



How to recognize and manage COVID-19-associated coagulopathy

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COVID-19 is frequently associated with abnormalities on coagulation testing and a coagulopathy driven by inflammation, intravascular coagulation activation, and microvascular thrombosis. Elevated D-dimer is the most common finding and is a predictor of adverse outcomes including thrombosis, critical illness, and death. Although COVID-19-associated coagulopathy has some similarities to disseminated intravascular coagulation, the platelet count is usually preserved, coagulation times are usually normal or minimally prolonged, and thrombosis is more common than bleeding, at least in noncritically ill patients. Bleeding is uncommon but may be a significant problem in critically ill patients, including those who may develop a consumptive coagulopathy with frank disseminated intravascular coagulation and those on extracorporeal membrane oxygenation. Blood product support to correct coagulopathy is reserved for bleeding patients or those requiring invasive procedures. Current recommendations suggest that all hospitalized patients should receive at least a prophylactic dose of anticoagulation. Results from a multiplatform randomized clinical trial suggest that therapeutically dosed anticoagulation may improve outcomes, including the need for organ support and mortality in moderately ill patients but not in those requiring critical care. The results of ongoing trials evaluating the impact of different antithrombotic strategies (therapeutic agents and intensity) on COVID-19 outcomes are eagerly awaited and are expected to have important implications for patient management. We also discuss COVID-19 vaccine-associated cytopenias and bleeding as well as vaccine-induced thrombotic thrombocytopenia, in which thrombosis is associated with thrombocytopenia, elevated D-dimer, and, frequently, hypofibrinogenemia.

LEARNING OBJECTIVES

- Recognize the coagulation derangements commonly encountered in COVID-19 associated with outcomes including thrombosis, need for critical care support, and mortality
- Appropriately monitor and manage coagulation abnormalities in hospitalized patients with COVID-19
- Recognize and manage the rare complications of COVID-19 vaccination-associated thrombocytopenia with bleeding and vaccine-induced thrombotic thrombocytopenia (VITT)

Introduction

The COVID-19 pandemic has contributed to significant mortality and morbidity across the world. Despite unprecedented public health efforts including the development of multiple effective vaccines, the pandemic continues to rage in many parts of the world, with novel viral variants leading to recurrent outbreaks. While COVID-19 is a predominantly respiratory illness, hemostatic and thrombotic complications are common.^{1,2} Early in the pandemic, a high prevalence of thromboembolic complications was observed in patients with COVID-19.^{3,4} Many patients exhibit laboratory evidence of a coagulopathy reminiscent of, but not identical to, disseminated intravascular coagulation (DIC), which is associated with thrombosis risk, critical illness, and all-

cause mortality.^{5,6} In critically ill patients, this coagulopathy may evolve into frank DIC. While less common than laboratory coagulopathy or thrombosis, bleeding occurs in up to 5% of hospitalized patients and has important implications for management.³ In this review we discuss our approach to COVID-19-associated coagulopathy (CAC) and bleeding.

CLINICAL CASE

A 51-year-old woman with hypertension and asthma presented with fever, cough, and dyspnea; polymerase chain reaction for SARS-CoV-2 was positive, and she was hospitalized due to the need for supplemental oxygen. Laboratory

Table 1. Similarities and differences between CAC and DIC/SIC

	CAC	DIC	SIC
Platelet count	↕	↓↓	↓
D-dimer	↑	↑↑	↑
PT/aPTT	↔↑	↑↑	↑
Fibrinogen	↑	↓↓	↓
Antithrombin	↔	↓	↓
VWF	↑	↑	↑
FVIII	↑	↑↓	↑
LA/aPL	+	-	-
Thrombosis	↑↑	↑	↑
Bleeding	↔↑	↑↑	↑

testing on admission revealed elevated dimerized plasmin fragment D (D-dimer; 1.4mg/L [0.00–0.49]) and fibrinogen (345mg/dL). Platelet count ($238 \times 10^9/L$) and prothrombin time (PT; 10.8 seconds) were normal. Activated partial thromboplastin time (aPTT) was prolonged (43 seconds [23.1–30.9]).

CAC

Laboratory findings in CAC

Coagulation derangements suggesting hypercoagulability are common in COVID-19. Markedly elevated D-dimer is the most common finding and is associated with adverse outcomes, including thrombosis, the need for critical care support, and overall mortality.^{3,5,7} Elevated D-dimer levels correlate with levels of inflammatory markers, including C-reactive protein, sedimentation rate, procalcitonin, and ferritin, supporting an association with the inflammatory state of COVID-19.³ However, fibrinogen levels are usually elevated/normal, a platelet count $<100 \times 10^9/L$ is uncommon,^{3,8} and the PT is normal at presentation in the majority of patients. Thus, in most cases CAC is distinct from the prototypical consumptive coagulopathies, such as sepsis-induced coagulopathy (SIC) and DIC (Table 1).^{9,10} Moreover, CAC is less likely to be associated with bleeding than thrombosis. These differences are probably due to

the fact that intravascular coagulation activation and microvascular thrombosis are relatively localized to the pulmonary circulation in CAC versus the more systemic activation of coagulation in DIC. Additionally, fibrinolysis is suppressed in CAC, which may contribute to the prothrombotic phenotype.^{11,12} Iba et al have proposed diagnostic criteria for CAC (Table 2).¹³

