer diagnosis are at increased risk for VTE and pulmonary embolism (PE) if they have recently been treated for cancer, have active cancer, have a cancer subtype linked to an increased risk for VTE, or have been admitted to an intensive care unit (ICU), according to a recent analysis.

Dr Ang Li of Baylor College of Medicine, in Houston, Texas, and colleagues examined data from 4098 patients enrolled in the COVID-19 and Cancer Consortium (CCC19) registry between March 17 and August 29, 2020. A total of 1813 patients who had been admitted to a hospital, had undergone follow-up lasting at least 4 weeks, and had known VTE outcomes were included in the analysis. Most patients (92%) were from the United States. Of these, 9% had a history of VTE, 19% were using anticoagulant agents before hospital admission, and 33% were using antiplatelet agents before hospital admission. During follow-up, VTE developed in a total of 8.8% of the patients (n=160), and PE developed in 5.1% (n=93).

Multivariable regression analysis revealed that VTE was significantly more likely to develop in patients admitted to an ICU than in those treated in a general ward; rates were 13.9% vs 6.5%, respectively. VTE also was more common among those who had recently received anti-cancer systemic therapy than in those who had not, in both the ICU patients (17.6% vs 10.3%, respectively) and the hospital ward patients (10.0% vs 4.1%, respectively). Having a cancer subtype linked to an increased risk for VTE (per the Khorana Risk Score for VTE in Cancer Patients, lung, ovarian, kidney, bladder, and testicular cancer and lymphoma are considered to be associated with a high risk, and pancreatic, stomach, and esophageal cancer are considered to be associated with a very high risk) also was a significant predictor of VTE. Bivariable analysis revealed that preadmission antiplatelet use was associated with less VTE, but not PE, whereas preadmission anticoagulant use was associated with less PE, but not VTE.

The authors concluded that information regarding VTE in patients with COVID-19 and cancer "will aid in developing a risk prediction tool for VTE in hospitalized patients with cancer and COVID-19."

Li A, Kuderer NM, Warner JL, et al. Incidence of and risk factors for venous thromboembolism among hospitalized patients with cancer and COVID-19: report from the COVID-19 and Cancer Consortium (CCC19) registry [ASH abstract 204]. *Blood*. 2020;136(1)(suppl).

Commentary: This study provides retrospective information culled from a large, carefully collected database that includes cancer patients with a diagnosis of COVID-19. Because many malignancies carry their own intrinsic risk for thrombogenesis, the idea that COVID-19 in combination with cancer might further increase the risk for VTE is logical. This study provides an important perspective on the incidence of VTE when cancer and COVID-19 are concurrent. It is not unexpected

that VTE risk in cancer patients with COVID-19 would correlate with the thoroughly validated Khorana Risk Score. The real importance of this study is that it provides an idea of the incidence of VTE in the cancer cohort, and it further dissects the risk according to important cancer clinical variables and according to cancer severity. The caveat here is that the incidence reported for each of the cancer cohorts is likely underestimated because the search for VTE was triggered predominantly by symptoms; the presence of asymptomatic VTE or incidental VTE is not yet known in cancer patients with COVID-19.

An interesting finding in this registry analysis is that less VTE, but not PE, occurred with antiplatelet use, and that less PE, but not VTE, occurred with anticoagulant use. These observations are compelling and need to be explored in more detail. Of note, the finding of benefit in patients with cancer does not appear to extend to a general population of patients with COVID-19 (see the next study).

Prior Use of Anticoagulants or Antiplatelets Not Linked to Reductions in Most Measures of COVID-19 Severity

Patients who are on anticoagulant or antiplatelet agents before hospitalization for COVID-19 do not appear to be at reduced risk for the development of serious outcomes, hospitalization, or death, according to a new study. They are less likely to require mechanical ventilation, however.

For the retrospective cohort study, Dr Gwendolyn Ho and colleagues at the Permanente Medical Group reviewed the medical events of patients in the Northern California Kaiser Permanente health system, a robust database. They identified 28,076 adults who had tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) between February 25 and July 31, 2020. Of these, 720 (3%) were on antiplatelet agents, 255 (1%) were on systemic anticoagulant agents, and 49 (<1%) were on both in the 90 days before COVID-19 was diagnosed. The majority of patients taking anticoagulant or antiplatelet agents were older, non-White, and obese and had 3 or more comorbidities.

After adjusting for sociodemographic and clinical characteristics, the researchers found no statistically significant associations between the long-term use of anticoagulant or antiplatelet agents before a COVID-19 diagnosis and several measures of disease severity: VTE, emergency department visits, inpatient hospitalization, ICU stays, and mortality. The only measure of COVID-19 severity that was reduced among patients taking anticoagulant or antiplatelet agents was the need for mechanical ventilation (odds ratio, 0.72; 95% CI, 0.53-0.99). The researchers also found that older age, male sex, greater number of comorbidities, hypertension, diabetes, and obesity were associated with an increase in disease severity. Non-White patients were more likely than White patients to require hospitalization and mechanical ventilation.

