Journal of Pharmaceutical Policy and Practice

COMMENTARY

Open Access

Evaluation of the prophylaxis and treatment of COVID-associated coagulopathy

Ali Elbeddini[1*], Rachel Gerochi[2] and Ahmed Elshahawi[3]

Abstract

Most of the current "literature" surrounding the presence of thrombosis in COVID-19 disease and appropriate prophylaxis/treatment modalities is certainly retrospective at best, and anecdotal at worst. But in these times of rapidly changing information and perspective, an assessment of all available data (including expert opinion) is the goal of this review. Bleeding risk factors for COVID-19-associated bleeding may include other systemic diseases, including hypertension, diabetes, cardiovascular disease, and immunosuppression. Individuals with hypertension should not discontinue their medication. Current evidence does not support changes in the management of hypertension. As COVID-19 progresses, coagulation pathways are activated as part of the host inflammatory response to limit the viral infection. Specifically, D-dimers, products of fibrin as it is degraded within clots, are elevated in many cases of hospitalized COVID-19 patients. D-dimers are an indicator of a clot (thrombus) formation and breakdown. More severe COVID-19 disease may lead to overt disseminated intravascular coagulation (DIC), associated with high mortality. DIC is a coagulopathy that may arise from the systemic inflammatory response to the virus and damaged tissue caused by the infection. Bleeding risk factors may include other systemic diseases, including hypertension, diabetes, cardiovascular disease, and immunosuppression. Individuals with hypertension should not discontinue their medication. Current evidence does not support changes in the management of hypertension. As COVID-19 progresses, coagulation pathways are activated as part of the host inflammatory response to limit the viral infection. Specifically, D-dimers, products of fibrin as it is degraded within clots, are elevated in many cases of hospitalized COVID-19 patients. D-dimers are an indicator of a clot (thrombus) formation and breakdown. More severe COVID-19 disease may lead to overt disseminated intravascular coagulation (DIC), associated with high mortality. DIC is a coagulopathy that may arise from the systemic inflammatory response to the virus and damaged tissue caused by the infection. My manuscript presents the risk and evidence around the COVID-19-associated coagulopathies

Background

One of the most common clinical findings in COVID-19 patients is the occurrence of thrombotic events despite thromboprophylaxis, leading to poorer outcomes and more ICU transfers. Although uncertain, there is a large consensus that hypercoagulability accompanying COVID-19 infection is the result of inflammatory responses to the virus that lead to coagulation pathways stimulation. Current literature concerning this coagulopathy and its prophylaxis/treatment in the COVID-19 population is certainly retrospective at best, and anecdotal at worst. In these times of rapidly changing information and perspective, an assessment of all available data, including expert opinion, is the goal of this commentary.

COVID-19-associated coagulopathy

Coagulopathy associated with COVID-19 has been described as similar to other pro-inflammatory disorders including anti-phospholipid syndrome, however, can be characterized as its own classification (Fig. 1) [1]. As COVID-19 progresses, coagulation pathways are

*Correspondence: aelbeddini@wdmh.on.ca
[1] Winchester District Memorial Hospital, 566 Louise Street, Winchester, ON KK0C2K0, Canada
Full list of author information is available at the end of the article

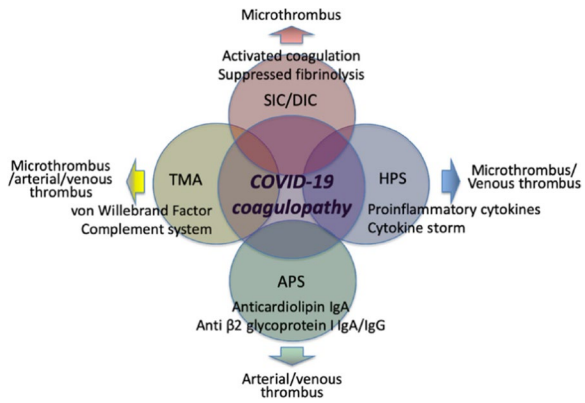


Fig. 1 Characteristic features of COVID-19-associated coagulopathy

activated during the host inflammatory response to limit the viral infection and create a procoagulant effect. Coagulopathy does not appear to stem from thrombotic properties of the virus itself, although this currently remains debateable [2–4]. This inflammatory response together with damaged tissue caused by the infection, in more severe COVID-19 cases, may lead to overt disseminated intravascular coagulation (DIC) and consequently an increased risk of mortality. Early reports indicate a DIC-like picture, although most describe issues strictly with clotting rather than having a bleed component [2, 5, 6]. Recent evidence has additionally shown a risk to both large vessels and potential wide-spread micro-thrombosis in several organ systems which may be a concern for end-organ damage and oxygenation. The latter may prove difficult in terms of diagnosing, and the former has challenges due to the risk of additional staff exposure for testing [7].

