



COVID-19 and its implications for thrombosis and anticoagulation

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Severe acute respiratory syndrome coronavirus 2, coronavirus disease 2019 (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 that 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, whereas 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. (*Blood*. 2020;135(23):2033-2040)

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has besieged us with its relentless worldwide march and high morbidity and mortality. Severe acute respiratory syndrome (SARS) coronavirus 2 (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 SARS and Middle East respiratory syndrome 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 frontline workers is nonexistent, 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 *Perspective*, we will review data for coagulation abnormalities that occur in association with COVID-19, and the clinical management questions likely to arise. Approaches to management will be discussed in the context of past management strategies and the unique issues of COVID-19. Our considerations are based on evolving data and consensus, and are 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 in "Inflammation and coagulation," which, if not checked, can lead to consumptive coagulopathy. The International Society of Thrombosis and Haemostasis (ISTH) not only has diagnostic criteria for overt DIC but also developed and validated a sepsis-induced coagulopathy (SIC) score.¹¹⁻¹³ Coagulation changes associated with SIC 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 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 in "COVID-19 coagulation data from Wuhan." 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.

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. "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, >3.4 million cases of COVID-19 have been reported worldwide with >242 000 deaths.¹⁷ 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 overrepresentation 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 activated partial thromboplastin time (aPTT), 5% elevated prothrombin (PT), 36% elevated D-dimer, and increased biomarkers of inflammation including interleukin-6 (IL-6), erythrocyte sedimentation rate, and C-reactive protein.¹⁸ Thrombocytopenia occurred in only 12%, however, 5 patients had other coinfections (1 bacterial, 4 fungal), and 4 had septic shock.¹⁸

Additional reports from another Wuhan hospital on the first 138 patients found minimal elevations in PT and normal aPTT.¹⁹ 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 was available for 33 patients who either recovered or died. Characteristics of the 5 non-survivors compared with the 28 survivors included rising D-dimer, progressive lymphopenia, and renal dysfunction. D-dimer levels appeared to diverge 5 days after onset of symptoms.¹⁹

In an analysis of 191 patients from 2 of the main Wuhan hospitals, mortality was reported to be 28% (54 patients).²⁰ Factors associated with mortality included an elevated D-dimer >1.0 $\mu\text{g/mL}$ on admission, increased PT, elevations in IL-6, and other biomarkers of inflammation, elevated troponin levels, and comorbidities including older age, hypertension, diabetes, and coronary artery disease. All 54 nonsurvivors 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. One-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 nonsurvivors and 118 survivors), a D-dimer level >1.0 $\mu\text{g/mL}$ at admission was associated with increased mortality with an odds ratio of 18.42 (2.64-128.55; $P = .003$).²⁰

Another early publication evaluated 1099 COVID-19 patients, and excluded individuals who did not require hospitalization.²¹ 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 of 173) experienced a primary outcome event compared with 3.6% in the nonsevere group.²² D-dimer was dichotomized as either <0.5 mg/L or >0.5 mg/L, with more patients with severe disease experiencing a primary outcome having D-dimer values >0.5 mg/L.²²