Major strengths of this study are the large number of patients and the fact that both outpatients and inpatients were included. However, the authors cautioned that the use of anticoagulant or antiplatelet agents after a COVID-19 diagnosis may have affected the outcome.

Ho G, Dusendang JR, Schmittdiel J, et al. Anticoagulant and antiplatelet use not associated with improvement in severe outcomes in COVID-19 patients [ASH abstract 206]. *Blood*. 2020;136(1)(suppl).

Commentary: In this large patient database, researchers examined a cohort of individuals with COVID-19 to determine if concurrent antiplatelet therapy or systemic anticoagulation affected the severity and progression of their disease. No relationship was seen between the use of antithrombotic agents and death or hospitalization rates, however. It is not clear what advantage less use of mechanical ventilation might provide if the death rate does not decrease. Interestingly, antiplatelet or anticoagulant use was not associated with a lower risk for VTE in the whole cohort, as it was in the study by Li and colleagues. The absence of a meaningful benefit with long-term antiplatelet or anticoagulant therapy in this observational study points to the need for adequately powered, carefully designed prospective trials. The lack of obvious efficacy of antithrombotic therapy may be due to the vagaries of registry studies.

Pathogen-Reduced COVID-19 Convalescent Plasma Associated With Trend Toward Reduced Mortality

Pathogen-reduced COVID-19 convalescent plasma (CCP) is associated with a trend toward reduced mortality, according to a phase 2 matched case-control study by Dr Nina Khanna and colleagues of the University Hospital of Basel, Switzerland. The researchers undertook the single-center, hypothesis-generating study because the effect of CCP on the outcomes of hospitalized patients is still unclear. Antibody properties of donor plasma may vary, and patient outcomes may depend on the plasma composition.

For the study, Dr Khanna and colleagues assigned 15 patients who were hospitalized with COVID-19 pneumonia to CCP plus usual care; they then selected 30 control patients who were matched according to disease severity at diagnosis and the use of tocilizumab (Actemra, Genentech). Each patient in the CCP group received 400 mL of pathogen-inactivated CCP from 2 of

11 donors over 48 hours; all plasma had been collected from the donors 1 to 3 months after mild COVID-19 infection, and pathogen reduction was accomplished with amotosalen plus ultraviolet A irradiation (Intercept Blood System, Cerus).

The researchers found that CCP samples from 9 of the 11 donors contained active antibodies, and that the pathogen reduction process did not affect the antibody profiles. A trend was noted toward a lower in-hospital mortality rate at 28 days in the CCP group than in the control group: 1 of 15 (6.7%) vs 6 of 30 (20.0%), respectively (*P*=.151). No statistically significant differences were found between the groups in progression to intubation, ICU admission, or days in the hospital. A trend toward better C-reactive protein normalization was found in the CCP group (*P*=.053). The patients who received CCP demonstrated an increase in SARS-CoV-2 antibodies after transfusion, except for 2 patients with a high level of antibodies before transfusion and 3 patients who had been pretreated with a CD20 antibody.

The study authors concluded that although more definitive studies using characterized CCP are required, the treatment appears to be safe and may be effective for hospitalized patients with COVID-19.

Khanna N, Weisser M, Hedstueck A, et al. Efficacy of COVID-19 pathogen inactivated convalescent plasma for patients with moderate to severe acute COVID-19: a case matched control study [ASH abstract 245]. *Blood*. 2020;136(1)(suppl).

Convalescent Plasma Linked to Improved Outcomes in Mexican Study

Patients with severe and life-threatening COVID-19 appear to benefit from receiving CCP, according to the results of a phase 1/2 study from Mexico.

The study, which was presented by Dr Fernando Pérez-Jacobo of the Hospital Central Norte Petróleos Mexicanos in Mexico City, encompassed 2 phases. In phase 1, researchers sought to identify the minimum effective dose of CCP in patients with COVID-19. They enrolled 10 adults with severe COVID-19 and 10 patients with life-threatening COVID-19. After administering doses of CCP ranging from 400 to 800 mL, they established that the effective dose of CCP was 2 bags (400 mL) in severe COVID-19 and 3 bags (600 mL) in life-threatening COVID-19.

The researchers are seeking to enroll 68 patients with severe disease and 52 patients with life-threatening disease in phase 2, in which the patients will receive the doses of CCP established in phase 1. So far they have administered CCP to 70 patients with either severe or life-threatening disease, and these patients are being compared with a historical group of patients with COVID-19 who were managed with other treatment strategies. After a median follow-up of 30 days, the overall survival rate was significantly higher in the CCP group than in the control group of patients with severe acute respiratory distress syndrome (ARDS; 61% vs 15%, respectively; *P*=.002), but this difference was not observed in those with mild or moderate ARDS.