Thrombocytopenia and PT prolongation are less common in COVID-19 but predict poor clinical outcomes. In an analysis of 201 hospitalized patients from China, prolonged PT on admission was associated with the development of acute respiratory distress syndrome (ARDS; hazard ratio, 1.56 [1.32–1.83]; $P < .001$).¹⁴ Interestingly, thrombocytopenia was present in only 18.8% of these patients compared to $>50\%$ in patients with ARDS from other infectious causes. Compared to non-COVID ARDS, COVID-19 is associated with higher PT, antithrombin, fibrinogen, and platelet count and lower aPTT and D-dimer levels.¹⁵ In a meta-analysis of 9 studies including 1779 COVID-19 patients, the platelet count was significantly lower in patients with severe disease and patients who died.¹⁶ Similarly, a marked decrease in plasma fibrinogen has been reported shortly before death in a number of patients.⁵ An early study by Tang et al noted a higher prevalence of DIC by International Society on Thrombosis and Haemostasis (ISTH) criteria on admission in nonsurvivors vs survivors (71.4% vs 0.6%). However, subsequent studies report a much lower incidence of DIC at initial presentation. For example, none of the 150 consecutive patients with COVID-19 and ARDS and only 2.2% of 388 consecutive patients hospitalized with COVID-19 in Milan met the criteria for DIC at presentation.^{15,17} Thus, overt DIC is uncommon in COVID-19 but may develop in critically ill patients.³

Based on the spectrum of coagulation abnormalities in COVID-19 that parallels disease severity, three stages of COVID-19 coagulopathy have been proposed (Figure 1).¹⁸ In stage 1, patients exhibit mild symptoms and mild localized inflammation and elevated D-dimer. Stage 2 is characterized by more severe symptoms requiring supplemental oxygen, with pulmonary inflammation and intravascular coagulation activation (elevated D-dimer, fibrinogen). Patients who progress to stage 3 require critical care support and demonstrate severe systemic inflammation and coagulopathy with markedly elevated D-dimer and fibrinogen, prolonged PT, and thrombocytopenia. A subset of these patients develops overt DIC that may be due to COVID-19 or bacterial superinfection and is associated with a high risk of bleeding and death.

Table 2. Proposed criteria for CAC compared with ISTH criteria for SIC and DIC

Proposed CAC criteria ¹³	ISTH SIC criteria ¹⁰	ISTH DIC criteria ⁹
≥2 of the following:	≥4 points:	≥5 points:
1) Platelet count $<150 \times 10^9/L$	1) Platelet count, $\times 10^9/L$	1) Platelet count, $\times 10^9/L$
2) D-dimer elevation $>2 \times ULN$	<150 but $\geq 100 = 1$	$<100 = 1$
3) PT prolonged $>1s$ or INR >1.2	$<100 = 2$	$<50 = 2$
4) Presence of micro and/or macrovascular thrombosis	2) INR	2) D-dimer
**Risk factors for the development of CAC include elevated fibrinogen and VWF and presence of lupus anticoagulant or antiphospholipid antibodies	>1.2 but $\leq 1.4 = 1$	increased $<5 \times ULN = 2$
	$>1.4 = 2$	$\geq 5 \times ULN = 3$
	3) SOFA score	3) PT
	1 = 1	prolonged $\geq 3s$ but
	$\geq 2 = 2$	$<6s = 1$
		prolonged $\geq 6s = 2$
		4) Fibrinogen
		$\leq 1.0g/L = 1$

INR, international normalized ratio; SOFA, Sequential Organ Failure Assessment; ULN, upper limit of normal.

