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COVID-19 and its implications for thrombosis and anticoagulation

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Abstract:

The SARS-CoV-2 coronavirus (COVID-19) induced infection can be associated with a coagulopathy, findings consistent with infection induced inflammatory changes as observed in patients with disseminated intravascular coagulopathy (DIC). The lack of prior immunity to COVID-19 has resulted in large numbers of infected patients across the globe and uncertainty regarding management of the complications that arise in the course of this viral illness. The lungs are the target organ for COVID-19; patients develop acute lung injury which can progress to respiratory failure, although multiorgan failure can also occur. The initial coagulopathy of COVID-19 presents with prominent elevation of D-dimer and fibrin/fibrinogen degradation products, while abnormalities in prothrombin time, partial thromboplastin time, and platelet counts are relatively uncommon in initial presentations. Coagulation test screening, including the measurement of D-dimer and fibrinogen levels, is suggested. COVID-19 associated coagulopathy should be managed as it would be for any critically ill patient, following the established practice of using thromboembolic prophylaxis for critically ill hospitalized patients, and standard supportive care measures for those with sepsis-induced coagulopathy or DIC. Although D-dimer, sepsis physiology, and consumptive coagulopathy are indicators of mortality, current data do not suggest the use of full intensity anticoagulation doses unless otherwise clinically indicated. Even though there is an associated coagulopathy with COVID-19, bleeding manifestations, even in those with DIC, have not been reported. If bleeding does occur, standard guidelines for the management of DIC and bleeding should be followed.

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Abstract (194 words)

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INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) pandemic has besieged us with its relentless worldwide march and high morbidity and mortality. The SARS-CoV-2 is a coronavirus with human infection designated as COVID-19 by the World Health Organization. Bats and birds serve as the typical coronavirus hosts, with zoonotic spread and a long-documented history of animal-animal-human transmission.¹ In December 2019, an outbreak of a new type of coronavirus was noted with a novel member of the coronavirus genera. The viral reservoir may be bats, given the high homology of SARS-CoV-2 to other SARS-like viruses found in bats.²

SARS-CoV-2 is like Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) viruses in the *Coronaviridae* family, with its positive-sense single-stranded RNA genome containing a surface glycoprotein that studs the viral envelope, giving it the characteristic corona on electron microscopic imaging.³ These peplomers are known as spike proteins, or S protein, and are thought to be responsible for the tropism it displays as they engage only with specific receptors on the cell surfaces of target organisms.⁴ SARS-CoV-2 appears to preferentially target respiratory epithelium where it enters host cells through the angiotensin-converting enzyme 2 (ACE2) receptor, similar to SARS-CoV.^{4,5}

Initial reporting of findings from China have helped inform and guide the world. Dissemination of information is important, yet within quick succession of the findings, the time needed to interpret and apply the information by front-line workers is non-existent, as hospitals and staff become overwhelmed with the rapid influx of COVID-19 patients. Guidance from subspecialists is critically important to help clinicians engaged in COVID-19 patient care, especially as multiple specialties are needed for patient management in intensive care unit (ICU) and non-ICU settings.

In this Perspectives manuscript, we will review data for coagulation abnormalities that occur in association with COVID-19, and clinical management questions likely to arise. Approaches to management will be discussed in the context of past management strategies and unique issues of COVID-19. Our considerations are based on evolving data and consensus, and for coagulopathy management in disseminated intravascular coagulopathy (DIC) applied to COVID-19 patients.

DEFINITIONS

Infectious complications in critically ill patients are known to activate multiple systemic coagulation and inflammatory responses that are vital for host defense but can lead to DIC.^{6,7} Microorganisms and their components induce the expression of numerous products, including tissue factor on monocytes and macrophages, by binding to pattern-recognizing receptors on immune cells.⁸⁻¹⁰ The triggering of host inflammatory reactions also results in increased production of proinflammatory cytokines that have pleiotropic effects, including activation of coagulation, described further below, which, if not checked, can lead to consumptive coagulopathy. The International Society of Thrombosis and Haemostasis (ISTH) has diagnostic criteria for overt DIC but also developed and validated a sepsis-induced coagulopathy (SIC) score.¹¹⁻¹³ Coagulation changes associated with sepsis-induced coagulopathy are less severe and occur earlier in septic patients than DIC. The changes occur as a continuum, with SIC progressing to DIC if the underlying etiology of sepsis is not resolved.¹²⁻¹⁴

Both the ISTH definitions of overt DIC and SIC have been used in reports on coagulation changes in patients with COVID-19 in the Chinese outbreak, which is why they are defined here.^{15,16} Differences in clinical outcomes were found based on classification as having SIC or DIC, as described below. During the early phase of SARS-CoV-2 infection, coagulation test abnormalities are seen but do not result in clinical bleeding. Whether the initial coagulation changes seen in infected patients progress linearly to SIC and then to DIC as a result of SARS-CoV-2 infection is not known at this time; many factors including treatment modalities may be responsible for the later development of SIC or DIC.