Incidence of thrombotic events have been as high as 25–50% in COVID-19 patients admitted to the ICU [8–10], with an increasing severity of illness correlated to a higher occurrence of these events. In comparison to deep vein thrombosis (DVT), pulmonary embolism (PE) is the more common of the two in this patient population [11]. Observations of terminal digits in some COVID-19 patients have shown vasculitis, which can potentially lead to this increase in PE and consequently worsened hypoxemia [12]. Most literature on the increased VTE incidence and thrombosis in the COVID-19 population come from Chinese literature where standard pharmacological thromboprophylaxis is not routinely provided [13], so there may be a bias of increased VTE coming from initial reports. It is important to note that more recent studies still observe relatively high rates of thrombotic events despite appropriate thromboprophylaxis [11]. Alternatively, the increase could be just a simple issue of earlier experience, observation, and time to study compared to the US and Europe. A multicentre study from the US studying 400 COVID-19 patients found the rate of radiographically confirmed VTE to be 4.8% and 7.6% in general wards and critically ill patients, respectively. All patients were reportedly on standard doses of prophylactic anticoagulation. In comparison to studies originating in China and Europe, these rates are much lower which may be attributed to the lack of a consistent protocol for imaging patients suspected of VTE. As a result, thrombotic events may have been missed and under reported [14]. Regardless of the incidence of VTE in this population, there is no question that there is significant morbidity and mortality due to COVID-19 associated coagulopathy.

Hypercoagulability markers

Beyond retrospective analyses, there are many case reports and anecdotal evidence from colleagues around the United States and globally indicating an observance of at least an increase in hypercoagulability markers, if not VTE itself. The debate over which labs or other findings to use as objective measures of risk assessment continues. Many institutions have developed formal protocols using D-dimer and fibrinogen levels, for example, while others have continued to assess based on patient-specific risks.

In many hospitalized COVID-19 patients, particularly ones characterized as "severe", there seems to be an increase in D-dimer levels. (We have seen up to the 20,000 range here.) An Italian study showed an average D-dimer of 4800, with all 24 patients studied exhibiting levels greater than normal [15]. Furthermore, a French report of VTE events looked at a prospective series of 150 patients with ARDS in the ICU, comparing it with a matched non-COVID historical ARDS cohort. Greater than 95% of the COVID cohort had a significantly elevated D-dimer and fibrinogen levels. Imaging was done for suspicion of thrombotic events and about 43% of COVID-19 patients had relevant VTE events. PE occurred in 25% of those with respiratory decline or rising D-dimer [16]. Elevated D-dimer (along with other elevated fibrin degradation products) was linked as a predictor of mortality in one single-center retrospective Chinese study; the average D-dimer for non-survivors was almost four times the survivor group [15]. A second dual-hospital retrospective study of 250 patients confirmed this, showing mortality linked with a D-dimer over 1000 [17]. A report of three cases of clinically significant coagulopathy resulting in multiple infarcts in a Chinese hospital detailed all three patients as having a D-dimer > 2000 (one with 21,000). These patients also all had elevations in anti-phospholipid antibodies [18]. In

another single-center retrospective study, D-dimer had a PPV for the development of VTE of > 70% once the level reached 1500 ng/ml (Fig. 2) [19]. High levels of D-dimer level may also be a useful marker of pulmonary fibrin deposition, an observation commonly documented in several other lung diseases such as ARDS [11]. In a single-site evaluation, a cohort with ARDS (about 42%) had D-dimer and PT elevations to a statistically significant degree compared to the non-ARDS group. However, neither were elevated to what most of us would consider a clinically significant degree [20].

There is also evidence of increases in fibrinogenand CRP in COVID-19 patients according to many reviews [21]. Since we typically see severe disease in the ICU, it is difficult to tease out from these observed elevations inflammatory effects versus clinically significant effects on the coagulation cascade [13, 16]. Besides this, there is a concomitant increase in von Willebrand Factor, Lupus anticoagulant, and Factor VIII [16]. These elevations, however, are still associated with critical illness, thrombosis and mortality [14]. Due to the lack of specificity, it is difficult to use this as a measure of thrombotic risk outside of trending for general inflammatory assessment.

