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# Coagulopathy in COVID-19

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## ABSTRACT

COVID-19-associated coagulopathy is common in patients with COVID-19, causing high rates of thrombotic complications that increase the morbidity and mortality. Markedly elevated levels of D-dimer with normal fibrinogen levels are the hallmark laboratory findings and correlate with severity of illness and risk of thrombosis. Aggressive VTE prophylaxis is paramount for all patients with COVID-19. Patients with very high D-dimer levels (6 times the upper limit of normal, greater than 3,000 ng/mL) have the greatest risk of thrombosis and may benefit from active screening and more intensive VTE prophylaxis.

**C** COVID-19-associated coagulopathy (CAC) and disseminated intravascular coagulation (DIC) are common phenomena in COVID-19 and are associated with a greater severity of illness and a higher risk of death.<sup>1-3</sup>

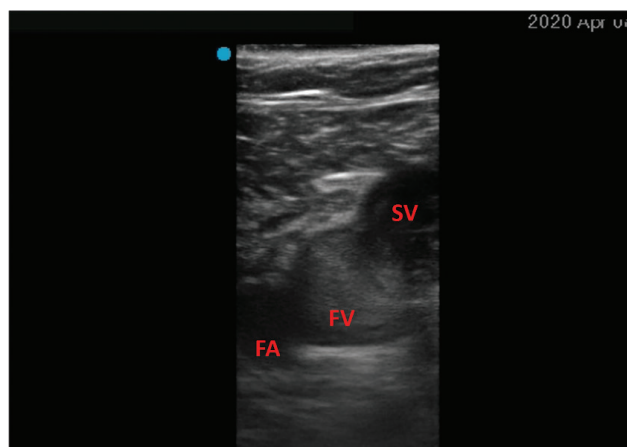
## CLINICAL MANIFESTATIONS

The clinical presentation of CAC is that of a highly prothrombotic state. Anecdotal evidence from China and Europe and our own initial experience indicate that critically ill COVID-19 patients without other risk factors for thrombosis manifest with various thrombotic events including microvascular thrombosis, venous and pulmonary thromboembolism, and acute arterial thrombosis.<sup>4</sup> Based on shared anecdotal experience across a wide variety of platforms, catheter-associated thrombosis and clotting of vascular access catheters and dialysis circuits leading to frequent interruption of continuous renal replacement therapy (CRRT) and a need for catheter replacement are especially problematic.

Two recent studies support this clinical impression,

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**Figure 1.** A short axis view of the femoral vein (FV), the femoral artery (FA) at the site of the saphenous vein inflow (SV). Amorphous echogenicity in the femoral vein, greater than that of the adjacent femoral artery is suggestive of "slow venous flow." The vein is fully compressible ruling out deep vein thrombosis at the site.

reporting a deep vein thrombosis (DVT) rate of 25%<sup>5</sup> and cumulative incidence rates of DVT, pulmonary embolism, and arterial thrombosis of 31%<sup>4</sup>; and 81% of events reported by Klok et al were pulmonary thromboemboli.<sup>4</sup>

In Cleveland Clinic ICUs, we are finding that point-of-care ultrasonography (POCUS) detects similar rates of DVT (estimated 25% to 30%) and frequent findings of "slow venous flow." This pattern, described as amorphous echogenicity in major veins, has been associated with an increased rate of DVT in subsequent examinations (Figure 1).<sup>6</sup>

## LABORATORY FINDINGS

The characteristic laboratory findings of CAC are dramatically elevated levels of D-dimer and fibrin degradation products, painting a picture of a highly prothrombotic state with high fibrin turnover. In contrast, other markers of DIC remain relatively unchanged.<sup>7</sup> The prothrombin time (PT) and activated partial thromboplastin time (aPTT) are only

mildly prolonged, if at all, and platelet counts are usually normal or only mildly decreased ( $100$  to  $150 \times 10^9/L$ ).<sup>8–10</sup>

Elevated D-dimer levels on presentation with COVID-19 are associated with more severe disease (D-dimer greater than  $0.5 \mu g/mL$  in 60% of patients with severe disease vs 43% with mild disease),<sup>3</sup> the need for ICU level of care,<sup>11</sup> and correlate with overall mortality. In a multivariable regression analysis of 191 patients, Zhou et al reported an odds ratio of death of 18.42 (2.64–128.55) for patients with a D-dimer  $> 1 \mu g/mL$  vs  $< 0.5 \mu g/mL$  on admission. D-dimer levels also correlate with the risk of venous thromboembolism (VTE), with a reported sensitivity, specificity, and positive predictive value of 70.0%, 96.7%, and 87.5%, respectively for a D-dimer level of  $3.0 \mu g/mL$ .<sup>1</sup> Patients in this study, however, did not receive routine VTE prophylaxis.