A more complete assessment of coagulation parameters, including D-dimer, PT, aPTT, fibrinogen, and antithrombin, in 183 COVID-19+ patients was analyzed by survivor status from admission through 14 days.¹⁵ At the time of publication, 78 patients (42.6%) had been discharged and 21 patients (11.5%) had died; the rest 84 (45.9%) were still hospitalized. A total of 15 of 21 nonsurvivors were diagnosed with overt DIC according to ISTH criteria, with median onset at 4 days (1-12 days) after admission; only 1 of the 78 discharged patients had evidence of DIC. Over their hospitalization, nonsurvivors 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 nonsurvivors, 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%, PaO₂/FiO₂ <300 mm Hg), 99 patients (22%) received prophylactic venous thromboembolism (VTE) anticoagulation for at least 7 days, with 94 patients treated with enoxaparin 40 to 60 mg per day, and 5 treated with unfractionated heparin (UFH) 10 000 to 15 000 U per day.¹⁶ Of the 449 patients, 22% (n = 97) had an ISTH SIC score of ≥4, and 29.8% of patients (134) had died at the time of reporting. Although no difference in 28-day mortality was seen between heparin- and nonheparin-treated patients overall, stratification by SIC score identified lower mortality in patients treated with heparin when the SIC score was ≥4 (40.0% vs 64.2%; P = .029) compared with a SIC score <4 (29.0% vs 22.6%; P = .419). A 20% reduction in mortality was observed when patients with D-dimer exceeding 3.0 μg/mL were treated with prophylactic doses of heparin (32.8% vs 52.4%; P = .017). Even using the SIC score, only 21.6% of severe cases met SIC criteria. However, patients with D-dimer >6 times the upper limit of normal did comprise a higher proportion of severe cases (161 of 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.²³⁻²⁵ In patients with SIC, 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, activate platelets, mast cells, and factor XII (FXII) in the contact pathway of coagulation, and exhibit other downstream roles in amplifying the procoagulant response of the intrinsic coagulation pathway.²⁶ Complement pathways also contribute to activation of coagulation factors.²⁷ Although neutrophil extracellular traps are present in thrombi, the individual neutrophil extracellular trap components of cell-free DNA and histones activate the contact pathway and enhance other prothrombotic pathways resulting in thrombin generation.^{10,28} Pathogen-associated molecular mechanisms are important aspects of the complex interactions between the immune response and coagulation and in sepsis.^{10,29} The inflammatory effects of cytokines also result in activated vascular endothelial cells and endothelial injury with resultant prothrombotic properties.^{10,30}

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.^{31,32} Vascular endothelial injury not only causes further thrombocytopenia and 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 that there may be a survival benefit in post hoc analyses.³³⁻³⁵ Subsequent reductions in coagulation factors associated with increased fibrinolysis that can occur during infections and sepsis are considered the fibrinolytic phase of DIC, but may be 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.^{6,24} As evidenced by the data from Tang et al, 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 C-reactive protein and erythrocyte sedimentation rate, and elevated fibrinogen at presentation.³⁶ 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 in non-ICU patients.³⁷ 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.^{7,38,39} 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 or cytokine storm, which may explain more dramatic changes in coagulation tests, including significantly elevated D-dimer, especially as the disease progresses.⁴⁰ As Tang et al demonstrated, fibrinogen levels in all patients were elevated on admission.¹⁵ Ranucci et al 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.⁴¹

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

Endotheliopathy and COVID-19

Consistent with vascular endothelial dysfunction with SIC, an endotheliopathy appears to contribute to the pathophysiology of microcirculatory changes in SARS-CoV-2 infections.^{30,42} The receptor for viral adhesion is an ACE2 receptor on endothelial cells,⁴³ with viral replication causing inflammatory cell infiltration, endothelial cell apoptosis, and microvascular prothrombotic effects.⁴⁴ Recent reports demonstrate viral inclusions within endothelial cells and sequestered mononuclear and polymorphonuclear cellular infiltration, with evidence of endothelial apoptosis in the postmortem of SARS-CoV-2 infection.⁴⁴ As a result, microcirculatory dysfunction contributes to the clinical sequelae in patients with COVID-19. From a clinical perspective, in addition to the systemic hypercoagulability and potential for thromboembolic complications, the described microvascular endothelial injury with microcirculatory clot formation noted in postmortem evaluation is consistent with a thrombotic microangiopathy that may occur in patients.⁴⁴ The endotheliopathy may also explain reports of cerebrovascular complications in younger patients, myocardial ischemia, and increasing reports of both micro- and macrocirculatory thromboembolic complications.^{6,7,44}

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 nonsurvivors, and the rapid drop in fibrinogen associated with DIC, can be seen within 7 to 11 days after onset of symptoms or 4 to 10 days after hospitalization.^{15,19,20} 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 and 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 is not frequently used,^{45,46} 22% of the cohort evaluated by Tang et al received prophylactic-dose low-molecular-weight heparin (LMWH) or 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 (PE).^{45,47,48} Early autopsy reports demonstrated microvascular thrombosis as well as marked inflammatory changes.⁴⁹ Those patients with severe COVID-19 at presentation and either SIC with a score of ≥ 4 or D-dimer elevated >6 times the 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 that 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 7 days of 11% (95% confidence interval [CI], 5.8-17) and 23% (95% CI, 14-33) at 14 days with a subdistribution hazard ratio (SHR) of 3.8 (95% CI, 1.3-12) for ICU patients compared with the wards (Saskia Middeldorp, Michiel Coppens, Thijs F. van Haaps, Merijn Foppen, Alexander P. Vlaar, Marcella C. A. Muller, Catherine C. S. Bouman, Ludo F. M. Beenen, Ruud S. Kootte, Jarom Heijmans, Loek P. Smits, Peter I. Bonta, Nick van Es, manuscript submitted April 2020; <https://www.preprints.org/manuscript/202004.0345/v1>).