The acronym COVID-19 associated coagulopathy (CAC) is being used to describe the coagulation changes in infected patients. The SARS-CoV-2 virus does not appear to have intrinsic procoagulant effects itself, although more information is needed. As discussed, the development of coagulation test abnormalities seen in SARS-CoV-2 infected patients is most likely a result of the profound inflammatory response. The “COVID-19 associated coagulopathy” early in infection reflects abnormalities in tests but does not fulfill the usual definition of a clinical coagulopathy where impaired ability to clot results in bleeding. Marked elevations in prothrombotic substrates may be balanced by both increased thrombin generation

and increased fibrinolysis; unfortunately, data assessing thrombin generation and fibrinolysis are not available.

COVID-19 COAGULATION DATA FROM WUHAN

At the time of this writing >2.9 million cases of COVID19 have been reported worldwide with >205,000 deaths (<https://coronavirus.jhu.edu/map.html>, accessed April 25, 2020). This staggering number of patients that is exponentially increasing must be considered when interpreting the data. Although initial reports are important, current event rates continue to change based on multiple factors that include increased testing availability, selection bias with over-representation of critically ill patients, and other variables that are not controlled for.

Evidence of abnormal coagulation parameters associated with COVID-19 appeared in early reports from China. Baseline characteristics of the first 99 patients hospitalized in Wuhan found that 6% had an elevated aPTT, 5% elevated PT, 36% elevated D-dimer, increased biomarkers of inflammation including interleukin-6 (IL-6), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP).¹⁷ Thrombocytopenia occurred in only 12%, however, 5 patients had other co-infections (1-bacterial, 4-fungal), and 4 had septic shock.¹⁷

Additional reports from another Wuhan hospital on the first 138 patients found minimal elevations in PT and normal aPTT.¹⁸ Of the patients requiring ICU admission, 26% had higher D-dimer levels, and 9% had shock. A complete set of clinical laboratory parameters for the hospital course were available for 33 patients who either recovered or died. Characteristics of the 5 non-survivors compared to 28 survivors included rising D-dimer, progressive lymphopenia, and renal dysfunction. D-dimer levels appeared to diverge 5 days after onset of symptoms.¹⁸

In an analysis of 191 patients from 2 of the main Wuhan hospitals, mortality was reported to be 28% (54-patients).¹⁹ Factors associated with mortality included an elevated D-dimer > 1.0 mcg/mL on admission, increased PT, elevations in IL-6, and other biomarkers of inflammation, elevated troponin levels, and co-morbidities including older age, hypertension, diabetes, and coronary artery disease. All 54 non-survivors met the definition of sepsis, and 50% had evidence of coagulopathy defined as a 3-second PT increase or a 5-second increase in aPTT. Half of these patients also had secondary infections, however, DIC was not assessed. In a multivariable logistic regression model of 171 patients with complete data for all variables (53 non-survivors

and 118 survivors), a D-dimer level greater than 1.0 mcg/mL at admission was associated with increased mortality with an OR of 18.42 (2.64-128.55, $p=0.003$).¹⁹

Another early publication evaluated 1099 COVID-19 patients, and excluded individuals who did not require hospitalization.²⁰ The primary composite outcome of ICU admission, ventilator support, or death occurred in 6.1% (67-patients), with a 1.4% mortality (15-patients). The investigators noted that compromised respiratory status and more severe disease on admission were associated with worse outcomes. Of the 173 patients who were classified with severe pneumonia at admission, based on the American Thoracic Society criteria, 24.9%(43/173) experienced a primary outcome event compared to 3.6% in the non-severe group.²¹ D-dimer was dichotomized as either less than or greater than 0.5 mg/liter, with more patients with severe disease experiencing a primary outcome having D-dimer values >0.5 mg/liter.²¹

