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We read with interest the International Society on Thrombosis and Haemostasis (ISTH) interim guidance on recognition and management of coagulopathy in COVID-19.¹ We applaud this group’s efforts in releasing a timely article on the pandemic affecting all regions of the globe. Although we agree that this interim guidance addresses important considerations for monitoring the disease process, we believe that the proposed treatment strategy of prophylactic low molecular weight heparin (LMWH) to treat severe COVID-19 coagulopathy is an unconvincing strategy. Patients that are critically ill with COVID-19 have hallmark signs of disseminated intravascular coagulation (DIC),² and as noted in the ISTH interim guidance and our own clinical practice, thrombosis is the overwhelming phenotype with rare bleeding complications. We address this concern with the existing data on the severe hypercoagulable state of COVID-19 victims and advocate for consideration of systemic anticoagulation with unfractionated heparin to prevent life-threatening micro- and macrovascular thrombosis to mitigate their associated consequences, up to and including progression of respiratory and organ failure.

First, as noted, it has become clear that critically ill COVID-19 patients are hypercoagulable. Although no reliable published epidemiologic data exist yet on thromboembolic complications, the clinical experience has been one of patients frequently clotting off their central venous catheters (eg, dialysis catheters), clogging their dialysis filters, and having unusually frequent thrombotic complications including ischemic limbs, strokes, and venous thromboembolism. These clinical observations are supported by several findings in hospitalized patients with COVID-19, including high D-dimer levels, high fibrinogen levels (especially in nonsurvivors), low antithrombin levels, a high incidence of venous thromboembolism (~20%), and nearly three-quarters of nonsurvivors meeting ISTH criteria for DIC, whereas in contrast just 0.6% of survivors meet them.³⁻⁸ It is not infrequent at our institutions to see patients with fibrinogen levels >700 mg/dL (and
even >900 mg/dL), which in addition to low antithrombin levels renders patients more resistant to heparin agents and suggests prophylactic heparin or LMWH doses may be inadequate,\(^9\) where such high fibrinogen levels also increase risk of thrombosis,\(^{10-13}\) and a prior randomized controlled trial has shown that high fibrinogen levels reduce efficacy of prophylactic dose heparin agents.\(^{14}\) Furthermore, the overall mortality rate for critically ill COVID-19 patients admitted to intensive care units has ranged from 22\% to 64\% (using reports from Hubei Province and Lombardy, Italy), where the overwhelming majority die of respiratory failure or associated complications.\(^{5,6,15}\) and a common feature of acute respiratory distress syndrome (ARDS) (regardless of cause) is the deposition of fibrin in the airspaces and fibrin-platelet microthrombi in the pulmonary vasculature to include on autopsy of COVID-19 patients.\(^{16-19}\) This microvascular thrombosis in the pulmonary system is likely to be a major contributor to their progressive respiratory dysfunction, and may also explain why it is common to see evidence of right heart strain on bedside echocardiograms in critically ill COVID-19 patients. As noted in the ISTH interim guidance, emerging data suggest there is a survival advantage for those patients with COVID-19 who receive administration of prophylactic-dose heparin agents.\(^{20}\) However, this is fundamentally flawed because the comparison is made against a group of patients in which no prophylactic heparin agent was given, and one would find these same "positive" results in virtually any disease causing severe illness such that this finding cannot be attributed to COVID-19-specific coagulopathy.

At this time in the United States, there are virtually no trials targeting the coagulation system in COVID-19 registered on clinicaltrials.gov. Although DIC is a long-studied phenomenon, there has never been a disease like COVID-19 that so consistently causes thrombotic DIC in large numbers of patients, and as such there are no good randomized controlled trials available to apply guidance for anticoagulation management. In the absence of clear data, it is our group's position that early initiation of therapeutic anticoagulation with unfractionated heparin should be considered before significant clinical deterioration to avoid further decline in patients without significant bleeding risks. Antithrombin supplementation may also be of utility. This may help alleviate inappropriate microvascular thrombosis that evidence suggests is a key feature of their pulmonary failure, the primary cause of death in COVID-19 patients. Following is our detailed rationale for why we suggest this course of action, as well as a proposed salvage therapy with fibrinolytic agents and a call to action for expeditious study of how to best manage coagulopathy in COVID-19 patients.

### 1.1 | RATIONALE FOR SYSTEMIC ANTICOAGULATION WITH UNFRACTIONATED HEPARIN

1. Although prophylactic doses of LMWH may be appropriate with mild and moderate forms of hospitalized COVID-19 patients, the severe form of the disease has a clear pattern of hypercoagulability with progression to organ failure. Hypercoagulability driving DIC-related organ failure has been documented for more than 60 years in the research setting,\(^{21}\) which can be treated with early systemic anticoagulation with heparin.\(^{22}\) Although not specifically studied in COVID-19, recommendations for management of DIC with a thrombotic phenotype by the British Society for Haemotology includes therapeutic anticoagulation with unfractionated heparin.\(^{23}\)

2. It has been known for decades that higher levels of fibrinogen render patients resistant to heparin in addition to the known reduced levels of antithrombin in COVID-19 patients.\(^{7,9}\) COVID patients at our institution have fibrinogen levels that are frequently >700 mg/dL and have been documented to reach >900 mg/dL, which outside of COVID-19 is extremely uncommon in the intensive care unit setting. Furthermore, hyperfibrinogenemia was demonstrated in a randomized control trial to reduce prophylactic efficacy in altering clot formation,\(^{14}\) suggesting that LMWH or unfractionated heparin at standard prophylactic dosing is at risk of missing its efficacy potential in severe COVID-19. Systemic anticoagulation would be a logical choice as a result, with ongoing measurements of coagulation (eg, anti-Xa levels) to ensure a therapeutic level is obtained and catered to the individuals underlying coagulopathy.