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⁺ patients with ARDS compared with a matched historic cohort without COVID-19 (11.7% vs 2.1%; $P < .008$).^{50,51} 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.⁵²

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. Although 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 an intermediate-intensity dose and 5.2% supported a therapeutic dose; the rest supported using the standard VTE prophylaxis dose for hospitalized patients with moderate to severe COVID-19 and lack of DIC.⁵³

Certainly, for obese patients, data suggest that 40 mg of daily enoxaparin dosing is insufficient in postoperative settings, based on the lack of achieving adequate plasma concentrations. Higher-weight-based dosing was well tolerated, with doses of 7500 U of UFH 3 times daily or 40 mg of enoxaparin twice daily.^{54,55} Increased heparin doses may also be necessary for prophylaxis to overcome the increases in procoagulant proteins that have been observed, including high levels of fibrinogen, FVIII, and von Willebrand factor, levels that are not encountered in postorthopedic joint replacement surgery or typical medically

Table 1. COVID-19–associated coagulopathy

Summary of findings
1. Coagulopathy is manifest as elevated fibrinogen, elevated D-dimers, and minimal change in PT, aPTT, 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 <ol style="list-style-type: none"> Noted to start at 4 d after admission in nonsurvivors Longer duration of hospital stay associated with increasing D-dimer and development of sepsis physiology
6. Bleeding manifestations are not common despite coagulopathy

ill patients.⁴¹ At this time, individual patient assessment incorporating baseline VTE risk factors and bleeding risk factors with clinical judgment is required. J.M.C. has supported increased prophylactic-dose anticoagulation for ICU patients at her institution based on internal audits finding increased VTE events with 40 mg of enoxaparin daily in ICU compared with ward patients.

Microvascular thrombosis: treatment

The basis of SIC 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 SIC. The physiologic anticoagulants including activated protein C, thrombomodulin, and antithrombin, 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 toward improved survival in septic patients.³³⁻³⁵ However, antithrombin levels have not been found to decrease significantly in COVID-19–infected patients.¹⁵

CAC 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 who develop overt DIC, standard guidance for blood component support is available.⁵⁶

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 toward 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, in which fibrin-platelet microthrombi form in the pulmonary microcirculation and parenchyma, observed in 1 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 (Weiren Luo, Hong Yu, Jizhou Gou, Xiaoxing Li, Yan Sun, Jinxiu Li, Lei Liu, manuscript submitted February 2020; <https://www.preprints.org/manuscript/202002.0407/v2>). 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 whether patients were given VTE prophylaxis on hospital admission, and no treatment data are provided to support this.⁵⁷ In prior trials of anticoagulation with sepsis, low-dose heparin has been used.⁵⁸ Past investigations of the biology of SARS viruses found that *in vitro* heparin reduced the coronavirus SARS-CoV infectivity by 50%.⁵⁹ Whether this is due to heparin acting as a nonspecific 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 FXa, which facilitates cell entry, is unclear.^{60,61} Although 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 who 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, 1 of the different causes of both hypercoagulability and heparin resistance. As a result, if there are concerns regarding aPTT measurements, following anti-FXa heparin levels for monitoring should be considered.⁶²

The question of using therapeutic-dose anticoagulation for presumed PE has been encountered in many ICUs around the world due to difficulty moving mechanically ventilated patients to computed tomography scanners and the desire to limit staff exposure to COVID-19+ patients. D-dimer is usually not helpful, given the significant baseline elevations in these patients. Clinical findings of sudden respiratory decompensation, evidence of

Table 2. Management strategy

COVID-19 ⁺	Coagulation tests	Standard-dose VTE PPX	Escalated-dose* VTE PPX	Therap. dose anti-coagulation
Outpatient		Consider†		
Inpatient	X			
Ward	X	X		
ICU	X		X	
Confirmed VTE	X			X
Presumed PE‡	X			X
ARDS	X		X	

Suggested approach to COVID-19 patients and coagulopathy. All admitted patients should have baseline PT, aPTT, fibrinogen, D-dimer, and platelet count. Following these values can give important information regarding status of the coagulation system and safety of using anticoagulation.