A more complete assessment of coagulation parameters, including D-dimer, PT, aPTT, fibrinogen, and antithrombin, in 183 COVID-19 positive patients was analyzed by survivor status from admission through 14 days.¹⁵ At the time of publication, 78 (42.6%) patients had been discharged, and 21 (11.5%) patients had died while the rest 84 (45.9%) were still hospitalized. A total of 15 of 21 non-survivors were diagnosed with overt DIC according to ISTH criteria, with median onset at 4 days (1-12 days) after admission, while only 1 of the 78 discharged patients had evidence of DIC. Over their hospitalization, non-survivors had evidence of progressive DIC with decreased fibrinogen, increased D-dimer, and increased PT, occurring 10 days after admission, although information regarding evidence of sepsis was not provided. Although antithrombin levels decreased late in the hospitalization for non-survivors, levels were not below normal in the majority.¹⁵

In an analysis of 449 patients classified as having severe COVID-19 (defined as respiratory rate >30 breaths/min, room air oxygen saturation $< 93\%$, $PaO_2/FiO_2 < 300$ mmHg), 99 patients (22%) received prophylactic VTE anticoagulation for at least 7 days, with 94 patients treated with enoxaparin 40-60 mg/day, and 5 treated with unfractionated heparin (UFH) 10,000-15000 U/day.¹⁶ Of the 449 patients, 22% ($n=97$) had an ISTH SIC score of ≥ 4 , and 29.8% (134) patients died at time of reporting. Although no difference in 28-day mortality was seen between heparin and non-heparin treated patients overall, stratification by SIC score identified lower mortality in patients treated with heparin when SIC score was ≥ 4 (40.0% vs. 64.2%, $p=0.029$)

compared with SIC score < 4 (29.0% vs 22.6%, $p=0.419$). A 20% reduction in mortality was observed when patients with D-dimer exceeding 3.0 mcg/ml were treated with prophylactic doses of heparin. (32.8% vs 52.4%, $p=0.017$) Even using the SIC score, only 21.6% of severe cases met SIC criteria. However, patients with D-dimer > 6 x ULN did comprise a higher proportion of severe cases, (161/446, 35.9%).¹⁶

INFLAMMATION and COAGULATION

Infection due to viral, bacterial, or fungal pathogens initiates complex systemic inflammatory responses as part of innate immunity. Activation of host defense systems results in subsequent activation of coagulation and thrombin generation as critical communication components among humoral and cellular amplification pathways, a term called thromboinflammation or immunothrombosis.²²⁻²⁴ In patients with sepsis-induced coagulopathy, the importance of the evolution from adaptive hemostasis to pathologically induced DIC with multiorgan failure continues to be evaluated. Coagulation is activated by the inflammatory response through several procoagulant pathways. Polyphosphates, derived from microorganisms, activates platelets, mast cells, and FXII in the contact pathway of coagulation, and exhibit other downstream roles in amplifying the procoagulant response of the intrinsic coagulation pathway.²⁵ Complement pathways also contribute to activation of coagulation factors.²⁶ Although neutrophil extracellular traps (NETs) are present in thrombi, the individual NET components of cell-free DNA and histones activate the contact pathway and enhance other prothrombotic pathways resulting in thrombin generation.^{10,27} Pathogen-associated molecular mechanisms (PAMPs) are important aspects of the complex interactions between the immune response and coagulation and in sepsis.^{10,28} The inflammatory effects of cytokines also result in activated vascular endothelial cells and endothelial injury with resultant prothrombotic properties.^{10,29}

Critically ill patients at high-risk of mortality may benefit from strategies to inhibit these responses, but the success of interventions may depend on the time course and evolution of the infection. Circulating serine protease inhibitors including antithrombin, C1 esterase inhibitor, and protein C are decreased in the setting of the inflammatory response to infection.⁷

Fibrinolytic shutdown that also occurs in sepsis is characterized by increased PAI-1 activity resulting in low D-dimers.^{30,31} Vascular endothelial injury causes further thrombocytopenia,

reduction of natural anticoagulants, but also hemostatic activation as the phenotypic expression of thrombotic DIC. Analysis of septic patients who are coagulopathic and receive serine protease inhibitors such as antithrombin or thrombomodulin suggest there may be a survival benefit in post-hoc analyses.³²⁻³⁴ Subsequent reductions in coagulation factors associated with increased fibrinolysis that can occur during infections and sepsis are considered the fibrinolytic phase of DIC, but maybe a late step with advanced disease, and might explain why high D-dimers are associated with progression of disease and worse outcomes. As a result, optimizing specific therapy may be based on the time course of disease.^{6,23} As evidenced by the data from Tang, SIC and overt DIC occur in patients in later stages of COVID-19 infection, while still hospitalized, often with septic physiology and multiorgan failure.^{15,16}