Interestingly, platelets tend to be WNL on admission in the majority of COVID-19 patients, although they may trend significantly lower in severe disease [22, 23]. Some researchers have suggested clinicians monitor PTT, platelet count and D-dimer concentrations every 2–3 days [22]. In one report, PTs were slightly elevated in just over 50% of patients (although not very significantly), and PTT was not statistically elevated on admitting in with an average result of just 31. In another, both PT and PTT were WNL in 197 patients, and PT was not elevated significantly elevated in a third [15, 17, 19]. PTT and PT were elevated in one evaluation of 24 patients in Italy, but again not to an appreciable degree [15]. There have been several reports, however, of PTTs being unreliable for assessing heparin therapy in these patients; Xa levels may be more accurate. Neither PT nor PTT seems to be a reliable value in assessing general coagulopathy in this population.

One study out of Italy reviewed TEG results from 24 patients admitted to an ICU with COVID-19 and ARDS and matched them with the results of 40 healthy adult comparators. By comparison, R (50% of COVID patients) and K (83%) values were shortened significantly, while MA (83%) was increased, and LY-30 (100%) was considerably lower in the COVID patients. It indicated that all patients had a state of hypercoagulability, although the authors did not characterize it as DIC [15]. Another investigation from Italy exhibited similar results [24].

Thromboprophylaxis and treatment

There is a continued debate regarding which patient populations should get which pharmacological intervention: full dose versus standard prophylaxis or even an increased prophylactic dose. The ISTH Guidelines recommend prophylaxis with LMWH for all COVID-19 patients barring contraindication (PLT < 25, or active bleeding), although they fail to indicate the recommended dosing [25]. They also provide a flowchart for assessing admission of COVID-19 patients that essentially indicates using only prophylactic LMWH for "markedly" elevated D-dimer unless an alternative diagnosis exists (Fig. 3).

The pharmacological doses required to help abate thrombosis in these patients is not well established. Studies and consensus statement/opinion papers have been inconsistent across the board, with proposed prophylactic doses of enoxaparin ranging from 40 mg/day to 0.5 mg/kg Q12H. Possibly most concerning is the fact that thrombosis is likely occurring despite anticoagulation even at therapeutic doses [26, 27]. Autopsies performed on 10 COVID-19 patients showed the presence of microthrombi in lung tissue, a possible marker of in situ pulmonary thrombosis. With the disproportionate occurrence of pulmonary clotting events without an increase in DVT, this may have implications on the

Cut-off (μg/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
1.0	85.0	77.0	54.8	94.0
1.5	85.0	88.5	70.8	94.7
2.0	80.0	90.2	72.7	93.2
2.5	70.0	93.4	77.8	90.5
3.0	70.0	96.7	87.5	90.8
3.5	65.0	96.7	86.7	89.4

Fig. 2 Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of different D-dimer cut-off levels for predicting VTE in COVID-19 patients [19]