3. High fibrinogen levels are associated with thrombosis,\(^{10-13}\) and when levels reach above 900 mg/dL there is a threefold increase in blood viscosity at low shear,\(^{24}\) such as is seen in the right heart (pulmonary) circulation. This completes the description of Virchow’s triad: hypercoagulability that is now known in COVID-19, stasis, and injury/inflammation from their ARDS. This is supported by autopsy findings in COVID-19.\(^{19}\) Therefore, a more aggressive regimen to anticoagulate these patients before end-organ microvascular thrombosis may be key to preventing their decline into ARDS and multiple organ failure.

4. There are recent concerns that COVID-19 patients harbor a high rate of pulmonary embolism that are missed due to primary lung injury from the virus.\(^{25}\) These patients are clinically too unstable to transport for imaging for definitive care. Suspected pulmonary embolism in COVID-19 patients that are already on mechanical ventilation nearly guarantees death, unless identified and treated promptly. Therefore, a more aggressive anticoagulation plan should be considered. In such a setting where urgent thrombolysis with Alteplase (tPA) may be indicated, having a patient on therapeutic LMWH may increase risk of bleeding that cannot be stopped, and further supports our position that therapeutic unfractionated heparin is likely more appropriate.

5. Renal failure commonly follows ARDS in COVID-19.\(^{26}\) This makes LMWH a less appealing drug for renal dosing and becomes more challenging to manage if bleeding occurs.

6. In vivo models of coronavirus infection demonstrate that endogenous heparan sulfate aids in viral entry into the host cell, and administration of unfractionated heparin functions as a sort of
1.2 | PROPOSED SALVAGE THERAPY WHEN ANTICOAGULATION FAILS

There is evidence in both animals and humans that fibrinolytic therapy in acute lung injury and ARDS improves survival, which supports that fibrin deposition in the pulmonary microvasculature contributes to ARDS, and in particular COVID-19 ARDS, where concomitant diagnoses of DIC on their laboratory values is observed in more than 70% of those who die of COVID-19. In advanced disease in COVID-19, systemic heparin will not break down the existing clot, at which point salvage therapy by using tPA to restore microvascular patency may have a role, and there are mounting off-label use reports of such an approach throughout the United States. Well-controlled studies are not available and optimal dosing regimens are completely unknown, so such an approach should be considered only as a last-ditch effort in a dying patient in which no other options exist until more complete descriptions and studies of this approach are available.

2 | SUMMARY AND CALL TO ACTION

In conclusion, we call for careful reconsideration of the ISTH interim guidance on recognition and management of coagulopathy in COVID-19 with a specific focus on recalibrating the proposed approach to the use of heparin in this disease process. We further call for an expedited randomized controlled trial in COVID-19 coagulopathy to evaluate unfractionated heparin and LMWH at therapeutic and prophylactic doses to answer the critical questions surrounding anticoagulation in hospitalized COVID-19 patients in this time of global crisis. The advanced form of COVID-19 has irrefutable evidence of DIC with a predominately thrombotic phenotype in which tens of thousands of patients are suffering from each day, and coagulation management for this disease needs to be pushed to the forefront without further delay.

KEYWORDS
acute respiratory distress syndrome (ARDS), anticoagulation, COVID-19, disseminated intravascular coagulation, International Society on Thrombosis and Haemostasis (ISTH)

CONFLICTS OF INTEREST
Dr. Barrett, Dr. Hunter, Dr. Yaffe, and Dr. Moore have patents pending related to both coagulation/fibrinolysis diagnostics and therapeutic fibrinolytics, and are passive cofounders and holds stock options in Thrombo Therapeutics, Inc. Dr. Barrett and Dr. Moore have received grant support from Haemonetics and Instrumentation Laboratories. Dr. Yaffe has previously received a gift of Alteplase (tPA) from Genentech, and owns stock options as a cofounder of Merrimack Pharmaceuticals.

AUTHOR CONTRIBUTION
Each author contributed to the composition of this manuscript and approve of its submission.

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decay receptor/sink to reduce viral infectivity and potentially augment viral clearance.
Type and dose of heparin in Covid-19: Reply

We thank the authors for their comments and feedback on the International Society on Thrombosis and Haemostasis interim guidance. Hypercoagulability is indeed a significant issue in Covid-19, and the hemostatic system is shifted markedly toward the procoagulant side in these patients. However, we cannot yet be certain that unfractionated heparin (UFH) is better than low molecular weight heparin (LMWH) in this scenario. Although UFH has been used for several years, it does have practical issues, mainly with respect to the need for frequent monitoring using activated partial thromboplastin time. In addition, as the authors pointed out correctly, markedly increased acute phase reactants including fibrinogen could contribute to heparin resistance making the use of UFH problematic (much more than LMWH). Among the reasons for heparin resistance, antithrombin deficiency is not common in Covid-19 patients, at least in the published literature. Despite these issues, UFH may still be preferred if there is marked renal impairment or need for reversibility for an urgent intervention. One of the latter situations is if the patients progress despite anticoagulant therapy. The authors of the letter had recently published a case series on the use of tissue plasminogen activator in Covid-19 patients which is certainly a consideration in patients who progress despite anticoagulant therapy.

At the time of writing the interim document, our aim was to highlight the urgent need to consider thromboprophylaxis in all patients who require hospital admission for Covid-19 to mitigate poor outcomes from the marked hypercoagulability. We do recognize...