Significant inflammation is present in patients with SARS-CoV-2 infection, based on elevated levels of IL-6, increased CRP and ESR, and elevated fibrinogen at presentation.³⁵ Given the tropism of the virus for ACE2 receptors, endothelial cell activation and damage with resultant disruption of the natural antithrombotic state is likely. An early report of COVID-19 patients in Wuhan measured proinflammatory cytokines and found elevated plasma concentrations that were higher in ICU patients than non-ICU patients.³⁶ This inflammation associated with COVID-19 and subsequent activation of coagulation is the probable cause for the elevated D-dimer levels, as increased levels have been associated with many conditions other than thromboembolism, with infection an important etiology.^{7,37,38} The finding that D-dimer would track with severity of disease and inflammation is not surprising given the evolving understanding of the interaction between inflammation and activation of coagulation. Some patients appear to have a more pronounced inflammatory response to infection with SARS-CoV-2, such as seen with systemic inflammatory response syndrome (SIRS) or cytokine storm, which may explain more dramatic changes in coagulation tests, including significantly elevated D-dimer, especially as the disease progresses.³⁹ As Tang demonstrated, fibrinogen levels in all patients were elevated on admission.¹⁵ Ranucci reported on 16 COVID-19 patients with acute respiratory distress syndrome (ARDS) requiring mechanical ventilation who had fibrinogen, D-dimer, and IL-6 levels measured. An important finding from this report was that increased IL-6 levels correlated with increased fibrinogen levels, demonstrating and confirming the link between inflammation and procoagulant changes; all patients had elevated IL-6 levels on admission.⁴⁰

Elevated D-dimer levels at admission or increasing D-dimer over time are both associated with increased mortality with COVID-19. Patients who develop septic physiology and septic shock are at increased risk of death, as are those who develop DIC even if it occurs in the absence of sepsis. The mechanisms that activate coagulation in SARS-CoV-2 infection are not known at present but appear to be linked to inflammatory responses rather than specific properties of the virus. Unlike other RNA type viruses associated with hemorrhagic manifestations such as Ebola and other hemorrhagic fever viruses, the coagulopathy seen with SARS-CoV-2 has not been reported to result in significant bleeding.⁵

ENDOTHELIALOPATHY and COVID19

Consistent with vascular endothelial dysfunction with sepsis induced coagulopathy, an endothelialopathy appears to contribute to the pathophysiology of microcirculatory changes in SARS-CoV-2 infections.^{29,41} The receptor for viral adhesion is an angiotensin-converting enzyme (ACE) 2 receptor on endothelial cells⁴², with viral replication causing inflammatory cell infiltration, endothelial cell apoptosis, and microvascular prothrombotic effects.⁴³ Recent reports demonstrate viral inclusions within endothelial cells and sequestered mononuclear and polymorphonuclear cellular infiltration, with evidence of endothelial apoptosis in post mortem of SARS-CoV-2 infection.⁴³ As a result, microcirculatory dysfunction contributes to the clinical sequelae in patients with COVID-19.

MANAGEMENT of COAGULATION ISSUES

Coagulation Test Surveillance

Hospitalized patients with newly confirmed or presumptive COVID-19 infection should have coagulation testing performed on admission, including D-dimer, PT, aPTT, fibrinogen, and platelet count, testing that can provide useful prognostic information. The rising D-dimer associated with non-survivors, and the rapid drop in fibrinogen associated with DIC, can be seen within 7-11 days after onset of symptoms or 4-10 days after hospitalization.^{15,18,19} Timing of elevated D-dimer, PT, and aPTT, with decreasing fibrinogen and platelet count, also coincides

with the duration of hospitalization, clearly starting between 7-10 days after admission, although increased D-dimer can start at day 4. These patients are critically ill with septic physiology; the progressive coagulation changes may indicate the development of DIC that may be independent of COVID-19 effects, and due to prolonged hospitalization, mechanical ventilation, superinfection, and other typical ICU etiologies.