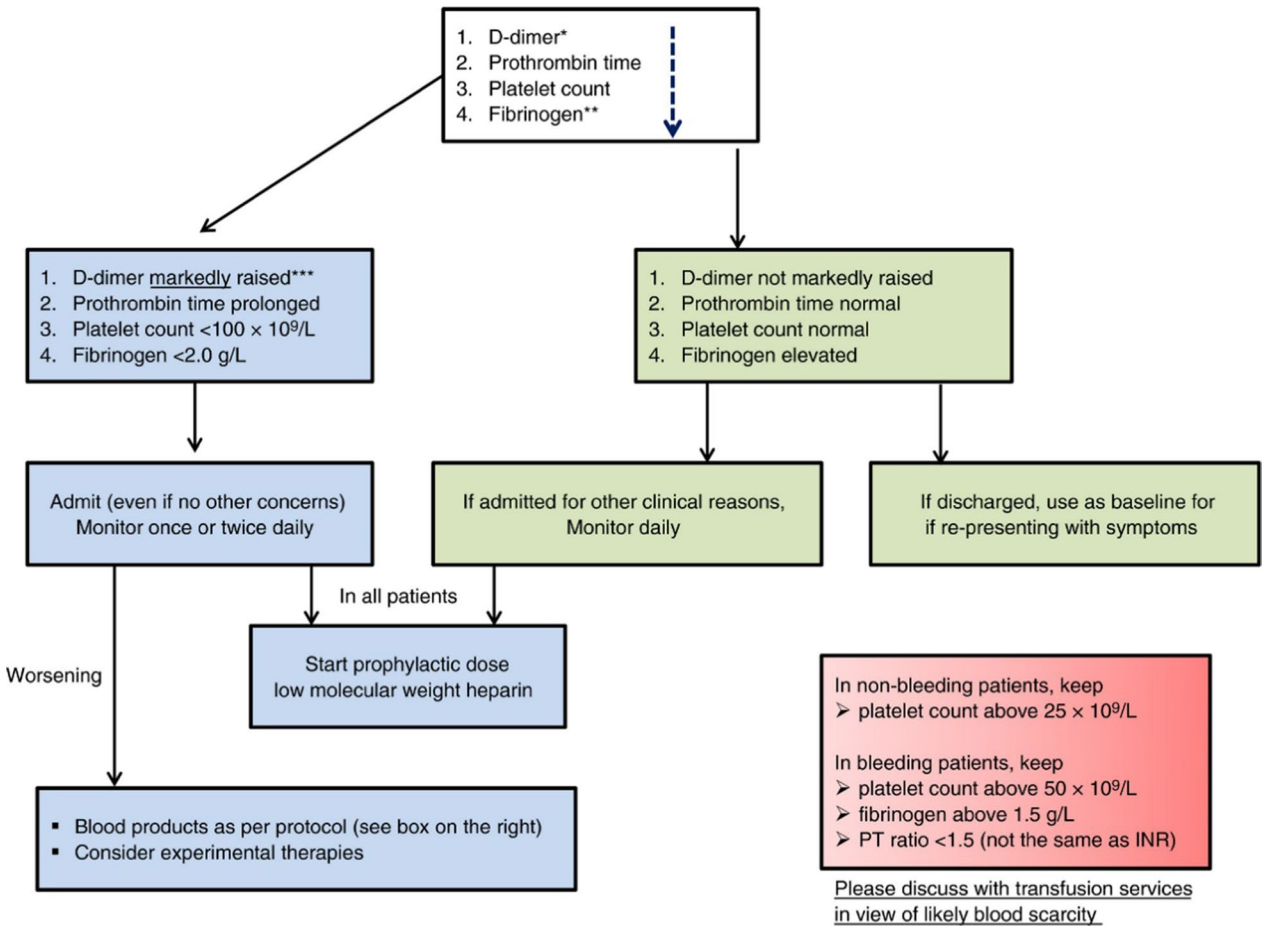


Fig. 3 ISTH algorithm for management of coagulopathy in COVID-19 [33]. Algorithm for the management of coagulopathy in COVID-19 based on simple laboratory markers. * The list of markers is given in decreasing order of importance. ** Performing fibrinogen assays may not be feasible in many laboratories, but monitoring the levels can be helpful after patient admission. *** Although a specific cut-off cannot be defined, a three- to four-fold increase in D-dimer values may be considered significant. Anyone of the values in this table may be regarded as significant

appropriate therapy for COVID-19 patients and whether anticoagulation is indeed the best course of action [11]. Cleveland Clinic and Emory have taken a tiered approach to management based on D-dimer and known thrombus (Figs. 4, 5) [20, 28]. Whether to prophylactically or fully anticoagulated patients who have no overt VTE is certainly still up for debate, with only a few societies providing initial guidance on dosing [14, 25, 29]. Outside of these, only small studies or opinion papers have touched on this topic as of yet. More will hopefully come. A current open-label study is being conducted in Switzerland to assess high versus low-dose anticoagulation in COVID-19 patients and its effects on venous and arterial thrombosis, DIC, and mortality [10].

Concerning heparin use, PTTs may be erratic, making use of them as a monitoring tool for full-dose unfractionated heparin (UFH) problematic. It may be prudent to consider using a Xa-based adjustment protocol if baseline PTTs are abnormal (pharmacists can help with this). An additional concern is that anti-thrombin three (AT-III) seems to be either down-regulated or simply reduced by consumptive processes from micro-emboli [28, 30]. Our stores of AT-III are absolutely essential for both UFH and low-molecular-weight heparin (LMWH) to bind to both thrombin and Xa, resulting in their subsequent anticoagulant effect (Fig. 6). AT-III is also used by fondaparinux (a direct Xa inhibitor). It is not required by other direct Xa inhibitors (rivaroxaban, apixaban) or direct thrombin inhibitors (argatroban, dabigatran). If AT-III is not present in sufficient amounts, the effect of heparinoids will be significantly blunted. Experimental models have shown the direct binding of heparin to the SARS-CoV spike protein 1, which is the viral anchor site for its interaction with ACE2. By binding to this protein, heparin can block the virus' entry into the cell. These effects lack evidence in clinical practice [31].

LEVEL 1 (standard prophylaxis): for patients without known thrombus AND a D-dimer < 3,000*:

Anticoagulation	Notes
LMWH 0.5mg/kg/day (Min 40 mg, Max 80 mg) OR For renal insufficiency: - if stable SCr and CrCl >15-30 ml/min, monitor anti-Xa and dose adjust	1. No need to routinely monitor anti-Xa levels if CrCl >30 ml/min and stable 2. For obese patients with renal insufficiency, can dose adjust UFH for BMI 25-35: 7500 units Q8H†; BMI > 35: 10000 units Q8H†
- if unstable SCr (SCr change by ±0.5 in 24 hours), anuria, or CrCl <15 ml/min, can use UFH 5000 units Q8H†	

On discharge: 7 days of continued prophylaxis with LMWH or DOAC (DOAC preferred). See discharge guidance below.