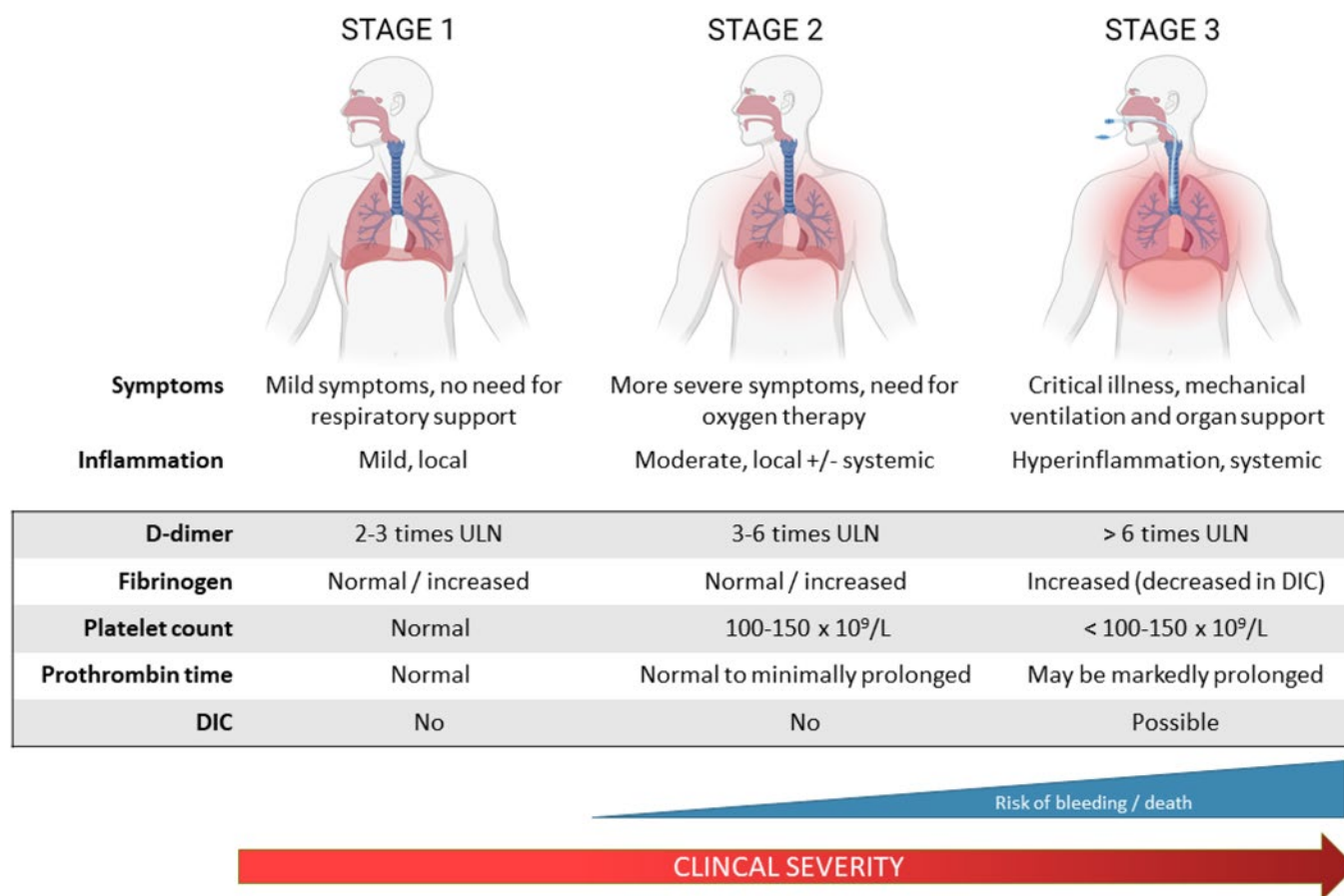


Figure 1. Stages of CAC. The spectrum of coagulation abnormalities in COVID-19 parallels disease severity. In stage 1, patients exhibit mild symptoms and evidence of mild localized inflammation and coagulopathy with elevations in D-dimer approximately 2 to 3 times the upper limit of normal. Stage 2 is characterized by more severe symptoms requiring supplemental oxygen with pulmonary inflammation and intravascular coagulation activation in the lungs as well as some systemic involvement. This is reflected in further D-dimer elevation to 3 to 6 times the upper limit of normal. Patients progressing to stage 3 require critical care with respiratory and other organ support and demonstrate severe systemic inflammation and coagulopathy with markedly elevated D-dimer and fibrinogen, prolonged PT, thrombocytopenia, and high incidence of thromboembolism. A proportion of these patients will develop overt DIC as a result of their COVID-19 illness or other superimposed infections.¹⁸

Antiphospholipid antibodies in COVID-19

The aPTT is prolonged in some patients with COVID-19. A likely explanation is the presence of a lupus anticoagulant (LA) or antiphospholipid antibodies (aPL). In a series of 56 hospitalized patients with COVID-19, LA was detected in 44.6%; 8.9% also had either anticardiolipin (aCL) or anti-beta-2-glycoprotein antibodies.¹⁹ Both traditional aPL (such as immunoglobulin [Ig] G and IgM aCL) and various "noncriteria" aPL (including anti-PS/PT as well as IgA isotypes of aCL and anti-beta-2-glycoprotein) have been detected in COVID-19. Whether these are transient aPL, as reported in other viral infections,²⁰ or persistent aPL, more likely to be associated with long-term thrombotic risk, is unknown. Moreover, LA assays must be interpreted with caution in critically ill patients due to potential confounding by anticoagulant therapy. High levels of acute phase reactants such as C-reactive protein can also cause false positives by prolonging in vitro clotting times. Prolonged aPTT due to LA may necessitate the use of the anti-factor Xa assay for monitoring heparin therapy.

Other coagulation parameters

In addition to the commonly evaluated laboratory parameters discussed above, elevated coagulation factor VIII (FVIII) and von Willebrand factor (VWF) are frequent findings in hospitalized COVID-19 patients and correlate with elevations in inflammatory markers.^{15,21-23} Nonsurvivors have lower antithrombin levels than survivors (84% vs 91%), but levels generally do not drop below 80%.^{5,15,22} In a study comparing 48 intensive care unit (ICU) to 30 general ward patients, fibrinolytic pathway parameters, including plasminogen activator inhibitor, tissue plasminogen activator, and thrombin activatable fibrinolysis inhibitor, were significantly higher in the ICU patients.²² Viscoelastic testing (thromboelastography, rotational thromboelastometry) reveals increased clot strength with contributions of both elevated fibrinogen and platelets.^{21,24} Fibrinolysis is also suppressed.^{11,12} Thrombin generation is normal to increased even in patients receiving prophylactic anticoagulation.²⁵ However, the clinical utility of these assays is uncertain, and they are not recommended outside of a research setting.

