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CHEST

Clotting and COVID-19

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Shortly following the initial reports of a novel corona virus in Wuhan China in December of 2020, descriptions of unusual and unexpected clinical manifestations of this primarily respiratory tract infection began to surface in the medical literature. One of these unexpected clinical manifestations of COVID-19 was an increased incidence of thromboembolism.[1] Initially, investigators noted patients with COVID-19 had remarkably high circulating levels of coagulation degradation byproducts that seemed correlated with patient outcomes.[2,3] As the pandemic progressed, clinicians from around the globe began to report higher than expected incidence of VTEs as well as cerebrovascular accidents in patients infected with the virus.[3-7]

Faced with an apparent increased incidence of VTEs, many institutions and some professional societies recommended the adjustment of previously accepted strategies of prophylactic anticoagulation for hospitalized and critically ill patients with COVID-19.[8,9] These recommendations often involved targeting higher levels of prophylactic anticoagulation based on risk factors such as disease severity, BMI, and surrogate markers of thrombosis or inflammation. Some recommended "treatment" doses of anticoagulation for the most severely ill patients. These deviations from previously accepted prophylactic anticoagulation practices were influenced by reports of increased survival in hospitalized patients with COVID-19 who were treated with escalating levels of anticoagulation.[10-12] However, increasing levels of anticoagulation is not without risk; thus, these decisions cannot be taken lightly due to the potential for patient harm.

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In this issue of *CHEST*, Taquard et al[13] examine the relationship between prophylactic doses of anticoagulation administered to critically ill patients with COVID-19 infection and the incidence of both thrombotic and bleeding events. They performed a retrospective chart review of patients who had been diagnosed with COVID-19 and admitted to eight French ICUs over a 20-day period from March to April 2020. The authors took advantage of evolving recommendations from the French Working Group on Perioperative Hemostasis and the French Study Group on Thrombosis and Hemostasis to increase the dose of prophylactic anticoagulation progressively in patients with COVID-19, based on a number of thrombotic risk factors.[9] These new anticoagulation directives occurred midway through the studied time period, which allowed the authors to investigate the impact of anticoagulation levels on outcomes. Clinical and laboratory data were collected from day 1 of ICU admission through day 14 and compared anticoagulation dosing to thrombotic and hemorrhagic events. The level of prophylactic anticoagulation was classified into two groups: standard and high dose (which included intermediate and therapeutic dose anticoagulation). The cumulative treatment coverage was then expressed as the number of evaluation periods covered by the anticoagulation strategy. Consistent with previous reports, the authors noted a thrombotic complication rate of 22.7% overall in the first 14 days of hospitalization, with pulmonary emboli accounting for the majority of thrombotic events (52% of the events reported). Increased dose prophylactic anticoagulation significantly decreased the risk of thrombosis. Specifically, a patient's cumulative exposure to higher prophylaxis dosing was associated with a reduced risk of thrombosis (hazard ratio [HR], 0.79; 95% CI, 0.65-0.95; $P = .014$). Interestingly, exposure to higher levels of anticoagulation was not associated with a significantly increased risk of bleeding in the first 2 weeks of treatment (HR, 1.11; 95% CI, 0.70-1.75). Unlike previous studies, however, increased

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cumulative exposure to higher dose anticoagulation did not improve mortality rates. The authors appropriately identify a number of weaknesses of their study that merit consideration, including its retrospective nature (a weakness shared by previous studies), the short duration of follow up (14 days), and the variable nature of anticoagulation received.

The study adds to the growing list of publications demonstrating a markedly increased incidence of macrovascular thrombosis in patients infected with COVID-19. This observation is in itself remarkable, and although similar reports of increased risk of VTE occurred during the SARs-CoV-1 and HIN1 outbreaks, the incidence in COVID-19 is particularly striking, in part due to the large number of patients impacted in this deadly pandemic.[14,15] The observation begs questions regarding mechanism or mechanisms of this apparent hypercoagulable state. Is this possibly a consequence of the intense inflammatory milieu resulting from SARS-CoV-2? Could a dysregulated immune response result in the generation of micro and macro thrombi? Can COVID-19 directly infect vascular endothelium or otherwise contribute to an endotheliopathy, more directly inducing prothrombotic changes.[16] These and other possible mechanisms are under active investigation; it is this essential work that will help guide our future therapeutic response to this devastating disease.

Interestingly, since the completion and submission of this study, we have learned via press release that three ongoing prospective randomized controlled trials (REMAP-CAP, ACTIV-4 and ATTACC) that were evaluating treatment dose prophylaxis in hospitalized moderately or critically ill patients with COVID-19 infection have halted enrollment in the critically ill cohort at the recommendation of the Data and Safety Monitoring Board. Enrollment continues for the moderately ill cohort. We of course must now wait for the data that guided this decision, but this is yet another example of the dizzying pace at which studies are designed and published and treatment recommendations are adjusted during this pandemic. The speed of the pandemic is matched only by the speed of scientific discovery; through the determined and selfless work of our clinicians and investigators, we have begun to see the tide turn in our favor.

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