

COAGULOPATHY IN COVID-19: REVIEW AND RECOMMENDATIONS

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The 2019 novel coronavirus (COVID-19) presents with a variety of phenotypes that range from asymptomatic to profound, rapid multiple organ dysfunction syndrome (MODS) and death. Proposed mechanisms for MODS in COVID-19 are multifactorial but include a hypercoagulable state with micro- and macro-circulatory thrombosis. A strong predictor of mortality is disseminated intravascular coagulation (DIC) with 71.4% of non-survivors meeting criteria for DIC while only 0.6% of survivors met these criteria in an early COVID-19 cohort¹. A significant increase in D-dimer and prothrombin with a decrease in fibrinogen in non-survivors at days 10-14 is also reported¹. This highlights the importance of regular and continued monitoring of these levels. Elevated D-dimer (above 1 µg/mL) was a strong and independent risk factor for death in this population².

This has stoked interest in the potential uses of anticoagulation in COVID-19. Specifically, the use of heparin has potential benefit over other anticoagulants due to its anticoagulant (decreased coronary thrombi, pulmonary emboli, and microvascular ischemia), anti-inflammatory (decreased lung inflammation and improving oxygenation) and potentially anti-viral properties.

As an anticoagulant, heparin may reduce thrombi in organ microcirculation, most notably in the pulmonary vasculature. Here, some have described hypoxia out of proportion to pulmonary compliance suggestive of pulmonary vasculopathy and increased dead space (and hemoglobinopathy outside the scope of this topic). The use of an anticoagulant appears to be associated with decreased mortality in all patients and particularly in patients with a sepsis induced coagulopathy score >3³. It should be noted that, like all cases of DIC, patients may progress to a hypocoagulable phenotype when fibrinogen levels begin to decrease. At this point stopping anticoagulation should be considered. The use of thromboelastography (TEG), in addition to other markers of coagulation, to guide decision making around starting and stopping anticoagulation is currently under investigation. Anecdotally, patients receiving continuous renal replacement therapy (CRRT) or extracorporeal membrane oxygenation (ECMO) may have increased coagulation-related complications and consideration of preemptive therapeutic anticoagulation may be warranted. In addition to increased clotting events, there seems to be an increased incidence of antithrombin-III deficiency leading to an inability to therapeutically anticoagulate with heparin. A number of centers have switched to bivalirudin as their anticoagulant of choice while on these circuits.

A small case series has gone further to propose the use of thrombolytics with tissue plasminogen activator (tPA) in refractory cases of hypoxia, demonstrating improvement in P/F ratios during prolonged infusions⁴. Multiple studies on tPA are currently enrolling patients.

Heparin's anti-inflammatory properties have the potential to benefit patients as well. The elevated D-dimer may be an indirect marker of increased inflammatory response in this population. In the theory of the immune-thrombosis relationship where inflammation and thrombin formation are directly correlated, heparin could decrease the inflammatory response by blocking thrombin formation. A meta-analysis reported decreased mortality with the use of early low-molecular weight heparin (LMWH) in a non-COVID-19 ARDS population⁵.

Finally, heparin may possess anti-viral properties by acting on SARS-CoV-2 surface receptor binding proteins and inhibiting viral attachment⁶.

Decisions to care for these critically ill patients are complicated by the rapidly evolving data and anecdotes. It is therefore required of all of us caring for these patients to make as thoughtful and informed clinical decisions as we can. We suggest, based on a review of the very limited current peer-reviewed literature with low quality of evidence combined with discussions with international clinicians on the frontlines:

- All patients with COVID-19 should undergo coagulation studies at admission, in particular: D-dimer, prothrombin time, and platelet count⁷.
- Because of the possibility of patients to develop coagulopathy later in their hospital course, routine serial measurements of coagulation studies should be undertaken in all COVID-19 patients. The ideal interval has not yet been defined⁷.
- All patients with COVID-19 should be placed on prophylactic doses of anticoagulation, preferably with LMWH, unless there is a contraindication, such as acute kidney injury (AKI), wherein unfractionated heparin is preferred^{3,8}.
- Therapeutic anticoagulation should be strongly considered in patients at high-risk for coagulopathy (including CRRT and ECMO), demonstrating signs of microthrombi-induced organ dysfunction, or with documented or strongly suspected macro-thromboembolism. Determination of high-risk patients by laboratory measures of coagulopathy may include: platelet count, prothrombin time, fibrinogen, fibrinogen-degradation products, D-dimer, and TEG^{1,7}. Of note, some centers are therapeutically anticoagulating all patients on admission when no absolute contraindications exist.
- Given the significant rate of AKI seen in COVID, intravenous contrast for imaging should be used with caution. Duplex ultrasonography, echocardiography, and clinical suspicion can play an increased role in these cases.
- Some early reports support extended-infusion tPA as a potential approach to refractory cases^{4,9}.
- Aspirin should be considered in cases with elevated troponin and cardiac dysfunction, particularly with elevated maximal amplitude on TEG¹⁰.

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