Protocol for the management of VTE risk and Disseminated Intravascular Coagulation in patients with SARSCoV-2 hospitalized in Tenon

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Background

Severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) was identified as the pathogen of coronavirus disease 2019 (COVID-19) which is associated with a severe inflammatory syndrome and pneumonia.
Published data from 183 patients infected with the SARSCoV-2 and COVID-19 pneumonia hospitalized to Tongji Hospital of Huazhong University of Science and Technology in Wuhan from January 1 to February 3, 2020 and monitored for clinical outcome until February 14 showed a mortality rate up to 11.5%. [i]

- Overt disseminated intravascular coagulation (DIC) was diagnosed in about 72% of the non-survivors (≥5 points according to the ISTH score) in later stages of COVID-19.
- The median time from admission to DIC manifestation was 4 days (range, 1-12 days). On the contrary, only one (0.6%) survivor matched the DIC criteria during hospital stay.
- The non-survivors had significantly higher D-Dimer and Fibrinogen-derived Proteins (FDP) levels, longer Prothrombin Time (PT) and activated-Partial Thromboplastin Time (aPTT) compared to survivors on admission. By the late hospitalization, the fibrinogen and antithrombin (AT) levels were also significantly lower in non-survivors, suggesting that conventional coagulation parameters abnormalities during course of COVID-19 might be significantly associated with poor prognosis.

The implication of blood coagulation alterations and DIC has been confirmed by another recently published study from China which analyzed clinical and biological data from 201 patients with confirmed COVID-19 pneumonia hospitalized at Jinyintan Hospital in Wuhan, China.[ii]

- About 85.6% of patients demonstrated high levels of sensitive C-reactive protein (CRP). Of the entire cohort, 41.8% of patients developed ARDS (Acute Respiratory Distress Syndrome), and 26.4% were admitted to the intensive care unit (ICU) 33.3% received mechanical ventilation, and 21.9% died.
- Elevated inflammation-related markers (CRP and serum ferritin), and elevated coagulation function–related indicators (PT and D-Dimers) were significantly associated with higher risk of ARDS development.
- The median time from admission to developing ARDS was 2 days (IQR, 1-4days). All of died patients have developed ARDS and received mechanical ventilation.
- Patients with ARDS who died had significant alterations of blood coagulation

biomarkers: increased levels of D-Dimers compared with patients with ARDS who survived (difference, 2.10 µg/mL; 95% CI, 0.89-5.27 µg/mL; p=0.001). The difference in median levels of D-Dimers between the death and survival groups was larger than that between the ARDS and non-ARDS groups, suggesting that DCI was on the pathway to death in some patients.

The importance of hypercoagulability and DIC in the deteriorating process of coronavirus-infected patients has been already reported in the studies performed at the period 2003 – 2005, during the coronavirus with severe acute respiratory syndrome (SARS) disease epidemy.[iii] Increased levels of D-Dimers and aPTT prolongation together with thrombocytopenia were observed in about 45% of affected patients. Post-mortem examinations in SARS patients indicated the presence of vascular fibrin thrombi, pulmonary alveoli capillary microthromboses or thromboembolic bronchial arterioles. [iv] These alterations are mandatory for the presence of a compensated DIC form[v]. Furthermore, patients with severe SARS suffered amplified inflammatory syndrome, which enhances the hypercoagulability, increases the risk of venous thromboembolism (VTE) and/or compensated DIC. Among several hypercoagulability biomarkers tested in SARS patients, increase of plasminogen activator inhibitor 1 (PAI-1) was found to be specific for acute pulmonary manifestation caused by the coronavirus (SARS-CoV) infection implicating de-regulation of fibrinolysis in the deterioration process in SARS-CoV patients.[vi]

All these data, from cohort studies - acknowledging their limitations - lead to the following conclusions:

1. Infection with SARSCoV-2 is associated with intense inflammatory response
2. Hospitalized patients with SARSCoV-2 pneumonia have biological signs of significant hypercoagulability
3. Some of them will develop compensated DIC which will progress to overt DIC within 3-4 days after their hospital admission.
4. High levels of D-Dimers (>1000 ng/ml) are associated with the pneumonia aggravation and evolution to ARDS with worse prognosis
5. High D-Dimers levels as well as low AT levels (acquired antithrombin deficiency) are associated with death
6. Overt DIC is associated with high risk of death (*so called DIC = Death Is Coming*), probably independently of ARDS severity.