PPX, prophylaxis; Therap., therapeutic.

*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 one-half the therapeutic dose for these patients. Anticoagulant options include LMWH, UFH, and fondaparinux. Direct oral anticoagulants (DOACs) can also be considered, but intermediate-intensity doses are not clear. Both fondaparinux and DOACs should be used with caution in patients with renal insufficiency due to their longer half-lives.

†Consideration for use of standard-dose VTE prophylaxis in infected patients with morbid obesity or past history of VTE. Although 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.

‡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.

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 cannot 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 of which 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 suggests that 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 in those 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 CAC in some might be driven by an unchecked inflammatory response to a pathogen for which there is no prior acquired immunity.

CAC 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.^{12,38,63,64} 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.

Authorship

Contribution: J.M.C. and J.H.L. equally contributed to the writing of this manuscript.

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Footnote

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REFERENCES

- Layton DS, Choudhary A, Bean AGD. Breaking the chain of zoonoses through biosecurity in livestock. *Vaccine*. 2017;35(44):5967-5973.
- Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China [published correction appears in *Nature*. 2020;580(7803):E7]. *Nature*. 2020;579(7798):265-269.
- Hulswit RJ, de Haan CA, Bosch BJ. Coronavirus spike protein and tropism changes. *Adv Virus Res*. 2016;96:29-57.
- Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. 2020;395(10224):565-574.
- Schnittler HJ, Feldmann H. Viral hemorrhagic fever--a vascular disease? *Thromb Haemost*. 2003;89(6):967-972.
- Iba T, Levy JH, Thachil J, Wada H, Levi M; Scientific and Standardization Committee on DIC of the International Society on