VTE Prophylaxis

All confirmed or suspected COVID-19 patients admitted to the hospital should be treated with pharmacologic VTE prophylaxis, given the high inflammatory state, unless there are specific contraindications. Although the incidence of VTE is low in the Asian population and therefore routine VTE prophylaxis not frequently used^{44,45}, 22% of the cohort evaluated by Tang received prophylactic dose low molecular weight heparin (LMWH) or unfractionated heparin (UFH).¹⁶ VTE prophylaxis in these patients may have been due to increasing experience treating patients with COVID-19, along with reports of microvascular thrombosis in early pathology specimens or pulmonary emboli.^{46,47,44} Early autopsy reports demonstrated microvascular thrombosis as well as marked inflammatory changes.⁴⁸ Those patients with severe COVID-19 at presentation and either SIC with a score of ≥ 4 or D-dimer elevated $> 6 \times$ upper limit of normal were found to have decreased mortality when treated with prophylactic doses of enoxaparin or UFH.

Additional reports of ICU patients with severe COVID-19 suggest the incidence of VTE is higher than historic ICU rates, even when using standard VTE prophylaxis. From the Netherlands, an initial report found a 27% cumulative incidence of VTE in ICU patients, with a second report finding a cumulative incidence of symptomatic VTE at seven days of 11% (95% CI 5.8–17) and 23% (95% CI 14 – 33) at 14 days with a SHR of 3.8 (95% CI 1.3 – 12) for ICU patients compared to the wards. (Middeldorp, S. *Preprints* **2020**, 2020040345, doi: 10.20944/preprints202004.0345.v1, accessed 042520.)

Both groups in the Netherlands increased the dose of VTE prophylaxis given to their ICU patients as a result of these findings. Two reports from France also highlight the increased risk of VTE in ICU patients. One center that had been previously studying ARDS noted increased VTE in COVID-19 positive patients with ARDS compared to a matched historic cohort without COVID-19 (11.7 versus 2.1%, $p < 0.008$).⁴⁹ (Helms https://www.esicm.org/wp-content/uploads/2020/04/863_author_proof.pdf accessed 04/25/20) Another center in France also found an increased prevalence of PE with an estimated cumulative incidence of 20.4% (95% CI 13.1-28.7) at 15 days. The frequency of 20.6% was higher than the 6.1% found in a cohort of ICU patients from the same time period the year before, and the 7.5% found in the 40 patients admitted to the ICU with influenza in 2019. Of the 22 PE that occurred in the first 107 patients admitted to the ICU, 20 occurred while patients were on standard dose VTE prophylaxis.⁵⁰

The apparent increased incidence of VTE in COVID-19 patients has generated fierce discussions regarding the escalation of anticoagulation intensity for VTE prophylaxis, even before publications confirmed the increase. While practice based on the results from randomized controlled trials is the ideal, the increasing numbers of patients and admissions currently precludes conducting well-run trials. Many centers have increased the dose of anticoagulation for prophylaxis to “intermediate intensity” doses such as 0.5 mg/kg twice a day of enoxaparin, using a risk-adapted strategy with increased doses based on levels of D-dimer, fibrinogen, ICU location, or other factors associated with increased risk. A Delphi method consensus document found that 31.6 % of participants supported intermediate intensity dose, 5.2% therapeutic dose, while the rest supported using standard VTE prophylaxis dose for hospitalized patients with moderate to severe COVID-19 and lack of DIC.

(<https://www.sciencedirect.com/science/article/pii/S0735109720350087?via%3Dihub>, accessed 04/19/20)

Certainly, for obese patients, data suggest that 40 mg daily enoxaparin dosing is insufficient in postoperative settings, based on lack of achieving adequate plasma concentrations. Higher weight-based dosing was well tolerated, with doses of UFH 7,500 units three times daily or enoxaparin 40 mg twice daily.^{51,52} Increased heparin doses may also be necessary for prophylaxis to overcome the increases in procoagulant proteins that has been observed, including high levels of fibrinogen, FVIII, and vWF, levels which are not encountered in post orthopedic

joint replacement surgery or typical medically ill patients.⁴⁰ At this time, individual patient assessment incorporating baseline VTE risk factors and bleeding risk factors with clinical judgment is required. One of the authors (JMC) has supported increased prophylactic dose anticoagulation for ICU patients at her institution based on internal audits finding increased VTE events with 40mg enoxaparin daily in ICU compared to ward patients.

