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4-14-2020

### Hypercoaguable State in Patients with Covid-19 Disease

George Washington University

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## Hypercoaguable state in patients with Covid-19 disease

**Date:** April 14, 2020

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The Incident Management Team asked for a review and potential therapeutic recommendations related to increasingly reported observations and reports of presence of a hypercoagulable state among some patients with COVID-19 disease.

Based on the available evidence reviewed thus far (17 reports/publications, a FAQ and guidelines by the American Society of Hematology, guidance by Massachusetts General Hospital Regarding Hematology Issues and Interim guidance from the International Society on Thrombosis and Haemostasis) we find:

- Currently published articles regarding anticoagulation or thrombotic risk factors in COVID-19 are insufficient to make any definitive treatment recommendation.
- All have been case report, case series, or retrospective studies with significant limitations due to sample size, retrospective nature of the analysis, lack of control groups, possible alternative explanations for the findings, and issues with correlation rather than necessarily causation
- Some papers and expert opinion suggest that the degree of hypoxia in severe COVID-19 can contribute to thrombosis itself through increasing blood viscosity and a hypoxia-inducible transcription-factor dependent signaling pathway
- The American Society of Hematology has issued (April 1, 2020) a FAQ with guidance regarding COVID-19 and Coagulopathy with these observations:
  - COVID-19 patients can develop COVID-19 associated coagulopathy (CAC). NB: ASH does not address whether there is a difference between their definition of CAC and DIC.
  - Non-survivors were frequently associated with high D-dimers on admission and throughout hospitalization

The American Society of Hematology proposes these clinical recommendations:

- Follow same lab parameters as DIC
- Emphasize treating underlying condition as in DIC
- Reserve blood product administration for those with active bleeding, invasive procedure, or those otherwise at high risk for bleeding complications similar to usual practice:
- Therapeutic anticoagulation not indicated unless evidence of VTE, continue patients already on anticoagulation for other reasons such as AF, or hold based on usual parameters
- Prophylactic dose LMWH should be given all hospitalized COVID pts despite abnormal coagulation tests in the absence of bleeding and held if platelets  $<25 \times 10^9/L$  or fibrinogen  $<0.5g/L$

- Limited data (ASH is likely referencing retrospective study by Tang et al.: Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy) suggests those with severe COVID infection (Sepsis-Induced Coagulopathy Score (SIC) score  $\geq 4$ ) or D-dimer  $>6\times$  ULN may have decreased mortality with prophylactic heparin product use for 7 days or more (majority of use was LMWH). *It is important to note patients with a bleeding diathesis were not included in this analysis.*
- Abnormal PT/INR, PTT by themselves are not contraindication for VTE prophylaxis, use mechanical prophylaxis when pharmacologic prophylaxis is contraindicated
- Current guidelines recommend some form of VTE prophylaxis in hospitalized patients based on risk-stratification and consideration of bleeding risk, thus this guidance from the American Society of Hematology is not much different compared to usual hospital practice in the absence of more data still advocates currently accepted practice for treatment of DIC
- Reviewing guidance from MGH (April 6, 2020) and ISTH (March 25, 2020), both prefer LMWH for VTE prophylaxis in hospitalized COVID-19 patients (in the absence of contraindications)
- There is very limited literature to suggest heparin may also have anti-inflammatory, endothelial protective, and possible anti-viral mechanisms that could explain improved outcomes related to prophylactic use of heparin products in severe COVID infection
- RCTs are needed to see if tPA is beneficial (so far only one 3-patient case series showing transient benefit in respiratory parameters) and whether there is role for higher dose LMWH/UFH based on weight or therapeutic doses as opposed to prophylactic dosing in US COVID patients as most patients are already receiving VTE prophylaxis when hospitalized and at higher risk for VTE compared to Chinese populations (in which most of the current data is derived)
- Reviewing guidance from MGH and ISTH, there is emphasis on collecting initial coagulation labs for all COVID-19 patients and monitoring those levels if admitted
- Importantly, ISTH considers markedly elevated D-dimer along with other abnormal coagulation parameters as indication for admission even if no other concerns given associated mortality risk (refer to algorithm provided on page 8 of their guidance)

Based on these data our recommendation is that GW should use the guidance provided by the American Hematology Society, and recommend utilizing the MGH guidance and ISTH guidance to inform individual clinical decision-making, especially for considerations regarding initiation of therapeutic anticoagulation. Decisions regarding therapeutic anticoagulation may benefit from institution of a written consent procedure prior to initiation, if not already in place, and would be best instituted in setting of research study enrollment and monitoring.

The guidance can be found below:

1. American Society of Hematology FAQ & guidelines: <https://www.hematology.org/covid-19/covid-19-and-coagulopathy>

2. Guidance by Massachusetts General Hospital Regarding Hematology Issues:  
<https://www.massgeneral.org/assets/MGH/pdf/news/coronavirus/guidance-from-mass-general-hematology.pdf>
3. Interim Guidance from the International Society on Thrombosis and Haemostasis:  
<https://onlinelibrary.wiley.com/doi/pdf/10.1111/jth.14810>

Clearly, data and information on this will evolve and the Intelligence Unit will provide updates as needed.