Klok et al did not report D-dimer levels, but reported coagulopathy (prolongation of PT  $> 3$  or aPTT  $> 5$  seconds) as independent risk factor for thrombosis.<sup>4</sup>

One case series of 3 patients with lower-extremity ischemia described an association of antiphospholipid antibodies (anti-cardiolipin immunoglobulin A [IgA], anti-beta-2-glycoprotein I IgA and IgG positive, lupus anticoagulant negative) and coagulopathy of COVID-19.<sup>12</sup> A recent study including 150 patients from ICUs across France showed a remarkably high rate of positive tests for lupus anticoagulant; 50 out of 57 patients who were tested for lupus anticoagulant (87.7%) to further evaluate an elevated aPTT tested positive.<sup>13</sup>

Progression of coagulopathy to overt DIC, as indicated by an International Society on Thrombosis and Hemostasis (ISTH) DIC score of 5 points or higher, is seen in 71.4% of all non-survivors, compared with only 0.6% of survivors.<sup>10</sup>

Progressive consumptive coagulopathy, with declining levels of antithrombin III, a rise in PT and aPTT, and dramatic further increase of D-dimer ( $> 15.0 \mu g/mL$ ) appears to be an indicator of severe and progressive disease, and develops late in the disease course (day 10 to 14) of non-survivors. Fibrinogen levels, which are elevated in the initial phase, drop late in the course of non-survivors and may signal impending death.<sup>10</sup> A recent meta-analysis of 9 studies with 1,779 COVID-19 patients examined thrombocytopenia as a marker for severity of disease. Thrombocytopenia at presentation was associated with an increased risk of severe disease and death, with a mean difference of  $31 \times 10^9/L$  between severe

and nonsevere disease. The authors noted great heterogeneity between studies, with reported rates of thrombocytopenia in severe disease ranging from 4% to 57%.<sup>8</sup>

## HISTOPATHOLOGY

Early histopathology reports describe findings of diffuse alveolar damage with profound inflammation, thrombosis, and thrombotic microangiopathy of small vessels and capillaries of the lung. Megakaryocytes within pulmonary capillaries with nuclear hyperchromasia and atypia, as well as neutrophils partially degenerated and entrapped in fibers, suggesting neutrophil extracellular traps, have also been noted.<sup>14</sup>

Endothelial cell injury and diffuse microvascular thrombosis suggestive of thrombotic microangiopathy is also reported in extrapulmonary organs and may explain acute onset of multiorgan failure without an otherwise obvious etiology.<sup>15</sup>

## PATHOPHYSIOLOGY

CAC is likely multifactorial, and COVID-19 patients share many of the classic VTE risk factors seen in adult respiratory distress syndrome (ARDS) from other causes, ie, immobilization, large vascular-access catheters, and systemic inflammation. The hallmark of COVID-19 is profound inflammation, described as “cytokine storm,” characterized by high levels of IL-1, IL-6, tumor necrosis factor alpha, and other inflammatory cytokines.<sup>11</sup> Inflammation is known to promote thrombosis through various mechanisms, including activation of the endothelium, platelets, monocytes, and the tissue factor/factor VIIa pathway, as well as altering fibrinolysis and natural anticoagulant pathways (thrombomodulin, proteins C and S, tissue-factor-pathway inhibitor).<sup>16,17</sup> Intense inflammation with thrombosis of pulmonary vessels is also seen in ARDS of other etiologies,<sup>18</sup> and it remains to be seen if these findings represent a distinct phenotype unique to COVID-19, or are a general indicator of the severity of inflammation of COVID-19.