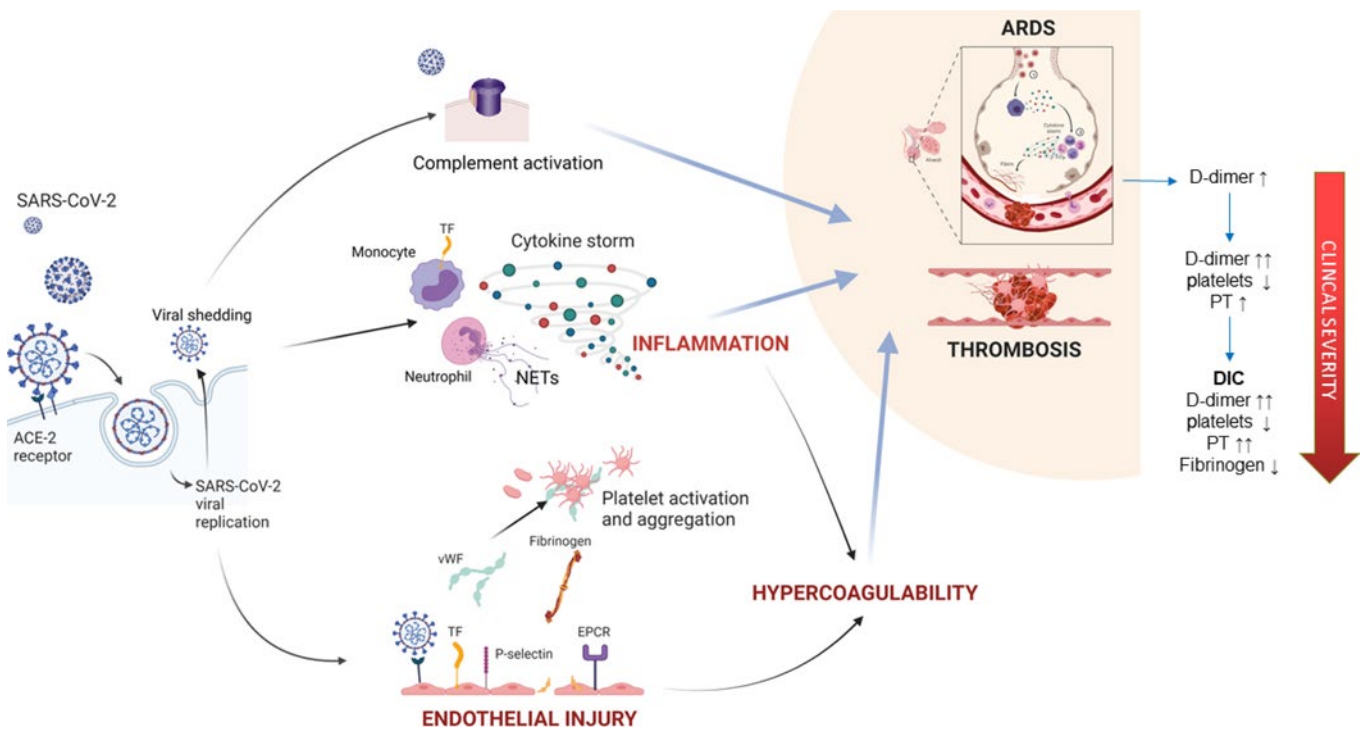


Figure 2. Pathogenesis of CAC. SARS-CoV-2 binds the angiotensin-converting enzyme 2 receptor on respiratory epithelium and endothelial cells. Viral replication and shedding lead to pneumocyte and endothelial cell apoptosis, triggering an inflammatory response, which in a portion of patients leads to pathogenic cytokine storm. These cytokines and endothelial injury result in procoagulant changes, including the release of VWF and FVIII and the upregulation of TF, P-selectin, and fibrinogen. Anticoagulant proteins such as endothelial protein C receptor, antithrombin, and thrombomodulin are downregulated. Fibrinolytic impairment also contributes to hypercoagulability. Neutrophil activation and the release of neutrophil extracellular traps further stimulate thrombosis, and platelets in COVID-19 may exhibit marked hyperreactivity. SARS-CoV-2 spike proteins may directly amplify complement, and contribute to vascular injury and microthrombosis. The coagulation derangements observed in COVID-19 are a direct result of microthrombosis, which is initially localized to the lungs, causing elevations in D-dimer and fibrinogen. As the disease progresses, more systemic inflammation and the activation of coagulation lead to thrombocytopenia and prolongation of clotting times. In some patients this may progress to a frank consumptive coagulopathy.