This analysis leads us to organize the management of the risk of vascular complications during the hospitalization of COVID-19 patients.

1. Hospitalized patients with pneumonia COVID-19 or SARSCoV-2 have a profile of significant blood hypercoagulability and a high risk of severe vascular complications including DIC and pulmonary embolism (PE). The simulation of VTE risk in COVID-19 "classic" patient using the validated IMPROVE score for medically ill patients (https://www.outcomes-umassmed.org/IMPROVE/risk_score/index.html) shows a minimum rate of symptomatic VTE around 2% whereas the hemorrhagic risk is quite lower. But, taking into consideration the presence of enhanced inflammatory syndrome, a

prothrombotic predictor not included in the score, and prolonged hospital stay the risk of symptomatic VTE is expected to be even higher and routine pharmacological thromboprophylaxis should be administered.[vii] Asymptomatic patients infected with SARS-CoV2 and hospitalized for another reason should also be considered as high risk. for VTE

2. Hospitalized patients with COVID-19 or SARSCoV-2 pneumonia are at high risk of DIC. Early diagnosis and targeted treatment of compensated DIC seems to be a critical component in the management of these patients.
3. Today we do not know
   - if the administration of fixed preventive doses of LMWH in COVID-19 infected patients can attenuate the evolution to overt-DIC
   - to what extent an eventual acquired-AT deficiency could compromise the antithrombotic efficacy such a heparin thromboprophylaxis (LMWH or UFH).
   - the extent of the potential resistance to LMWH or UFH due to non specific binding of heparin chains with plasma proteins related to the inflammatory reaction (i.e. Platelet Factor 4, Neutrophils Extracellular Traps…).

Action plan

A. ***Management of VTE risk***:

All hospitalized patients with confirmed *COVID-19 or* SARSCoV-2 infection - independently of the reason of hospitalization - i.e. COVID-19 pneumonia or any other reason including surgical intervention etc) – should routinely receive pharmacological thromboprophylaxis according to the following therapeutic schema:

1. Cockcroft-Gault *>30 ml/min* : Lovenox® 4000 UI anti-Xa once daily upon admission
2. Cockcroft-Gault *30 - 20 ml/min* : Innohep® 4500 anti-Xa IU/ml
3. Cockcroft-Gault *< 20 ml/min* : Calciparin® 5000 IU twice daily
4. *The score 4T for HIT should be routinely applied* : All patients receiving heparin – from any administration route and any indication - should be considered at risk of Heparin Induced Thrombocypenia because the incidence of this complication in CORVID-19 is absolutely unknown. Probably this risk increases because of the intense inflammatory syndrome and the immunological deregulation provoked by the viral infection.

B. ***Management of DIC***

All hospitalized patients with confirmed COVID-19 should be routinely assessed for DIC according to the following procedure.[5,viii]

1. *ISTH-DIC score for (a)* non-overt (compensated) and (b) overt DIC (Table 1A and B) from the 1st day of hospitalization and every day thereafter
2. Patients at high score (≥5 points) should receive targeted treatment
3. Targeted treatment should be defined together with the Thrombosis group (probably we should set-up a specific group and procedure for the management of COVID19-DIC/VTE)
4. Potential therapeutic options are:
   a. intensification of the antithrombotic treatment in case of thrombotis
   b. correction of AT-deficiency, which among others compromises the efficacy of the treatment with LMWH or UFH
   c. Targeted treatment of overt DIC aiming restoration of clotting factor deficiency, hypofibrinogenemia and thrombocytopenia and adapted antithrombotic treatment.