Serum proteomic profiling of patients with severe acute respiratory syndrome (SARS) identified an N-terminal fragment of complement C3C-alpha, a central component of the complement pathway, as a sensitive biomarker of early SARS.<sup>19</sup> Murine models of SARS-CoV and Middle East respiratory syndrome coronavirus have shown that complement activation is a major contributor to lung injury and other organ failure. Complement inhibition in these models reduced organ damage and inflammation.<sup>20,21</sup>

Therapeutic use of complement blockade in COVID-19 has been suggested, but clinical data are not yet available.<sup>22</sup>

One mechanism of microvascular thrombosis that may be specific for SARS-CoV is its affinity for angiotensin-converting enzyme 2 (ACE2), which is expressed on alveolar epithelial type II cells and various extrapulmonary tissues including endothelial cells. Endothelial cell activation may represent a unique mechanism of COVID-19-mediated microvascular injury, thrombosis, and subsequent multisystem organ failure.<sup>23,24</sup>

The rate of 87.7% lupus anticoagulant positive patients reported by Helms et al is striking<sup>13</sup> and needs to be verified, but again points to an important role of endothelial injury as a key mechanism of multiorgan failure and coagulopathy of COVID-19. The “two-hit” model of thrombosis associated with antiphospholipid syndrome proposes that after a first hit causes injury to the endothelium, antiphospholipid antibodies potentiate thrombus formation as a second hit.<sup>25</sup> Activation of the contact system due to increased vascular permeability and thrombotic microangiopathy warrant further exploration.<sup>26</sup>

## ■ MANAGEMENT

At present, there are only limited data to effectively guide the management of CAC. The approach outlined below describes the Cleveland Clinic consensus based on the data available and on anecdotal experience. It tries to balance the risk and benefits of empiric therapy, while minimizing the use of resources (such as personal protective equipment) and exposure of caregivers to COVID-19.

Management strategies currently vary greatly among institutions and are likely to change as we learn more about this novel disease in the near future.

## ■ LABORATORY TESTING

Based on the characteristic laboratory findings of CAC described above, we monitor D-dimer, fibrinogen, PT-international normalized ratio, and aPTT every 48 hours. We defined a D-dimer at least 6 times the upper limit of normal (3,000 ng/mL fibrinogen equivalent units [FEU]) as the threshold value to define high-risk patients.<sup>5,10</sup>

There are currently no data to guide how to address a hypercoagulable pattern on viscoelastic testing (thromboelastography or rotational thromboelastometry). In line with current guidance from the American Society of Hematology (ASH) and the ISTH, we do not routinely use viscoelastic testing to

assess hypercoagulability.<sup>27</sup>

Since antiphospholipid antibodies and lupus anticoagulant have been reported in COVID-19, we recommend testing for these, if the aPTT is spontaneously elevated, and prefer the use of anti-Xa assays to monitor anticoagulation. Anti-Xa assay may, however, be affected by high levels of bilirubin (6.6 mg/dL) or triglycerides (> 360 mg/dL),<sup>28</sup> which are often elevated in COVID-19 patients with cytokine storm. Triglyceride levels should therefore be monitored routinely and considered as a possible source of error in patients on anticoagulation that are difficult to maintain within therapeutic target range.

## ■ IMAGING

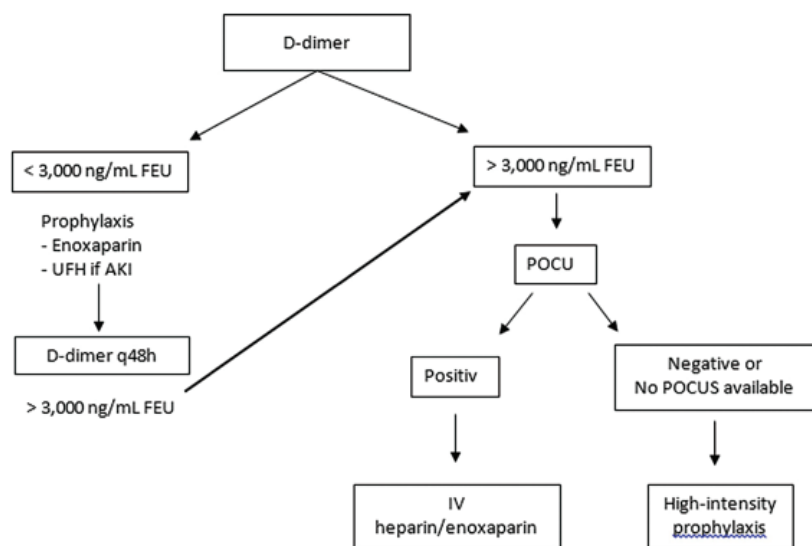
To limit caregiver exposure, we minimize formal bedside vascular studies or travel outside the ICU for computed tomographic angiography; instead, we rely heavily on POCUS to assess for evidence of VTE whenever possible.