Pathogenesis of CAC

Thromboinflammation is central to the pathophysiology of CAC, which is driven by a combination of direct effects of viral infection on pulmonary vascular endothelium, a local and systemic inflammatory response, and cross talk between the inflammatory and coagulation pathways (Figure 2). Pathogenic mechanisms contributing to CAC have been reviewed in detail by Iba et al¹³: (1) direct viral effects and inflammation: SARS-CoV-2 enters respiratory epithelium and endothelium via the angiotensin-converting enzyme 2 receptor. Direct endothelial effects include procoagulant changes such as surface adhesion molecule expression and the release of VWF and FVIII. Viral replication and shedding trigger an inflammatory response, or "cytokine storm." Proinflammatory cytokines IL-1 β , IL-6, and tumor necrosis factor upregulate procoagulant molecules, including tissue factor (TF), P-selectin, fibrinogen, FVIII, and VWF; (2) neutrophil extracellular traps: neutrophil activation and release of neutrophil extracellular traps promote platelet activation, phosphatidylserine exposure, activation of factor V and factor XI, and thrombin generation²⁶; (3) complement activation: SARS-CoV-2 spike proteins directly activate complement,²⁷ and complement deposition and microthrombosis are observed in the lungs, skin, kidneys, and hearts of patients with severe disease²⁸;

(4) effects on coagulation and fibrinolytic systems: hypoxia and vasoconstriction induce the expression of TF and plasminogen activator inhibitor disrupting the balance between coagulation and fibrinolysis.²⁹ Patients with COVID-19 have increased thrombin and plasmin generation potential and an increase in fibrin formation,²⁵ consistent with other reports of decreased fibrinolysis.^{11,12} Perturbation of the balance between thrombin generation (fibrin clot formation) and plasmin generation (fibrinolytic pathways) is critical to the pathophysiology of COVID-19.^{11,21} In severe COVID-19, the lag time to thrombin, plasmin, and fibrin formation is increased, suggesting a loss in coagulation-activating mechanisms in severe disease.²⁵ While coagulation activation is initially restricted to the lungs and manifests as an increase in D-dimer, severe disease is characterized by systemic inflammation and disseminated microthrombosis causing a consumptive coagulopathy.

Bleeding in COVID-19

Bleeding is infrequent in the setting of CAC, which has a predominantly prothrombotic phenotype. Helms et al reported bleeding complications in 2.7% of 150 patients with COVID-related ARDS.¹⁵ Among 2773 hospitalized COVID-19 patients from New York, major bleeding was reported in 1.9% not on therapeutic

anticoagulation and in 3% of those on therapeutic anticoagulation.³⁰ However, in an analysis of 400 patients hospitalized with COVID-19 in Boston, Al-Samkari et al found a higher overall bleeding rate of 4.8%; major bleeding occurred in 2.3%, including 5.6% of critically ill patients, and was associated with a platelet count $<150 \times 10^9/L$ at admission (Odds Ratio 2.90 [1.05–7.99]).³ Preliminary data from a multiplatform, randomized controlled trial found a 0.9% and 1.9% rate of major bleeding in noncritically ill participants on prophylactic or therapeutic anticoagulation, respectively.³¹ Among critically ill patients, however, major bleeding occurred in 3.1% on therapeutic anticoagulation and 2.4% on thromboprophylaxis.³²

Among patients with COVID-19 ARDS treated with extracorporeal membrane oxygenation (ECMO), major bleeding occurs in $>40\%$, including intracranial bleeding in up to 12%, which is significantly higher than the 2% to 6% bleeding rate reported in non-COVID-19 ECMO cohorts.^{33,34} DIC, shear stress-induced acquired von Willebrand syndrome, COVID-19-associated endothelitis, and intensive anticoagulation are implicated in severe bleeding on ECMO.³⁴ The anticoagulation required for ECMO and the activation of coagulation from artificial surfaces may confound interpretation of coagulation studies. Careful interpretation is required to balance anticoagulation, bleeding, and thrombosis in patients receiving ECMO.

Management of CAC

Which laboratory parameters should be evaluated in CAC?

In outpatients with COVID-19, there is currently insufficient evidence to recommend monitoring of coagulation markers, including D-dimer, platelet count, PT, and fibrinogen, since these are unlikely to have an impact on management. For hospitalized patients, we agree with the interim recommendations from the ISTH and the American Society of Hematology to serially monitor D-dimer levels, platelet count, PT, and fibrinogen since these help with risk stratification.³⁵ Worsening of these parameters may warrant more aggressive critical care support and consideration of investigational therapies. D-dimer elevation is nonspecific and need not prompt imaging for venous thromboembolism (VTE) in the absence of clinical symptoms or signs of VTE.³⁶ However, increasing D-dimer in the setting of decreasing C-reactive protein may warrant screening for VTE.

Role of blood product transfusion

There is no evidence that blood component therapy to correct abnormal laboratory parameters improves outcomes in the absence of bleeding. In patients with bleeding or those needing invasive procedures, we suggest transfusion of platelets to maintain a platelet count $\geq 50 \times 10^9/L$, cryoprecipitate if fibrinogen is $<150\text{mg/dL}$, and plasma for an international normalized ratio ≥ 1.8 after correcting fibrinogen. Four factor prothrombin complex concentrate (25 units/kg) may be used instead of plasma in patients with severe coagulopathy and bleeding to avoid volume overload that can worsen respiratory status.