**At EDH, D-dimer threshold = 3.0 FEU/ml (i.e., 6x ULN).*

†Consider Q12H regimen on the floor

LEVEL 2 (intermediate dosing): for patients without known thrombus AND a D-dimer ≥ 3,000*:

Anticoagulation	Notes
LMWH 1mg/kg/day OR For unstable SCr, anuria, or CrCl ≤30 ml/min: Heparin gtt, low-standard without bolus	1. Where able, monitor anti-Xa for LMWH for all patients 2. As able, baseline LE dopplers should be checked (formal vs. POCUS) in these patients, with repeat for changes in clinical status 3. For patients with stable renal function, LMWH preferred over heparin gtt given volume infusion with gtt. 4. For non-ICU patients, consider initiating DOAC (no loading doses) while inpatient if clinically appropriate (see dosing chart)

On discharge: Continue treatment for 4-6 weeks with DOAC or LMWH (DOAC preferred). See discharge guidance below.

**At EDH, D-dimer threshold = 3.0 FEU/ml (i.e., 6x ULN).*

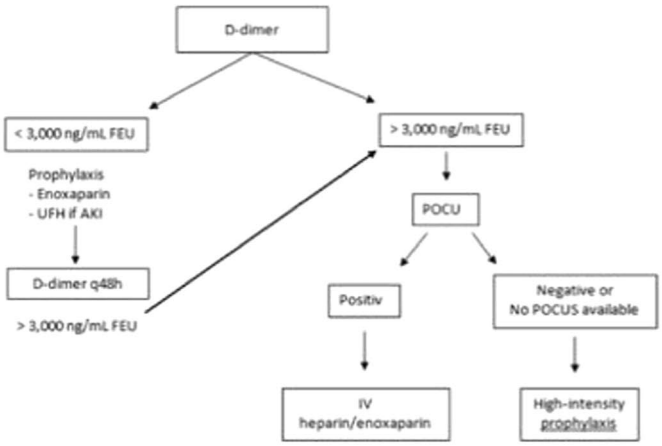
LEVEL 3 (therapeutic dosing): for patients with known or suspected VTE, or otherwise unexplained increase in oxygen requirement, dead space, or organ failure (e.g., AKI, MSOF) with concern for microvascular thrombi.

Anticoagulation	Notes
LMWH 1mg/kg/q12h OR Stable renal function and CrCl 15-30 ml/min: LMWH 1 mg/kg/qday (Goal anti-Xa remains 0.6-1) OR Unstable SCr, anuria, or CrCl ≤15 ml/min: Heparin gtt, high-standard with bolus	1. Where able, monitor anti-Xa levels for LMWH for all patients 2. If concern for heparin resistance when dose of heparin exceeds 24 units/kg/hr (or 3-4mg/kg/ 24 hrs of LMWH) and still subtherapeutic (e.g., anti-Xa not at goal), consider switching to a DTI (argatroban/ bivalirudin) while inpatient. 3. In patients with AT level of <50%, start directly with DTI. 4. For non-ICU patients, consider initiating DOAC (with loading doses) while inpatient if clinically appropriate (see dosing chart below).

Fig. 4 Emory protocol—April 22, 2020

Conversely, UFH has been shown to exhibit anti-inflammatory effects [32, 33], and there is also some evidence that LMWH may do the same [8, 34]. This could prove beneficial beyond anti-thrombosis in this patient population with well-established hyper-inflammatory states.

Regarding the use of thrombolytics: in a pre-guideline consensus statement provided by Chinese and French



Our current approach is based on point of care ultrasound screening for VTE and intensified prophylaxis in high-risk patients.
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.

	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 *AKI definition: Doubling of creatinine in 48h or anuria	**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
	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*** *AKI definition: Doubling of creatinine in 48h or anuria	≤ 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
	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			

Fig. 5 Cleveland Clinic thrombosis risk assessment [36]