High-risk patients (D-dimer greater than 3,000 ng/mL FEU) are assessed for DVT using a 3-point compression POCUS examination of the bilateral lower extremities. A POCUS DVT examination and echocardiography are also recommended for any patient with sudden cardiopulmonary decline that cannot be explained by an alternative etiology. A positive POCUS is highly specific and does not require confirmation by formal vascular ultrasonography.<sup>29</sup> Given the high incidence of pulmonary embolism described, confirmatory studies (formal vascular ultrasonography or computed tomographic angiography) are warranted in cases with contraindications for empiric anticoagulation and high clinical suspicion of VTE despite negative POCUS, or if POCUS is not available.

POCUS should be bundled with other care (for example, ultrasonography-guided vascular access), to minimize use of personal protective equipment and caregiver exposure to COVID-19 as much as possible.

## ■ TREATMENT

Heparin anticoagulation seems to be the obvious response to such a hypercoagulable process. In addition to its antithrombotic effect, heparin may have anti-inflammatory, anti-complement,<sup>30</sup> and direct antiviral effects that may be beneficial in COVID-19. Heparin inhibits neutrophil activation, binds inflammatory cytokines, and reduces endothelial activation.<sup>31</sup> Experimental models have also shown that heparin directly binds to SARS-CoV spike-protein1, which acts as the viral anchor site for SARS-CoV–



**Figure 2.**

ACE2 interaction, and thereby blocks cell entry.<sup>32</sup>

While promising, these effects have yet to be demonstrated in clinical practice, and specific data on the management of CAC are extremely limited.

One study of 449 patients with severe COVID-19 showed no overall mortality difference (29.7% vs 30.3%,  $P = .910$ ) between patients who did not and those who did receive heparin (94 patients on low-molecular-weight heparin, 5 patients on unfractionated heparin; prophylactic doses). There was, however, a significant difference in mortality rates (32.8% vs 52.4%,  $P = .017$ ) in the subgroup of patients with a D-dimer more than 6 times the upper limit of normal ( $> 3 \mu\text{g/mL}$ ). The authors concluded that heparin improves mortality rates in patients with severe COVID-19 and cited a Chinese consensus statement as recommending anticoagulation in severe COVID-19.<sup>33</sup> It must be emphasized that this study retrospectively compared heparin prophylaxis vs no prophylaxis. It remains unclear if therapeutic anticoagulation would provide additional benefit.

Thrombolysis in patients that deteriorate despite anticoagulation has also been suggested. A small case series of patients with persistent severe hypoxia and markedly elevated D-dimer showed improvement in oxygenation after low-dose tissue plasminogen activator. Despite initial improvement and no reported adverse effects, the ultimate outcome in this series was poor.<sup>34</sup>

Given this lack of evidence, the ASH and ISTH currently do not recommend treatment above and beyond standard prophylaxis unless there is an

established indication. Both societies strongly recommend DVT prophylaxis in all patients on admission using low-molecular-weight heparin (unfractionated heparin in renal failure, fondaparinux in heparin-induced thrombocytopenia) and stress that prophylaxis should be continued even in the setting of thrombocytopenia (platelet count  $> 25 \times 10^9/\text{L}$ ).<sup>27,35</sup>

Our current approach is based on POCUS screening for VTE and intensified prophylaxis in high-risk patients (Figure 2, Table 1). We divide patients into 3 categories:

- **Category 1:** D-dimer greater than 3,000 ng/mL FEU and no evidence of VTE. Patients in category 1 receive standard DVT prophylaxis and are monitored using serial D-dimer testing.
  - **Category 2:** D-dimer greater than 3,000 ng/mL FEU, POCUS-negative. Patients in category 2 receive intensified DVT prophylaxis.
  - **Category 3:** Patients with confirmed thrombosis receive full anticoagulation.
- In patients with high clinical suspicion of VTE and no contraindication for anticoagulation, full anticoagulation should be initiated empirically, if POCUS or confirmatory tests are not immediately available.