Anticoagulation

As with other coagulopathies, treatment of the underlying condition is the only definitive solution. Based on the association of D-dimer and other coagulation markers with severe disease, mortality, and thrombosis, at least prophylactic-dose anticoagulation is recommended in hospitalized patients with COVID-19.^{1,36,37} No-

tably, this recommendation is identical to that for other acutely ill inpatients. In the absence of significant renal impairment, we encourage the use of low-molecular-weight heparin (LMWH) over unfractionated heparin (UFH) to avoid possible heparin resistance with UFH. If UFH is used, we suggest monitoring anti-factor Xa levels due to potential confounding of the aPTT due to elevated FVIII and fibrinogen or LAs. Further, anticoagulation recommendations may need to be modified for patients with severe thrombocytopenia, bleeding risk, and extremes of body weight. Early in the pandemic, there were reports of thrombosis despite standard thromboprophylaxis. Based on these reports and extreme laboratory derangements, clinicians frequently escalated anticoagulation to intermediate or even therapeutic intensity. However, whether a higher intensity of anticoagulation reduces morbidity or mortality without an unacceptable increase in bleeding risk remains uncertain and is being evaluated in multiple trials.

Preliminary data from a multiplatform, randomized controlled trial comprising 3 global studies (REMAP-CAP, ATTACC, and ACTIV-4A) comparing the effects of standard-dose vs full-dose heparin on the primary outcome, a composite of 21-day “organ support-free” days and in-hospital mortality, were recently made available as preprints.^{31,32} The enrollment of moderately ill patients was stopped early for superiority; therapeutic anticoagulation reduced the requirement for organ support and mortality (OR 1.29 [1.04–1.61]) irrespective of baseline D-dimer.³¹ Meanwhile, the enrollment of critically ill patients was halted due to futility, with no decrease in mortality and a higher rate of major bleeding with therapeutic anticoagulation.³² These apparently discrepant results suggest that perhaps therapeutic heparin works best if started early. The INSPIRATION study reported that in critically ill patients with COVID-19, intermediate- vs prophylactic-dose LMWH did not result in a decrease in the composite end point of thrombosis, extracorporeal membrane oxygenation, or mortality within 30 days.³⁸ The multinational pragmatic RAPID COVID COAG trial (NCT04362085) is evaluating therapeutic vs prophylactic doses of LMWH or UFH in hospitalized, noncritically ill COVID-19 patients with elevated D-dimer on the composite outcome of ICU admission, noninvasive positive pressure ventilation, mechanical ventilation, and death at 28 days. The ACTION trial, a pragmatic trial at 31 sites in Brazil, compared in-hospital therapeutic anticoagulation with rivaroxaban (92%) or enoxaparin followed by rivaroxaban until day 30 vs prophylactic-dose enoxaparin or UFH in hospitalized patients with elevated D-dimer. There was no difference in the primary efficacy outcome of time to death and duration of hospitalization and supplemental oxygen use through 30 days but significantly more bleeding in the rivaroxaban group.³⁹ Pending the final results of these and other studies, the American Society of Hematology guideline panel suggests prophylactic over intermediate or therapeutic dosing in moderately and severely ill patients with COVID-19 without confirmed or suspected VTE. Higher-intensity anticoagulation may be preferred in moderately ill (non-ICU, stage 2) patients deemed at high thrombotic and low bleeding risk. Therapeutically dosed anticoagulation is appropriate for patients with preexisting indications such as atrial fibrillation and mechanical heart valves and, if needed, to maintain extracorporeal circuits and vascular access devices.

COVID-19 vaccines: cytopenias, bleeding, and thrombosis

The COVID-19 vaccines have proven to be highly safe and effective and remain the most promising tool in containing the COVID-19 pandemic. Cases of immune thrombocytopenia and bleeding, including life-threatening hemorrhage, have been diagnosed after exposure to the mRNA-based vaccines produced by Moderna (mRNA-1273) and Pfizer-BioNTech (BNT162b2).⁴⁰ Fortunately, the majority of these respond to immune thrombocytopenia-directed treatments such as intravenous Ig and corticosteroids.⁴⁰ It is unclear whether this represents a causal relationship or a coincidental association; however, a recent analysis from the Vaccine Adverse Event Reporting System reported that the incidence of thrombocytopenia after either mRNA vaccine was 0.8 per million doses, which is no higher than the background rate of immune thrombocytopenia (3.3 per 100 000 adults).⁴¹

More recently, rare cases of a vaccine-induced thrombotic thrombocytopenia (VITT) were reported after administration of the adenoviral vector vaccines (ChAdOx1 nCoV-19 and Ad26.COV2.S).⁴² The estimated incidence is 1 case per 100,000 exposures with a slight female preponderance, and it occurs more commonly in younger (<55–60 years) individuals, although this could reflect the demographics of individuals vaccinated early. Occurring 4 to 30 days post-vaccination, VITT is associated with thrombocytopenia and thrombosis, particularly at unusual sites such as the cerebral or splanchnic circulations, along with high levels of platelet-activating IgG antibodies that recognize platelet factor 4 (PF4) in the absence of heparin. Anti-PF4/heparin antibodies are detectable by enzyme-linked immunosorbent assays, but rapid immunoassay may yield false-negative results. Functional assays should be performed in the presence and absence of PF4. The standard serotonin release assay may yield false-negative results as VITT antibodies exhibit PF4-dependent activity and may demonstrate decreased reactivity in the presence of heparin. Patients with VITT frequently have a consumptive coagulopathy with elevated D-dimer and hypofibrinogenemia. VITT is associated with high mortality, with cerebral hemorrhage as the leading cause of death. Treatment with a nonheparin anticoagulant and intravenous Ig is recommended, with platelet transfusions reserved for bleeding. While much is still to be learned about the incidence, pathogenesis, and optimal management of VITT, given the millions of individuals vaccinated worldwide, these hematologic complications are vanishingly rare and should not hinder vaccination efforts.