C. ***Biological evaluation in patients hospitalized for biologique des patients hospitalisés pour COVID-19 aimitn***

1. Early diagnosis and follow up of the DIC
2. Monitoring of the targeted treatments for the DIC
3. Optimisation of the thromboprophylaxis
4. Targeted hemostatic treatment in case of bleeding

Risk assessment: Does the patient have an underlying disorder known to be associated with DIC	**Yes = 2**	**No = 0**
	Evolution	
Major Criteria	***Rising (=-1)***	***Stable (0)***	***Falling (1)***
Platelet count	(give the value)___	(give the value)___	(give the value)___
>100 x10^9/L = 0			
<100 x10^9/L = 1			
PT prolongation	(give the value)___	(give the value)___	(give the value)___
<3 sec = (give the value)____			
>3 sec = (give the value) ____			
Fibrin related marker	(give the value)___	(give the value)___	(give the value)___
Normal = (give the value) ____			
Raised = (give the value) ____			
Specific Criteria			
Antithrombin			
Normal (= -1): (give the value)_____			
Low (= 1): (give the value)_____			
Protein C			
Normal (= -1): (give the value)_____			
Low (= 1): (give the value)_____			
Total score	_____		

Table 1A. Scoring system for non-overt DIC endorsed by International Society on Thrombosis and Haemostasis

		Score

D-Dimers	Strong increase (x 2 – 3) Moderate increase (x1.5) No increase	3 2 0
Platelet count (x G/L)	<50 50 - 100 >100	2 1 0
Fibrinogen level (mg/dl)	<1.0 ≥1.0	1 0
Prothrombin time (sec.)	>6 sec 3 - 6 sec <3 sec	2 1 0

Diagnosis of DIC if score is ≥5 points

Table 1B. Scoring system for overt DIC endorsed by International Society on Thrombosis and Haemostasis