The CCP infusions were well tolerated. Only 6 adverse events were reported in the 70 patients, who received a total of 164 bags; these included 1 case of transfusion-associated circulatory overload that resolved with the use of loop diuretics, 1 case of VTE, 1 episode of grade 1 fever, and 3 cases of grade 1/2 rash.

The authors will continue enrollment in phase 2 of their study until they have accrued a total of 120 patients.

Pérez-Jacobo F, Villela L, Velásquez-Vega E. Phase I and preliminary results of a phase II Study (TERAPLASCoV2) of convalescent plasma in patients with severe and life-threatening pneumonia caused by Sars-Cov-2 [ASH abstract 246]. *Blood*. 2020;136(1)(suppl).

Commentary: These 2 studies, which describe the experience of administering CCP to patients with COVID-19, illustrate the frustration, confusion, desperation, and hope of investigators involved in the race to find an effective passive immunotherapy approach to mitigating the course of this viral infection. The results of both studies are promising, but neither one conclusively determines whether CCP reduces mortality. Fortunately, randomized, prospective placebo-controlled studies have demonstrated more promising results. In an article published online on January 6, 2021, in the *New England Journal of Medicine*, Libster and colleagues reported a 50% reduction in progression to severe disease with the administration of CCP less than 72 hours after the onset of mild COVID-19 symptoms vs placebo.

A major caveat regarding trials of CCP is the inability to measure the amount of COVID-19–neutralizing antibody content in donor CCP, along with the variability of such antibody content among recipients. The studies describe the measurement of detectable COVID-19 antibodies in donor CCP and in recipients, but these antibodies may not be neutralizing, and assays to determine whether they are in fact neutralizing generally are not available. Furthermore, the increasing availability and promising results of other passive immunity therapies, such as the combination of casirivimab and imdevimab—monoclonal antibodies directed against the spike protein of SARS-CoV-2—may render CCP a less-important therapeutic option.

Registry Quantifies Rate of Thromboembolic Events in Hospitalized Patients With COVID-19

The rate of VTE in the 90 days following hospital discharge after a diagnosis of COVID-19 was 1.55% in a large multihospital health system, according to an ongoing prospective registry called CORE-19. This rate is approximately 2-fold higher than that previously seen among patients hospitalized for acute infections, said Dr Dimitrios Giannis of Northwell Health in Manhasset, New York. The 90-day rates of arterial thromboembolism (ATE) and all-cause mortality (ACM) were 1.71% and 4.83%, respectively.

Dr Giannis and his colleagues collected data on 11,249 patients with COVID-19 who were hospitalized between March 1 and May 31, 2020, and were part of the Northwell Health system. The protocols of Northwell Health stipulate the use of low-molecular-weight heparin, direct oral anticoagulants, or low-dose aspirin after hospital discharge in patients hospitalized with COVID-19 who are at high risk for thrombosis. The study analyzed data for the first 90 days after discharge.

As of August 7, 2020, data were available on 4906 adults with an average age of 61 years. In addition to calculating the rates of VTE, ATE, and ACM, the researchers found that the 12.7% of patients who received an anticoagulant at discharge were 46% less likely to reach a composite endpoint of VTE, ATE, and ACM (ACM accounted for most of this composite endpoint). Factors that increased the odds of reaching the composite endpoint included age older than 75 years, a personal history of VTE, ICU admission, chronic renal disease, a personal history of peripheral arterial disease, a personal history of carotid occlusive disease, an International Medical Prevention Registry on Venous Thromboembolism D-Dimer (IMPROVEDD) VTE risk score of 4 or higher, and coronary artery disease.

The authors recommended further study to identify which patients hospitalized for COVID-19 could benefit from thromboprophylaxis after hospital discharge.

Giannis D, Allen SL, Davidson A, et al. Thromboembolic outcomes of hospitalized COVID-19 patients in the 90-day post-discharge period: early data from the Northwell CORE-19 Registry [ASH abstract 443]. *Blood*. 2020;136(1)(suppl).

Commentary: The results derived from this robust observational study examining patients with COVID-19 following hospital discharge have led to important changes in COVID-19 care. Patients with COVID-19 patients comprise one of the most critically ill medical populations, and so are at risk for VTE after discharge. Furthermore, they are frequently discharged to their home as soon as possible, without the opportunity to convalesce in subacute rehabilitation facilities. They are likely to be immobile at home. This study found a 46% reduction in VTE, ATE, and ACM with anticoagulation at discharge; however, an elevated risk for both VTE and arterial thrombotic complications remains. Furthermore, VTE prophylaxis is associated with a risk for major bleeding. Additional clinical trials are necessary to determine which patients with COVID-19 will benefit from safe and effective outpatient VTE and arterial thrombotic prophylaxis. Certainly, this abstract forewarns clinicians to be more vigilant for the development of thrombotic events after discharge and should motivate researchers to develop surveillance strategies.

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