CLINICAL CASE (Continued)

Our patient had findings typical of CAC with an elevated d-dimer and fibrinogen with normal platelets and PT. An LA was detected, accounting for her prolonged aPTT. She received a prophylactic dose of LMWH in addition to dexamethasone. D-dimer trended up to a peak of 4.1mg/dL, and platelet count dropped to $118 \times 10^9/L$ on day 5 of hospitalization. PT remained normal. Oxygen requirements peaked at 4L by nasal cannula on day 9 and gradually improved over the following week. No thrombotic events occurred. She was discharged home without outpatient thromboprophylaxis on day 15. Repeat testing to determine whether her LA is persistent was pending at discharge.

Summary

Inflammation, intravascular coagulation activation, and microvascular thrombosis cause coagulation derangements in COVID-19. Elevated D-dimer and fibrinogen levels are the most common finding and are predictive of adverse outcomes, including the need for critical care and mortality. In contrast to DIC, thrombocytopenia is rare, and the PT/aPTT are usually normal or minimally prolonged. Some patients exhibit aPTT prolongation due to aPL. Bleeding, while rare, may occur in critically ill patients that develop a consumptive coagulopathy and those on ECMO. Blood-product support to correct the coagulopathy is reserved for bleeding patients or those requiring invasive procedures. The results of ongoing trials evaluating the impact of higher-intensity anticoagulation on COVID-19 outcomes are eagerly awaited. Until then, all hospitalized patients should receive standard thromboprophylaxis.

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Conflict-of-interest disclosure

Gloria F. Gerber: no competing financial interests to declare. Shrutu Chaturvedi: no competing financial interests to declare.

Off-label drug use

Gloria F. Gerber: the off-label use of prothrombin complex concentrate is discussed. Shrutu Chaturvedi: the off-label use of prothrombin complex concentrate is discussed.