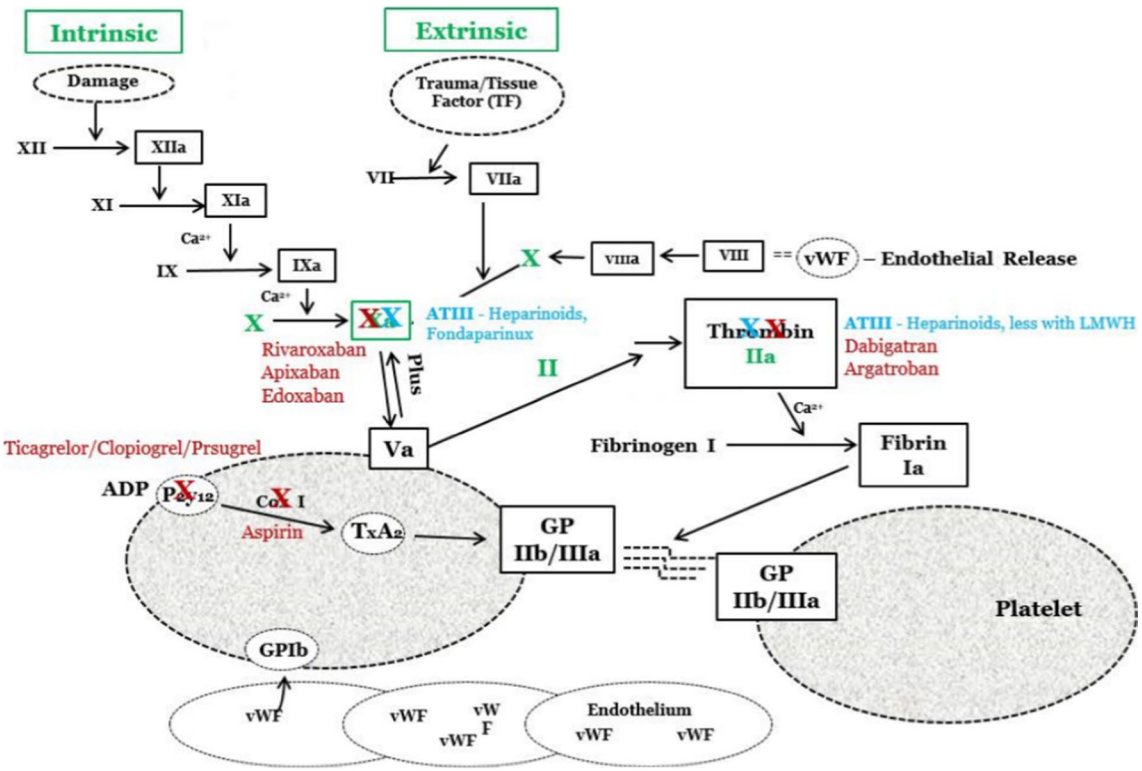


Fig. 6 Coagulation cascade

physicians that was just published on 4/21/20, recommendations include the use of thrombolytic rescue therapy for severe cases of COVID-19 with abrupt/severe hypotension and/or hemodynamic deterioration in combination with findings from bedside Echo [35]. The use of alteplase in non-COVID ARDS has been described in the literature previously based on the intertwined processes of inflammation and coagulation [36]. Some have recommended in COVID patients with acute decompensation using alteplase 25 mg bolus over 2 h, followed by 25 mg over the next 22 h (or about 1 mg/h for the remainder of the 50 mg dose) [37]. There have been discussions around the use of other anticoagulant modalities such as plasma exchange to treat thrombotic microangiopathy. Theoretically, the delivery of high volumes of plasma may result in the replacement of missing factors such as complement proteins and the removal of excess inflammatory mediators. More evidence is required to evaluate the efficacy of this treatment, preferably in a controlled trial setting [38].

Recommendations for *N*-acetyl heparin (NAH)

Pharmacological DVT prophylaxis should be applied in all critically ill COVID-19 known or rule-out cases barring contraindications (active bleeding, PLT < 25).

Patients with no known thrombus and a D-dimer < 1000:

- Consider initiating standard prophylaxis with enoxaparin 0.5 mg/kg SQ daily or heparin 5000 units SQ Q8H (or weight-based of 70 units/kg AdjBW if obese) in patients with significant renal impairment. For enoxaparin, anti-Xa monitoring should be applied in cases of extremes of weight, mild/moderate renal dysfunction, or elderly (> 65yo).
- Monitor coagulation parameters, including D-dimer Q48H.

Patients with no known thrombus and a D-dimer ≥ 1000:

- Consider initiating high-dose prophylaxis with enoxaparin 0.5 mg/kg SQ Q12H or heparin 7500 units SQ Q8H (or weight-based of 70 units/kg adjusted BW if obese) in patients with significant renal impairment.
- Anti-Xa monitoring should be applied in all cases of high-dose enoxaparin prophylaxis in this population
- Monitor coagulation parameters, including D-dimer Q48H.
- Consider reducing to standard prophylaxis if D-dimer resolves

Patients with known or suspected thrombus, or acute change in oxygenation, ventilation, hemodynamic status, or end-organ function:

- Consider initiating full-dose anticoagulation of enoxaparin 1 mg/kg SQ Q12H or heparin drip (may also consider heparin SQ at therapeutic dosing: 333 units/kg SQ × 1, followed by 250 units/kg SQ Q12h, with Xa levels 6 h after a dose at SS—pharmacists have access to this protocol).
- Anti-Xa monitoring should be applied in all cases of treatment-dose enoxaparin in this population
- Alternatively, may consider alteplase 25 mg IV over 2 h, followed by 1 mg/h for 25 h in known pulmonary thrombosis or acute decompensation.