Microvascular Thrombosis: Treatment

The basis of sepsis-induced coagulopathy management strategy is the rapid and timely treatment of the underlying infection, however, no specific antiviral therapy for SARS-CoV-2 is available to date. Overall management considerations should include assessment for concomitant infections in critically ill septic patients, especially with acute lung injury and ARDS.

Heparin and its derivatives for VTE management are important, but have demonstrated limited efficacy in previous reports for sepsis-induced coagulopathy. The physiologic anticoagulants that include activated protein C, thrombomodulin, and antithrombin have been previously studied in randomized clinical trials also demonstrated limited efficacy, however, all patients with sepsis were included, not just those with sepsis-associated coagulopathy and DIC. *Post-hoc* database analyses examining septic patients with laboratory proven DIC report decreased mortality examining antithrombin and thrombomodulin supplementation, and a trend towards improved survival in septic patients.³²⁻³⁴ However, antithrombin levels have not been found to decrease significantly in COVID-19 infected patients.¹⁵

COVID-19 associated coagulopathy should be managed like any other coagulopathy, including sepsis-associated DIC. Patients with COVID-19 coagulopathy alone may not develop SIC, DIC, or a bleeding diathesis or need for blood component replacement. For those that develop overt DIC, standard guidance for blood component support is available.⁵³

Microvascular thrombosis may also be responsible for multiorgan failure in patients with prolonged infection, but the early lung impairment appears to be due to the inflammatory, reactive, and viral effects on pulmonary tissue. Patients with sepsis should be treated with standard, supportive care. Although the use of anticoagulants or other physiologic agents might mitigate microvascular thrombosis and possibly end-organ dysfunction, no survival advantages have been found in prior trials in patients with sepsis, despite the apparent trend towards anticoagulation conferring a survival advantage in small subsets. Patients with sepsis alone or

sepsis and SIC or overt DIC should continue to receive prophylactic anticoagulation as previously discussed.

Microvascular Thrombosis: Prevention

The concept of using full-dose anticoagulation in COVID-19 patients for preventing microvascular thrombosis during severe infection has been considered. Infection can result in the development of ARDS, where fibrin-platelet microthrombi form in the pulmonary microcirculation and parenchyma, observed in one postmortem lung infected with COVID-19, a syndrome consistent with thrombotic DIC microvascular thrombosis, noted in an early pathology specimen in a non-peer reviewed report (<https://www.preprints.org/manuscript/202002.0407/v2>, accessed 041920). However, there are no data to support full dose anticoagulation at this time for this indication. As described, prior studies using anticoagulants in the setting of DIC have found no decrease in mortality. One report suggests using full-dose anticoagulation, citing a case of what appears to be skin necrosis from DIC (purpura fulminans), however it is unclear if patients were given VTE prophylaxis on hospital admission, and no treatment data are provided to support this.⁵⁴ In prior trials of anticoagulation with sepsis, low dose heparin has been used.⁵⁵ Past investigations of the biology of SARS viruses found that in vitro heparin reduced the coronavirus SARS-CoV infectivity by 50%.⁵⁶ Whether this is due to heparin acting as a non-specific polyanion blocking the charged spike protein from binding its host cell receptor, or whether it is due to specific inhibition of cleavage of the S protein into activated components by coagulation factor Xa which facilitates cell entry, is unclear.^{57,58} While theoretically interesting, these mechanisms are not well defined for SARS. There are no data for interaction of heparin with SARS-CoV-2 and no role for the clinical use of heparins to decrease infectivity in patients.

Clinical indications for therapeutic anticoagulation

For COVID-19 patients with other indications for anticoagulation, such as new or recent diagnosis of VTE, atrial fibrillation, mechanical cardiac valves, or long-term secondary VTE prevention, anticoagulation should be continued at full dose or a dose equivalent to their current dose. For inpatients, especially those that are critically ill, the use of LMWH or UFH for any indication is preferred instead of a direct oral anticoagulant given their shorter half-lives and ability for parenteral administration. COVID-19 patients have been shown to have increased

levels of fibrinogen, one of the different causes of both hypercoagulability and heparin resistance. As a result, if there are concerns regarding aPTT measurements, following anti-factor Xa heparin levels for monitoring should be considered.⁵⁹

The question of using therapeutic dose anticoagulation for presumed pulmonary emboli (PE) has been encountered in many ICU around the world due to difficulty moving mechanically ventilated patients to CT scanners and the desire to limit staff exposure to COVID-19 positive patients. D-dimer are usually not helpful, given the significant baseline elevations in these patients. Clinical findings of sudden respiratory decompensation, evidence of right heart strain on echocardiography, or DVT seen on lower extremity ultrasound performed for these reasons, have been used to increase to therapeutic dose anticoagulation. We can't argue with the pragmatic necessity of using therapeutic anticoagulation in this setting based on clinical perspectives.