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References

- Iba T, Levy JH, Connors JM, Warkentin TE, Thachil J, Levi M. Managing thrombosis and cardiovascular complications of COVID-19: answering the questions in COVID-19-associated coagulopathy. *Expert Rev Respir Med.* 2021;15(8):1003–1011.
- Iba T, Levy JH, Levi M, Connors JM, Thachil J. Coagulopathy of coronavirus disease 2019. *Crit Care Med.* 2020;48(9):1358–1364.
- Al-Samkari H, Karp Leaf RS, Dzik WH, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood.* 2020;136(4):489–500.
- Nopp S, Moik F, Jilma B, Pabinger I, Ay C. Risk of venous thromboembolism in patients with COVID-19: a systematic review and meta-analysis. *Res Pr Thromb Haemost.* 2020;4(7):1178–1191.
- 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.
- 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.
- Zhang L, Yan X, Fan Q, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. *J Thromb Haemost.* 2020;18(6):1324–1329.
- 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.
- 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.
10. Ding R, Wang Z, Lin Y, Liu B, Zhang Z, Ma X. Comparison of a new criteria for sepsis-induced coagulopathy and International Society on Thrombosis and Haemostasis disseminated intravascular coagulation score in critically ill patients with sepsis 3.0: a retrospective study. *Blood Coagul Fibrinolysis*. 2018;29(6):551–558.
 11. Hardy M, Michaux I, Lessire S, et al. Prothrombotic disturbances of hemostasis of patients with severe COVID-19: a prospective longitudinal observational study. *Thromb Res*. 2021;197(January):20–23.
 12. Wright FL, Vogler TO, Moore EE, et al. Fibrinolysis shutdown correlation with thromboembolic events in severe COVID-19 infection. *J Am Coll Surg*. 2020;231(2):193–203.e1203e1.
 13. Iba T, Warkentin TE, Thachil J, Levi M, Levy JH. Proposal of the definition for COVID-19-associated coagulopathy. *J Clin Med*. 2021;10(2):191.
 14. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;180(7):934.
 15. Helms J, Tacquard C, Severac F, et al; CRICS TRIGGERSEP (Clinical Research in Intensive Care and Sepsis Trial Group for Global Evaluation and Research in Sepsis) Group. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med*. 2020;46(6):1089–1098.
 16. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. *Clin Chim Acta*. 2020;506(July):145–148.
 17. Lodigiani C, Iapichino G, Carenzo L, et al; Humanitas COVID-19 Task Force. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res*. 2020;191(July):9–14.
 18. Thachil J, Cushman M, Srivastava A. A proposal for staging COVID-19 coagulopathy. *Res Pract Thromb Haemost*. 2020;4(5):731–736.
 19. Harzallah I, Debliquis A, Drenou B. Lupus anticoagulant is frequent in patients with Covid-19. *J Thromb Haemost*. 2020;18(8):2064–2065.
 20. Abdel-Wahab N, Talathi S, Lopez-Olivo MA, Suarez-Almazor ME. Risk of developing antiphospholipid antibodies following viral infection: a systematic review and meta-analysis. *Lupus*. 2018;27(4):572–583.
 21. Panigada M, Bottino N, Tagliabue P, et al. Hypercoagulability of COVID-19 patients in intensive care unit: a report of thromboelastography findings and other parameters of hemostasis. *J Thromb Haemost*. 2020;18(7):1738–1742.
 22. Nougier C, Benoit R, Simon M, et al. Hypofibrinolytic state and high thrombin generation may play a major role in SARS-CoV2 associated thrombosis. *J Thromb Haemost*. 2020;18(9):2215–2219.
 23. Blasi A, von Meijenfeldt FA, Adelmeijer J, et al. In vitro hypercoagulability and ongoing in vivo activation of coagulation and fibrinolysis in COVID-19 patients on anticoagulation. *J Thromb Haemost*. 2020;18(10):2646–2653.
 24. Ranucci M, Ballotta A, Di Dedda U, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. *J Thromb Haemost*. 2020;18(7):1747–1751.
 25. Bouck EG, Denorme F, Holle LA, et al. COVID-19 and sepsis are associated with different abnormalities in plasma procoagulant and fibrinolytic activity. *Arterioscler Thromb Vasc Biol*. 2021;41(1):401–414.
 26. Middleton EA, He XY, Denorme F, et al. Neutrophil extracellular traps contribute to immunothrombosis in COVID-19 acute respiratory distress syndrome. *Blood*. 2020;136(10):1169–1179.
 27. Yu J, Yuan X, Chen H, Chaturvedi S, Braunstein EM, Brodsky RA. Direct activation of the alternative complement pathway by SARS-CoV-2 spike proteins is blocked by factor D inhibition. *Blood*. 2020;136(18):2080–2089.
 28. Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. *Transl Res*. 2020;220(June):1–13.
 29. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood*. 2020;135(23):2033–2040.
 30. Paranjpe I, Fuster V, Lala A, et al. Association of Treatment Dose Anticoagulation With In-Hospital Survival Among Hospitalized Patients With COVID-19. *J Am Coll Cardiol*. 2020;76(1):122–124.
 31. Lawler PR, Goligher EC, et al. Therapeutic anticoagulation in non-critically ill patients with Covid-19. *medRxiv*. Preprint posted online 17 May 2021.
 32. Zarychanski R. Therapeutic anticoagulation in critically ill patients with Covid-19—preliminary report. *medRxiv*. Preprint posted online 12 March 2021.
 33. Schmidt M, Hajage D, Lebreton G, et al; Groupe de Recherche Clinique en Reanimation et Soins intensifs du Patient en Insuffisance Respiratoire aigue (GRC-RESPIRE) Sorbonne Université; Paris-Sorbonne ECMO-COVID Investigators. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: a retrospective cohort study. *Lancet Respir Med*. 2020;8(11):1121–1131.
 34. Lebreton G, Schmidt M, Ponnaiah M, et al; Paris ECMO-COVID-19 Investigators. Extracorporeal membrane oxygenation network organisation and clinical outcomes during the COVID-19 pandemic in Greater Paris, France: a multicentre cohort study. *Lancet Respir Med*. 2021;9(8):851–862.
 35. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost*. 2020;18(5):1023–1026.
 36. Cuker A, Tseng EK, Nieuwlaet R, et al. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. *Blood Adv*. 2021;5(3):872–888.
 37. Barrett CD, Moore HB, Yaffe MB, Moore EE. ISTH interim guidance on recognition and management of coagulopathy in COVID-19: a comment. *J Thromb Haemost*. 2020;18(8):2060–2063.
 38. Sadeghipour P, Talasaz AH, Rashidi F, et al; INSPIRATION Investigators. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: the INSPIRATION randomized clinical trial. *JAMA*. 2021;325(16):1620–1630.
 39. Lopes RD, de Barros E, Silva PGM, Furtado RHM, et al; ACTION Coalition COVID-19 Brazil IV Investigators. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. *Lancet*. 2021;397(10291):2253–2263.
 40. Lee EJ, Cines DB, Gernsheimer T, et al. Thrombocytopenia following Pfizer and Moderna SARS-CoV-2 vaccination. *Am J Hematol*. 2021;96(5):534–537.
 41. Welsh KJ, Baumblatt J, Chege W, Goud R, Nair N. Thrombocytopenia including immune thrombocytopenia after receipt of mRNA COVID-19 vaccines reported to the Vaccine Adverse Event Reporting System (VAERS). *Vaccine*. 2021;39(25):3329–3332.
 42. Arepally GM, Ortel TL. Vaccine-induced immune thrombotic thrombocytopenia: what we know and do not know. *Blood*. 2021;138(4):293–298.