Conclusions

Due to its rapid emergence and spread, evidence surrounding COVID-19-associated bleeding disorders is still lacking. Of the proposed hypercoagulability markers, D-dimer testing appears to be a key laboratory test to monitor coagulability and predict patient prognosis. Monitoring parameters such as fibrinogen, PT and PTT are not reliable in this population. Despite the debate on the most appropriate approach in terms of thromboprophylaxis in COVID-19 patients, there is not enough evidence to support the use of higher than standard prophylactic doses and there are still concerns that patients treated with therapeutic doses may still experience thrombotic events. Indication of potential in situ pulmonary thrombi brings uncertainty to whether anticoagulant prophylaxis is even appropriate in the first place and increased doses may result in unnecessarily greater adverse effects for patients. More robust research is required to support the use of other treatment or preventative modalities such as plasma exchange.

Acknowledgements
I would like to acknowledge the support from the pharmacy team in facilitating the data collection.

Authors' contributions
AIE: original manuscript preparation, conceptualization, data curation, analysis of the paper, literature search, data collection, writing, reviewing and editing, driving for the ideas and thoughts. RG, AhE: original manuscript preparation, analysis of the paper, literature search, data collection, writing, reviewing and editing, driving for the ideas and thoughts. All authors read and approved the final manuscript.

Funding
I know of no conflict of interest with this publication, and there has been no financial support for this work that could have influenced the outcome.

Availability of data and materials
Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

Competing interests
No known competing interest to declare.

Author details
[1] Winchester District Memorial Hospital, 566 Louise Street, Winchester, ON KK0C2K0, Canada. [2] Leslie Dan Faculty of Pharmacy, University of Toronto, 144 College st, Toronto M5S 3M2, Canada. [3] University of Toronto Medical School, U 1 King's College Circle, Medical Sciences Building, Room 2109, Toronto, ON M5S 1A8, Canada.

Received: 22 July 2020 Accepted: 7 October 2020
Published online: 26 October 2020

References

1. Iba T, et al. The unique characteristics of COVID-19 coagulopathy. Crit Care. 2020;24(1):1–8. https://doi.org/10.1186/s13054-020-03077-0.
2. COVID-19 and its implications for thrombosis and anticoagulation. Hospital Medicine Virtual Journal Club. 2020. https://journalclub.wustl.edu/2020/04/28/covid-19-and-its-implications-for-thrombosis-and-anticoagulation/. Accessed 9 May 2020.
3. JH C. Thromboinflammation and the hypercoagulability of COVID-19. 2020. https://www.ncbi.nlm.nih.gov/pubmed/32302453. Accessed 9 May 2020.
4. Han H, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clin Chem Lab Med. 2020;58(7):1116–20. https://doi.org/10.1515/cclm-2020-0188.
5. Tandfonline.com. 2020. https://www.tandfonline.com/doi/pdf/10.1080/22221751.2020.1741327. Accessed 9 May 2020.
6. Magro C, Mulvey J, Berlin D, Nuovo G, Salvatore S, Harp J, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. 2020.
7. Anticoagulation Guidance Emerging for Severe COVID-19—pragmatic choices dominate as guidelines are shaping up: China_Flu. Reddit.com. 2020. https://www.reddit.com/r/China_Flu/comments/gbrq3h/anticoagulation_guidance_emerging_for_severe/. Accessed 9 May 2020.
8. Klok F, Kruip M, van der Meer N, Arbous M, Gommers D, Kant K, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020;191:145–7.
9. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost. 2020;18:1421–4.
10. Beun R, Kusadasi N, Sikma M, Westerink J, Huisman A. Thromboembolic events and apparent heparin resistance in patients infected with SARS-CoV-2. Int J Lab Hematol. 2020;42:19–20.
11. Al-Ani F, et al. Thrombosis risk associated with COVID-19 infection. A scoping review. Thromb Res. 2020;192:152–60. https://doi.org/10.1016/j.thromres.2020.05.039.