- Thrombosis and Haemostasis. The progression from coagulopathy to disseminated intravascular coagulation in representative underlying diseases. *Thromb Res.* 2019;179:11-14.
7. Iba T, Levy JH, Wada H, Thachil J, Warkentin TE, Levi M; Subcommittee on Disseminated Intravascular Coagulation. Differential diagnoses for sepsis-induced disseminated intravascular coagulation: communication from the SSC of the ISTH. *J Thromb Haemost.* 2019;17(2):415-419.
 8. Woei-A-Jin FJ, van der Starre WE, Tesselaar ME, et al. Procoagulant tissue factor activity on microparticles is associated with disease severity and bacteremia in febrile urinary tract infections. *Thromb Res.* 2014;133(5):799-803.
 9. Gould TJ, Lysov Z, Swystun LL, et al; Canadian Critical Care Translational Biology Group. Extracellular histones increase tissue factor activity and enhance thrombin generation by human blood monocytes. *Shock.* 2016;46(6):655-662.
 10. Iba T, Levy JH. Inflammation and thrombosis: roles of neutrophils, platelets and endothelial cells and their interactions in thrombus formation during sepsis. *J Thromb Haemost.* 2018;16(2):231-241.
 11. Suzuki K, Wada H, Imai H, Iba T, Thachil J, Toh CH; Subcommittee on Disseminated Intravascular Coagulation. A re-evaluation of the D-dimer cut-off value for making a diagnosis according to the ISTH overt-DIC diagnostic criteria: communication from the SSC of the ISTH. *J Thromb Haemost.* 2018;16(7):1442-1444.
 12. Iba T, Levy JH, Warkentin TE, Thachil J, van der Poll T, Levi M; Scientific and Standardization Committee on DIC, and the Scientific and Standardization Committee on Perioperative and Critical Care of the International Society on Thrombosis and Haemostasis. Diagnosis and management of sepsis-induced coagulopathy and disseminated intravascular coagulation. *J Thromb Haemost.* 2019;17(11):1989-1994.
 13. Taylor FB Jr, Toh CH, Hoots WK, Wada H, Levi M; Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH). Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost.* 2001;86(5):1327-1330.
 14. Iba T, Levy JH, Yamakawa K, Thachil J, Warkentin TE, Levi M; Scientific and Standardization Committee on DIC of the International Society on Thrombosis and Haemostasis. Proposal of a two-step process for the diagnosis of sepsis-induced disseminated intravascular coagulation. *J Thromb Haemost.* 2019;17(8):1265-1268.
 15. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost.* 2020;18(4):844-847.
 16. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost.* 2020;18(5):1094-1099.
 17. Johns Hopkins University. Coronavirus Resource Center. <https://coronavirus.jhu.edu/map.html>. Accessed 25 April 2020.
 18. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet.* 2020;395(10223):507-513.
 19. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA.* 2020;323(11):1061-1069.
 20. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020;395(10229):1054-1062.
 21. Guan WJ, Ni ZY, Hu Y, et al; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* 2020;382(18):1708-1720.
 22. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med.* 2019;200(7):e45-e67.
 23. Engelmann B, Massberg S. Thrombosis as an intravascular effector of innate immunity. *Nat Rev Immunol.* 2013;13(1):34-45.
 24. Delabranche X, Helms J, Meziani F. Immuno-haemostasis: a new view on haemostasis during sepsis. *Ann Intensive Care.* 2017;7(1):117.
 25. Jackson SP, Darbousset R, Schoenwaelder SM. Thromboinflammation: challenges of therapeutically targeting coagulation and other host defense mechanisms. *Blood.* 2019;133(9):906-918.
 26. Smith SA, Mutch NJ, Baskar D, Rohloff P, Docampo R, Morrissey JH. Polyphosphate modulates blood coagulation and fibrinolysis. *Proc Natl Acad Sci USA.* 2006;103(4):903-908.
 27. Subramaniam S, Jurk K, Hobohm L, et al. Distinct contributions of complement factors to platelet activation and fibrin formation in venous thrombus development. *Blood.* 2017;129(16):2291-2302.
 28. Noubouossie DF, Reeves BN, Strahl BD, Key NS. Neutrophils: back in the thrombosis spotlight. *Blood.* 2019;133(20):2186-2197.
 29. Rittirsch D, Flierl MA, Ward PA. Harmful molecular mechanisms in sepsis. *Nat Rev Immunol.* 2008;8(10):776-787.
 30. Iba T, Levy JH. Derangement of the endothelial glycocalyx in sepsis. *J Thromb Haemost.* 2019;17(2):283-294.
 31. Semeraro F, Colucci M, Caironi P, et al. Platelet drop and fibrinolytic shutdown in patients with sepsis. *Crit Care Med.* 2018;46(3):e221-e228.
 32. Levy JH, Koster A, Quinones QJ, Milling TJ, Key NS. Antifibrinolytic therapy and perioperative considerations. *Anesthesiology.* 2018;128(3):657-670.
 33. Iba T, Arakawa M, Ohchi Y, et al. Prediction of early death in patients with sepsis-associated coagulation disorder treated with antithrombin supplementation. *Clin Appl Thromb Hemost.* 2018;24(suppl 9):1455-1495.
 34. Kienast J, Juers M, Wiedermann CJ, et al; KyberSept Investigators. Treatment effects of high-dose antithrombin without concomitant heparin in patients with severe sepsis with or without disseminated intravascular coagulation. *J Thromb Haemost.* 2006;4(1):90-97.
 35. Yamakawa K, Levy JH, Iba T. Recombinant human soluble thrombomodulin in patients with sepsis-associated coagulopathy (SCAR-LET): an updated meta-analysis. *Crit Care.* 2019;23(1):302.
 36. Chen G, Wu D, Guo W, et al. Clinical and immunologic features in severe and moderate coronavirus disease 2019 [published online ahead of print 27 March 2020]. *J Clin Invest.* doi:10.1172/JCI137244.
 37. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395(10223):497-506.
 38. Levi M, Scully M. How I treat disseminated intravascular coagulation. *Blood.* 2018;131(8):845-854.
 39. Lippi G, Bonfanti L, Saccenti C, Cervellin G. Causes of elevated D-dimer in patients admitted to a large urban emergency department. *Eur J Intern Med.* 2014;25(1):45-48.
 40. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet.* 2020;395(10229):1033-1034.
 41. Ranucci M, Ballotta A, Di Dedda U, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome [published online ahead of print 17 April 2020]. *J Thromb Haemost.* doi:10.1111/jth.14854.
 42. Saffarzadeh M, Juenemann C, Queisser MA, et al. Neutrophil extracellular traps directly induce epithelial and endothelial cell death: a predominant role of histones. *PLoS One.* 2012;7(2):e32366.
 43. Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation.* 2005;111(20):2605-2610.
 44. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19 [published online ahead of print 20 April 2020]. *Lancet.* doi:10.1016/S0140-6736(20)30937-5.
 45. Stein PD, Kayali F, Olson RE, Milford CE. Pulmonary thromboembolism in Asians/Pacific Islanders in the United States: analysis of data from the National Hospital Discharge Survey and the United States Bureau of the Census. *Am J Med.* 2004;116(7):435-442.
 46. Zakai NA, McClure LA. Racial differences in venous thromboembolism. *J Thromb Haemost.* 2011;9(10):1877-1882.
 47. Danzi GB, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19