## CONTINUOUS RENAL REPLACEMENT THERAPY

Given the high rate of clotting on dialysis circuits, all patients on continuous renal replacement therapy receive unfractionated heparin at a rate of 500 U/h. If ongoing clotting is observed, we increase systemic heparin to moderate the aPTT target range (acute coronary syndrome nomogram). The target aPPT may be adjusted if clotting continues despite systemic heparin.

## DURATION OF ANTICOAGULATION

Anticoagulation should be continued for 6 weeks for catheter-associated thrombosis and at least 3 months for VTE. Convalescent patients with persistently elevated D-dimer (greater than 2 times the upper limit of normal) may benefit from extended prophylaxis or treatment.<sup>36,37</sup>

## SUMMARY

COVID-19-associated CAC is common, accompanied by high rates of thrombotic complications and



TABLE 1

	Category 1 D-dimer < 3,000 ng/mL FEU Standard prophylaxis	Category 2 D-dimer > 3,000 ng/mL FEU High-intensity prophylaxis	Category 3 Confirmed VTE
Standard dose	Enoxaparin 40 mg SC q24h	Enoxaparin 40 mg SC q12h	IV Heparin DVT/PE nomogram or Enoxaparin 1 mg/kg SC q12h
Renal failure	CrCl > 10-30mL/min: Enoxaparin 30 mg SC q24h	CrCl < 30 mL/min or AKI: Enoxaparin 40 mg SC q24h	IV heparin DVT/VTE nomogram
<u>*AKI definition:</u> Doubling of creatinine in 48h or anuria	CrCl < 10 mL/min or AKI*: UFH 5,000 U SC q12h	CrCl < 10 mL/min or AKI*: UFH 7500 U SC q12h	
	CRRT: 500 U/h through circuit Circuit clotting: IV ACS nomogram	CRRT: 500 U/h through circuit Circuit clotting: IV ACS nomogram	
Obesity			
Standard	> 100 kg: Enoxaparin 40 mg SC q12h > 120 kg: Enoxaparin 60 mg SC q12h	> 100 kg: Enoxaparin 60 mg SC q12h > 120 kg: Enoxaparin 80 mg SC q12h	IV Heparin DVT/PE nomogram or Enoxaparin 1 mg/kg SC q12h – up to 150 mg  Above 150 kg use UFH
Renal failure CrCl < 30mL/min or AKI*	≤ 120 kg: 7,500 U q12h > 120kg: 10,000U q12h	≤ 120 kg: 7,500 U q8h > 120kg: 10,000U q8h	IV heparin DVT/PE nomogram
<u>*AKI definition:</u> Doubling of creatinine in 48h or anuria	CRRT: 500 U/h through circuit Circuit clotting: IV Heparin ACS* nomogram	CRRT: 500 U/h through circuit Circuit clotting: IV Heparin ACS* nomogram	
IV Heparin ACS nomogram: initial dose 60-U/kg bolus, 12 U/kg/h			
- Target aPTT 49 – 67 seconds			
- Target heparin anti-Xa 0.2 – 0.5 until/ml			

ACS = acute coronary syndrome; AKI = acute kidney injury; aPTT = activated partial thromboplastin time; CrCl = creatinine clearance; CRRT = continuous renal replacement therapy; DVT = deep vein thrombosis; FEU = fibrinogen equivalent units; IV = intravenous; PE = pulmonary embolism; SC = subcutaneously; UFH = unfractionated heparin

associated with high rates of morbidity and mortality. Markedly elevated levels of D-dimer with normal fibrinogen levels are the hallmark laboratory findings. D-dimer levels correlate with severity of illness and risk of thrombosis. Aggressive VTE prophylaxis is paramount for all patients with COVID-19. The subgroup of patients with very high D-dimer levels (6

times the upper limit of normal, greater than 3,000 ng/mL) carries the greatest risk of thrombosis and death and may benefit from active screening and more intensive VTE prophylaxis. Current management is based largely on case reports and anecdotal experience, and controlled studies are urgently needed to better guide care.

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