CONCLUSION

The COVID-19 pandemic has disrupted the usual flow of medical knowledge and management, both are moving forward at a furious pace. Clinicians are faced with a pathogen whose behavior continues to be defined, and are desperately looking for treatments that might improve patient outcomes. Evaluation of the Wuhan data suggest the coagulopathy with COVID-19 is a result of the inflammatory response to SARS-CoV-2 infection resulting in thromboinflammation and driving thrombosis. It is more pronounced in those presenting with more severe disease symptoms, and who develop SIC and overt DIC. A summary of these findings can be found in Table 1. The lack of immunity to SARS-CoV-2 has resulted in a high number of infected patients. The severity of COVID-19 associated coagulopathy in some might be driven by an unchecked inflammatory response to a pathogen for which there is no prior acquired immunity.

COVID-19 associated coagulopathy should be managed as it would be for any hospitalized patient, following the established practice of VTE prophylaxis for critically ill patients, and standard supportive care measures for those with SIC or DIC. Our suggested management approach to monitoring and anticoagulation use is outlined in Table 2., Patients should be closely monitored for the development of thrombosis Although D-dimer, sepsis physiology, and

microvascular thrombosis are associated with mortality, current data do not support the use of therapeutic doses of anticoagulation for these findings. Despite the associated coagulopathy with COVID-19, bleeding manifestations without other associated factors have not been reported. If bleeding does occur, standard guidance for the management of SIC, DIC, and bleeding should be followed.^{12,37,60,61} A rapid global community effort has been made to integrate new information to help guide patient care with COVID-19. Our understanding of this new human pathogen is rapidly evolving, and our approach to patient management continues to evolve.

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JMC and JHL equally contributed to the writing of this manuscript.

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JHL: Serves on research, data safety, or advisory committees for CSL Behring, Instrumentation Labs, Janssen, Merck, Octapharma

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Table 1. COVID-19 Associated Coagulopathy

1. Coagulopathy is manifest as elevated fibrinogen, elevated D-dimers, and minimal change in PT, PTT , and platelet count in early stages of infection
2. Increasing Il-6 levels are correlated with increasing fibrinogen levels
3. Coagulopathy appears to be related to severity of illness and resultant thromboinflammation and not intrinsic viral activity
4. Elevated D-dimer at admission is associated with increased mortality
5. Rising D-dimer after admission precedes multiorgan failure and overt DIC
 - a. Noted to start at 4 days after admission in non-survivors
 - b. Longer duration of hospital stay associated with increasing D-dimer and development of sepsis physiology
6. Bleeding manifestations are not common despite coagulopathy

COVID-19 positive	Coagulation tests	Standard dose VTE prophylaxis	Escalated ¹ dose VTE prophylaxis	Therapeutic dose anticoagulation
Outpatient		Consider ²		
Inpatient	X			
Ward	X	X		
ICU	X		X	
Confirmed VTE	X			X
Presumed PE ³	X			X
ARDS	X		X	

Table 2. Management Strategy

Suggested approach to COVID-19 patients and coagulopathy. All admitted patients should have baseline PT,PTT, fibrinogen, D-dimer, and platelet count. Following these values can give important information regarding status of the coagulation system and safety of using anticoagulation. ¹ There are no data to support the use of an increased anticoagulant dose for prophylaxis, except in small studies in obese patients. Given the increased rates of VTE reported in COVID-19 infected ICU patients, many centers are using increased doses such as half the therapeutic dose for these patients. Anticoagulant options include LMWH, UFH, and fondaparinux. DOAC can also be considered, but intermediate intensity doses are not clear. Both fondaparinux and DOAC should be used with caution in patients with renal insufficiency due to their longer half-lives. ² Consideration for use of standard dose VTE prophylaxis in infected patients with morbid obesity or past history of VTE. While routine use in outpatients is not recommended, use in immobile infected outpatients, especially with other increased risks for VTE, can be considered on a case by case basis based on severity of illness or as incorporated into local practice. ³ Presumed PE is based on clinical findings of change in respiratory status, evidence of right heart strain on echocardiogram, and the inability to obtain imaging.