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Invited Commentary

Fibrinolysis Shutdown in COVID-19-Associated Coagulopathy: A Crosstalk among Immunity, Coagulation, and Specialists in Medicine and Surgery

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INTRODUCTION: "ENDOTHELIITIS"-INDUCED IMMUNOTHROMBOSIS CAUSED BY SARS-CoV-2 INFECTION

In this issue, in the review by Meizoso and colleagues,[1] the authors provide a pathophysiologic tour de force of the

unique hemostatic derangement in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection called coronavirus disease 2019 (COVID-19)-associated coagulopathy (CAC). The authors concisely describe the dysregulated "crosstalk" between innate immunity and coagulation, which results in what has now been commonly termed "immunothrombosis."[2] However, this immunothrombotic crosstalk is not only limited to the pathophysiology of CAC, but may also be applied clinically by the physicians caring for these patients. The unique experience of the critical care trauma surgeon in trauma resuscitation, and now CAC, has provided these experts singular insight into the pathophysiologic underpinnings of CAC. This unique coagulopathy associated with SARS-CoV-2 infection is a function of the "cytokine storm," as the authors clearly depict in Figure 1 of their review. This inflammatory storm of immunothrombosis is defined by a global "endotheliitis," characterized by an initial fibrinolysis shutdown with enhanced proclivity to form microvascular and macrovascular thromboses.[2] Meizoso and coauthors,[1] other critical care trauma surgeons, and nonsurgical medical colleagues, have applied their knowledge and experience with fibrinolysis shutdown in trauma-induced coagulopathy, sepsis-induced coagulopathy, and now CAC, where it is a nearly ubiquitous finding on presentation and a consistent marker of disease severity.[3,4] This brief and accurate review highlights and clarifies the following similarities between trauma and sepsis and the significance of CAC within the context of the fibrinolytic spectrum.

CROSSTALK IS BETWEEN INNATE IMMUNITY AND COAGULATION, AS WELL AS BETWEEN MEDICAL AND SURGICAL SPECIALTIES

The pathophysiologic crosstalk of CAC is not only between innate immunity and coagulation, which leads to microvascular immunothromboses, but also involves communication within a broad collaboration of medical and surgical disciplines.

The clinical manifestations of the immunothrombotic crosstalk require treatment with meticulous bedside goal-directed anticoagulation for these complicated patients. Judicious anticoagulation may be guided by plasma-based common coagulation tests (CCT)s such as prothrombin time, international normalized ratio, partial thromboplastin time, anti-Xa levels, platelet count, and fibrinogen, as well as adjunctive whole blood viscoelastic tests (VET)s, such as thromboelastography and rotational thromboelastometry, to determine the hemostatic competence of these CAC patients.[5] The critical care trauma surgeon, with a long history of VET-guided resuscitation for trauma-related and surgical hemorrhage, has taken the lead in treating patients with CAC, as demonstrated by this review by Meizoso and coauthors.[1] In the future, critical care trauma surgeons may be more often requested to render an opinion on not only trauma and the hemorrhaging surgical patient, but also on these CAC patients.[6,7] Hence, the importance of this timely and concise review in a venue directed toward surgeons.

COVID-19 PATIENTS IN FIBRINOLYSIS SHUTDOWN CLOT AND BLEED AT THE SAME TIME

The timeliness of this publication is significant because the authors have wisely chosen to address not only the hypercoagulability that manifests by fibrinolysis shutdown in CAC, but the opposite end of the spectrum as well: the tendency of hospitalized and anticoagulated COVID-19 patients to "bleed and clot at the same time." Specifically, as Meizoso and colleagues[1] mention in their review, the recent interim findings of the multi-platform randomized controlled trials (mpRCTs), which have addressed therapeutic anticoagulation in COVID-19 patients, have identified that moderately ill patients with COVID-19 benefit from early therapeutic anticoagulation before admission to the ICU. However, early administration of full therapeutic anticoagulation in critically ill patients had the opposite outcome. Due to futility and a signal toward harm in this severely ill cohort, the ICU arm of the trial was halted.[8-10] This raises the possibility that early administration of unfractionated heparin in patients with CAC, guided by close monitoring with partial thromboplastin time and anti-Xa levels along with adjunctive VETs, may allow physicians to "thread the needle" of anticoagulation—similar to protocols for anticoagulating patients treated with extracorporeal membrane oxygen. In turn, improved hemostatic monitoring and personalized anticoagulation may confirm the hypothesis that early therapeutic anticoagulation for patients with CAC may prevent deterioration and thrombohemorrhagic manifestations simultaneously, so long as intensive bedside precision-based medicine is used to guide anticoagulation with VETs as well as the common coagulation tests.[4,10,11]

"SPECTRUM OF INQUIRY": THE LARGE RCTs VS SMALL HYPOTHESIS-GENERATING OBSERVATIONAL STUDIES OF PRECISION-BASED MEDICINE

Finally, this review addresses the important epistemologic question regarding the significance of smaller hypothesis-

generating studies based on clinical observation and mechanistic rationale, particularly during a period of early scientific discovery such as the SARS-CoV-2 pandemic.[12-14] Rapid deployment of the 3 mpRCTs concerning therapeutic anticoagulation in the COVID-19 patient is an example of pandemic-response, research-based rapid innovation. Yet, this review highlights the importance of small trials, such as the few studies which, early in the pandemic, advocated for full therapeutic anticoagulation to treat the microvascular thromboses of these patients and even advocated for the administration of tPA.[14,15]

Much as the spectrum of fibrinolysis can be studied and applied to trauma- and sepsis-induced coagulopathies, the intellectual pursuit of the cause and treatment of CAC on one end of the "spectrum of inquiry" involves large RCTs driven by epidemiologic constructs. At the other end of the "spectrum of inquiry" are the smaller, observational, and personalized precision-based medicine studies driven by a mechanistic rationale, which also enable the testing of important pathophysiologic hypotheses.[12] During this unique time in the history of medicine, the use of both forms of inquiry will more quickly lead to consensus regarding the methods and timing of anticoagulation for COVID-19 patients. This pandemic, which introduced CAC, has provided the opportunity for hematologists, anesthesiologists, emergency physicians, medical intensivists, and critical care trauma surgeons to meet on the same playing field, and has advanced their evolution toward further collaboration.[6,7,16] As represented by this excellent review by Meizoso and colleagues,[1] the *Journal of the American College of Surgeons* may be congratulated for providing its prestigious venue for cross-hybridization of ideas among medical and surgical specialists. The future is indeed an exciting place for physicians caring for the hemorrhaging patient, whether related to trauma or similar etiologies.[6,7] The initiative taken by critical care trauma surgeons in understanding the pathophysiology of CAC has demonstrated the importance of shared responsibility in not only scientific inquiry among medical and surgical specialties, but also the overlapping duties for providing care to these remarkably interesting and complicated COVID-19 patients.

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