- pneumonia: a random association? [published online ahead of print 30 March 2020]. *Eur Heart J*. doi:10.1093/eurheartj/ehaa254.
48. Xie Y, Wang X, Yang P, Zhang S. COVID-19 complicated by acute pulmonary embolism. *Radiology. Cardiothoracic Imaging*. 2020;2(2): e200067.
 49. Tian S, Hu W, Niu L, Liu H, Xu H, Xiao S-Y. Pulmonary pathology of early-phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. *J Thorac Oncol*. 2020;15(5):700-704.
 50. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19 [published online ahead of print 10 April 2020]. *Thromb Res*. doi:10.1016/j.thromres.2020.04.013.
 51. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients in severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med*. In press;
 52. Poissy J, Goutay J, Caplan M, et al; Lille ICU Haemostasis COVID-19 Group. Pulmonary embolism in COVID-19 patients: awareness of an increased prevalence [published online ahead of print 24 April 2020]. *Circulation*. doi:10.1161/CIRCULATIONAHA.120.047430.
 53. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. *J Am Coll Cardiol*. In press.
 54. Pannucci CJ, Fleming KI, Holyday K, Moulton L, Prazak AM, Varghese TK Jr. Enoxaparin 40 mg per day is inadequate for venous thromboembolism prophylaxis after thoracic surgical procedure. *Ann Thorac Surg*. 2018; 106(2):404-411.
 55. Wang TF, Milligan PE, Wong CA, Deal EN, Thoenke MS, Gage BF. Efficacy and safety of high-dose thromboprophylaxis in morbidly obese inpatients. *Thromb Haemost*. 2014; 111(1):88-93.
 56. Wada H, Thachil J, Di Nisio M, et al; The Scientific Standardization Committee on DIC of the International Society on Thrombosis Haemostasis. Guidance for diagnosis and treatment of disseminated intravascular coagulation from harmonization of the recommendations from three guidelines. *J Thromb Haemost*. 2013;11(4):761-767.
 57. Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection—a review of immune changes in patients with viral pneumonia. *Emerg Microbes Infect*. 2020;9(1):727-732.
 58. Iba T, Levy JH, Raj A, Warkentin TE. Advance in the management of sepsis-induced coagulopathy and disseminated intravascular coagulation. *J Clin Med*. 2019;8(5):
 59. Vicenzi E, Canducci F, Pinna D, et al. Coronaviridae and SARS-associated coronavirus strain HSR1. *Emerg Infect Dis*. 2004; 10(3):413-418.
 60. Du L, Kao RY, Zhou Y, et al. Cleavage of spike protein of SARS coronavirus by protease factor Xa is associated with viral infectivity. *Biochem Biophys Res Commun*. 2007;359(1): 174-179.
 61. Kam YW, Okumura Y, Kido H, Ng LF, Bruzzone R, Altmeyer R. Cleavage of the SARS coronavirus spike glycoprotein by airway proteases enhances virus entry into human bronchial epithelial cells in vitro. *PLoS One*. 2009;4(11): e7870.
 62. Smyth SS, McEver RP, Weyrich AS, et al; 2009 Platelet Colloquium Participants. Platelet functions beyond hemostasis. *J Thromb Haemost*. 2009;7(11):1759-1766.
 63. Levy JH, Goodnough LT. How I use fibrinogen replacement therapy in acquired bleeding. *Blood*. 2015;125(9):1387-1393.
 64. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haem*. 2020;18(5):1023-1026.