12. Liu PP, et al. The science underlying COVID-19. Circulation. 2020;142(1):68–78. https://doi.org/10.1161/circulationaha.120.047549.
13. Feature | Thrombosis and COVID-19: FAQs for current practice—American College of Cardiology. American College of Cardiology. 2020. https://www.acc.org/latest-in-cardiology/articles/2020/04/17/14/42/thrombosis-and-coronavirus-disease-2019-covid-19-faqs-for-current-practice. Accessed 9 May 2020.
14. Al-Samkari H, et al. COVID and coagulation: bleeding and thrombotic manifestations of SARS-CoV2 infection. Blood. 2020. https://doi.org/10.1182/blood.2020006520.
15. Panigada ME. Hypercoagulability of COVID-19 patients in Intensive Care Unit. A report of thromboelastography findings and other parameters of hemostasis. 2020. https://www.ncbi.nlm.nih.gov/pubmed/32302438. Accessed 9 May 2020.
16. Consult QD. Consult QD. 2020. https://consultqd.clevelandclinic.org/tag/venous-thromboembolism-vte/. Accessed 9 May 2020.
17. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054–62.
18. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, Chen H, Ding X, Zhao H, Zhang H, Wang C. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl J Med. 2020. https://doi.org/10.1056/NEJMc2007575.
19. Coronavirus (COVID-19) clinical guidance repository. AAMC. 2020. https://www.aamc.org/coronavirus-covid-19-clinical-guidance-repository. Accessed 9 May 2020
20. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, 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;180:934–43.
21. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323:1061–9.
22. Marietta ME. COVID-19 and haemostasis: a position paper from Italian Society on Thrombosis and Haemostasis (SISET). 2020. https://www.ncbi.nlm.nih.gov/pubmed/32281926. Accessed 9 May 2020.
23. Bowles L, Platton S, Yartey N, Dave M, Lee K, Hart DP, MacDonald V, Green L, Sivapalaratnam S, Pasi KJ, MacCallum P. Lupus anticoagulant and abnormal coagulation tests in patients with Covid-19. N Engl J Med. 2020. https://doi.org/10.1056/NEJMc2013656.
24. Spiezia L, Boscolo A, Poletto F, Cerruti L, Tiberio I, Campello E, et al. COVID-19-related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure. Thromb Haemost. 2020. https://doi.org/10.1055/s-0040-1710018.
25. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost. 2020;18:1023–6.
26. Llitjos JF, Leclerc M, Chochois C, Monsallier JM, Ramakers M, Auvray M, Merouani K. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost. 2020. https://doi.org/10.1111/jth.14869.
27. (COVID-19) C, Health E, Disease H, Disease L, Management P, Conditions S et al. Blood clots are another dangerous COVID-19 Mystery. WebMD. 2020. https://www.webmd.com/lung/news/20200424/blood-clots-are-another-dangerous-covid-19-mystery. Accessed 9 May 2020.
28. Ranucci M, Ballotta A, Di Dedda U, Bayshnikova E, Dei Poli M, Resta M, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. J Thromb Haemost. 2020;18:1747–51.
29. Preventing COVID-19 complications with low- and high-dose anticoagulation—Full Text View—ClinicalTrials.gov. Clinicaltrials.gov. 2020. https://clinicaltrials.gov/ct2/show/NCT04345848. Accessed 9 May 2020.
30. The versatile heparin in COVID-19. Onlinelibrary.wiley.com. 2020. https://onlinelibrary.wiley.com/doi/epdf/10.1111/jth.14821. Accessed 9 May 2020.
31. Mucha SR, et al. Coagulopathy in COVID-19. Cleveland Clin J Med. 2020. https://doi.org/10.3949/ccjm.87a.ccc024.
32. Li X, Ma X. The role of heparin in sepsis: much more than just an anticoagulant. 2020.
33. Mousavi S, Moradi M, Khorshidahmad T, Motamedi M. Anti-inflammatory effects of heparin and its derivatives: a systematic review. 2020.
34. E Y. The anti-inflammatory effects of heparin and related compounds. 2020. https://www.ncbi.nlm.nih.gov/pubmed/17727922. Accessed 9 May 2020.
35. MacLaren R, Stringer K. Emerging role of anticoagulants and fibrinolytics in the treatment of acute respiratory distress syndrome. 2020.
36. Wang J, Hajizadeh N, Moore EE, McIntyre RC, Moore PK, Veress LA, Yaffe MB. Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): a case series. J Thromb Haemost. 2020. https://doi.org/10.1111/jth.14828 (Epub ahead of print).
37. Intensive Care Medicine, Volume 0, Issue 0. Springer. Link.springer.com. 2020. https://link.springer.com/journal/134/onlineFirst. Accessed 9 May 2020.
38. Levi M, et al. Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol. 2020;7(6):e438. https://doi.org/10.1016/s2352-3026(20)30145-9.

Publisher's Note