Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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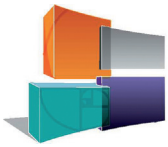

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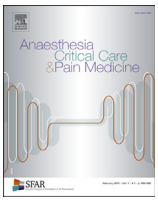

Letter to the Editor

COVID-19 associated coagulopathy: The crowning glory of thrombo-inflammation concept

At the time of this writing, > 3 million cases of the SARS-CoV-2 virus-induced human disease, the Coronavirus disease 2019 (COVID-19), have been reported worldwide with > 210,000 deaths. Although the lungs are "ground zero" [1], the virus's reach can extend to any organs including the heart and blood vessels, kidneys, gut and brain. Evidence of abnormal coagulation markers in COVID-19 appeared in early reports from China [2]. It includes elevated fibrinogen and D-dimers, minimal changes in PT, PTT and platelet count in early stages of infection, no antithrombin deficiency, coagulopathy being related to severity of illness, overt Disseminated Intravascular Coagulation (DIC; ISTH criteria) being an end-stage evolution in the most severe cases, mainly in non-survivors. Further studies evidenced elevated D-dimers on admission (> 1000 ng/mL) associated with increased mortality [3]. Then accumulating reports described a high incidence of venous thromboembolic events VTE, also of arterial events, in ICU patients. The COVID-19 associated coagulopathy (CAC) quickly became an issue of clinical management, hoping to limit deleterious clinical consequences and improve the prognosis.

A recent paper comprehensively discusses about COVID-19 and its implications for thrombosis and anticoagulation [4].

It reviews the inseparable links between inflammation and coagulation. Intravascular fibrin generation has been described during the last decade as an effector of innate immunity: activation of coagulation generates thrombin, which drives many amplifications pathways. This concept is resumed as thrombo-inflammation [5]. The inflammatory response observed in patients with sepsis-induced coagulopathy can activate coagulation using several pathways (polyphosphates, complement pathway, granulocyte NETosis expelling cell-free DNA and histones) but the cytokines and chemokines generated by the challenged immune system can also activate monocytes and vascular endothelial cells leading to a prothrombotic phenotype. We have no evidence that the SARS-CoV-2 virus can directly activate coagulation. However, significant inflammation is present in patients with the viral infection, based on elevated levels of IL-6, CRP and fibrinogen at presentation, and elevated plasma concentrations of proinflammatory cytokines were found, with higher levels in ICU-patients. Some patients do have a "cytokine storm", which may explain more dramatic changes in coagulation tests. The mechanisms that activate coagulation in SARS-CoV-2 infection are not fully understood but appear to depend on the intensity of the individual inflammatory reaction, not on direct specific viral activities. We however now have some evidence showing that the virus infects endothelial cells, which bear the receptor for viral adhesion, the ACE2 molecule. This can induce endothelial apoptosis, thus eliminating the key cell regulating the biocompatibility shield between circulating blood flow and tissues. This may be a central player in coagulation activation and thrombogenesis.

A coagulation test surveillance is proposed for hospitalised patients, testing being performed on admission then according to evolution, including D-dimer, PT, aPTT, fibrinogen and platelet count, both to give some prognostic information but also to early detect the onset of DIC in case of progressive changes (7–11 days after the onset of symptoms or 4-10 days after hospitalisation).

Pharmacologic VTE prophylaxis has early been proposed to be mandatory for all confirmed or suspected patients entering the hospital, as it is in inflammatory medical patients, also due to increasing data reporting high VTE incidences culminating in severe patients admitted in ICU (Table 1). Passionate and stormy arguments are exchanged on the anticoagulation intensity for VTE prophylaxis, with a frequent posture "more is better". No trial result is available. Some key opinion leaders have pushed intermediate-dose LMWH for thromboprophylaxis, sometimes based on a risk-adapted strategy based on fibrinogen, D-dimers, ICU location. . . but most support standard thromboprophylaxis for hospitalised patients with moderate to severe COVID-19 and no DIC. Obese patients have a doubling of their daily injection. Individual patient assessment incorporating an evaluation of the bleeding risk is required. Of note, COVID-19 coagulopathy do not result in significant bleeding.

The treatment of microvascular thrombosis, which may also be responsible for multiorgan failure, is problematic due to the absence of treatment against the virus. Heparin and derivatives have demonstrated limited efficacy in sepsis-induced coagulopathy. Antithrombin and soluble thrombomodulin may have a trend towards increased survival in septic patients with laboratory

Table 1
Summary of the anticoagulant-based management strategy proposed for inpatients with COVID-19 in the paper under comment [4]. Coagulation tests are recommended in each situation, in order to evaluate the status of the coagulation system and the safety of using anticoagulation. Standard dose VTE prophylaxis should be considered in outpatients.

	Ward	ICU	VTE		ARDS
			Confirmed	Presumed PE[b]	
Anticoagulation dose					
Prophylactic					
Standard dose	X				
Intermediate dose[a]		X			X
Therapeutic			X	X	

Anticoagulant options: LMWH, UFH and fondaparinux. Direct oral anticoagulants are used in some centres, but intermediate intensity doses are not defined. Renal insufficiency is a strong modulator of the anticoagulant option.

[a] No supporting data except in small studies and obese patients. Many centres use an escalation strategy, giving half the therapeutic dose.

[b] Based on clinical symptoms such as change in respiratory status, right heart strain on echocardiogram, faced to the inability to obtain imaging.

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proven DIC. COVID-19 associated coagulopathy should be managed like other coagulopathy, including sepsis-associated DIC.

The prevention of microvascular thrombosis has been considered using full-dose anticoagulation to avoid the fibrin-platelet microthrombi form in the pulmonary microcirculation and parenchyma observed in post mortem findings. There is however no data to support full-dose anticoagulation at this time for this indication and in prior trials of anticoagulation with sepsis low-dose heparin was used. There is also no data for a direct interaction between heparin and the virus, and the use of heparins to decrease infectivity cannot be supported.

Concerning therapeutic anticoagulation (treatment of VTE, atrial fibrillation, mechanical cardiac valves, long-term VTE prophylaxis), the use of LMWH or standard heparin over direct oral anticoagulants is preferred given their parenteral administration and shorter half-life. Anti-factor Xa monitoring must be used, the inflammatory reaction inducing a resistance of coagulation tests to heparins. In ICU patients, in case of acute clinical/echocardiographic findings highly evoking pulmonary embolism, the difficulty to obtain objective imaging in mechanically ventilated patients sometimes leads to a the pragmatic use of a therapeutic anticoagulation.

This very complete and wise overview hatches questions. Are we sure that elevated D-dimers in COVID-19 uniformly mean an intravascular fibrin generation, meaning a clinical prognosis? Is worsening coagulopathy a consequence of poor outcomes, or at least a partial cause? Do we have any demonstration that anticoagulant-based treatments can have an inverse dose-effect relationship between their intensity and the severity of the coagulopathy? Are anticoagulants really the best approach for limiting thrombotic complications of the thrombo-inflammation process, or do we have to test multi-drug approaches, including anticytokine treatments...? COVID-19 coagulopathy marks the end of too simple thrombotic risk models and leads us into a complex domain fuelled by polymorphic, sometimes systemic alterations affecting multiple interconnected biological systems, which we do not yet know how to qualify, explore and quantify. Deep questioning and unbridled creativity are more than ever hoped.

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Disclosure of interest

The authors declare that they have no competing interest.

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