Schedule for laboratory monitoring of blood coagulation biomarkers

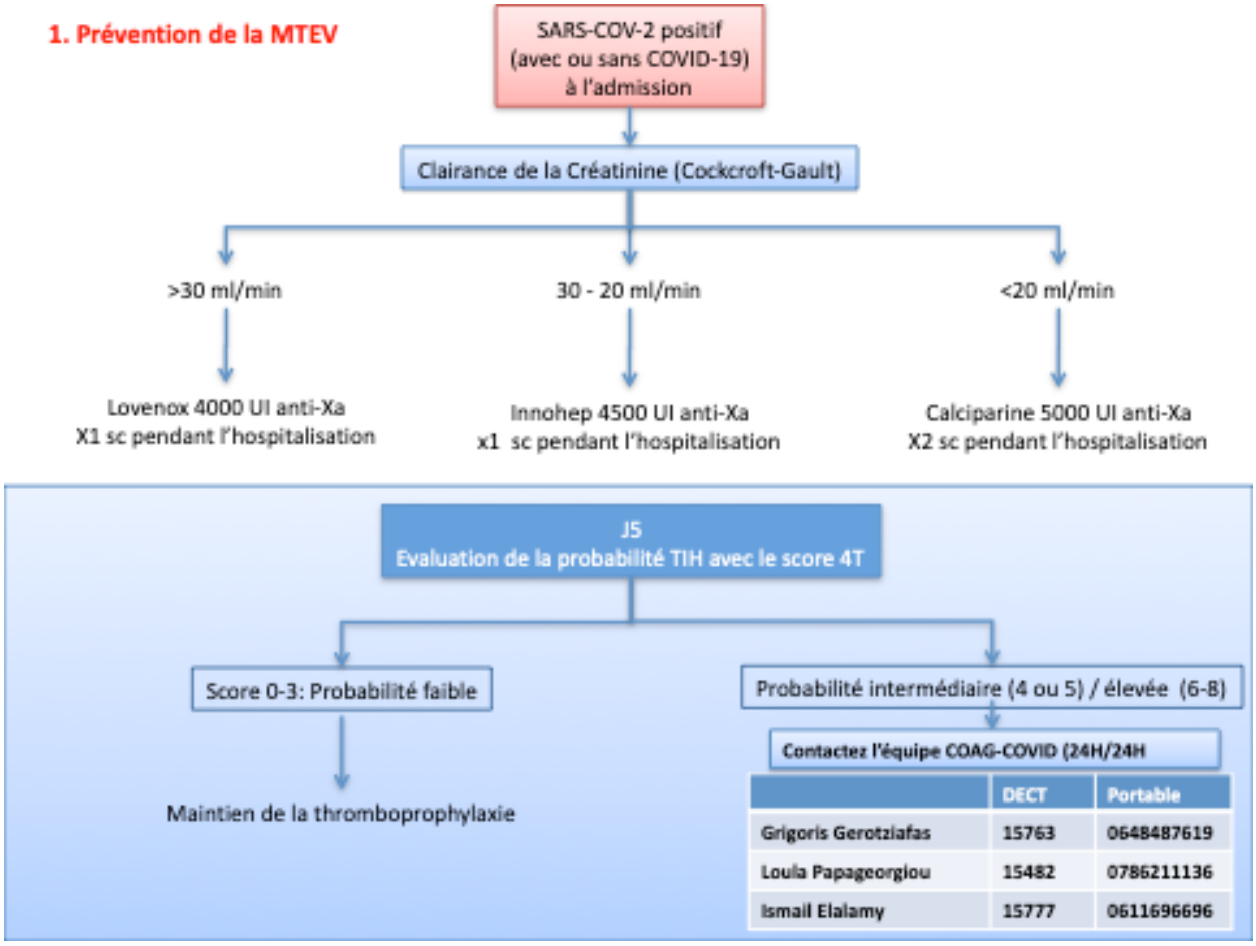
Hematolgical tests	1st day	Daily assessment	On demand for DIC treatment monitoring and bleeding risk evaluation	Timing and laboratory of assessment
Hemogram	X	X		24h/24h 8:00 – 16:00 at the central lab 16:00 – 8:00 at the LBU 1 citrated tube
Platelet count	X	X		
PT	X	X		
INR	X	X		
aPTT	X	X		
Fibrinogen	X	X		
D-Dimers	X	X		
anti-Xa activity		X		
Antithrombin (AT)	X	X		To be discussed according to the context
Protein C (PC)	X	X		
Algorithm for PT, or aPTT or combined PT and aPTT prolongation	X			
ROTEM: INTEM	X		X	
ROTEM: EXTEM	X		X	
ROTEM: FIBTEM	X		X	
ROTEM: diluted	X		X	
Multiplate ASPI-test	X		X	
Multiplate ADP-test	X		X	
Plasma biobank*	X			
DNA-biobank	X			

*Plasma samples from the residual plasma volume will be conserved in -20°C in order to perform translational research aiming to identify specific biomarkers of hypercoagulablity informative for the risk of ARDS and death.

The following biomarkers will be measured by Dr Patrick VanDreden

1. activated tissue factor activé (TFa)
2. Factor VIIa
3. TFPI
4. factor von Willebrand,
5. Factor V
6. Soluble thrombomodulin
7. P-Selectine
8. Procoagulant Phospholipids Clotting Time (PPLct)
9. Neutrophils Extracellular Traps (NETs)
10. Marqueur endothélial (i.e. CD105 et CD135)
11. Metaloproteinase MM9

Algorithmes de gestion du risque de complications vasculaires chez les patients hospitalisés avec une infection par le virus SARS-CoV-2

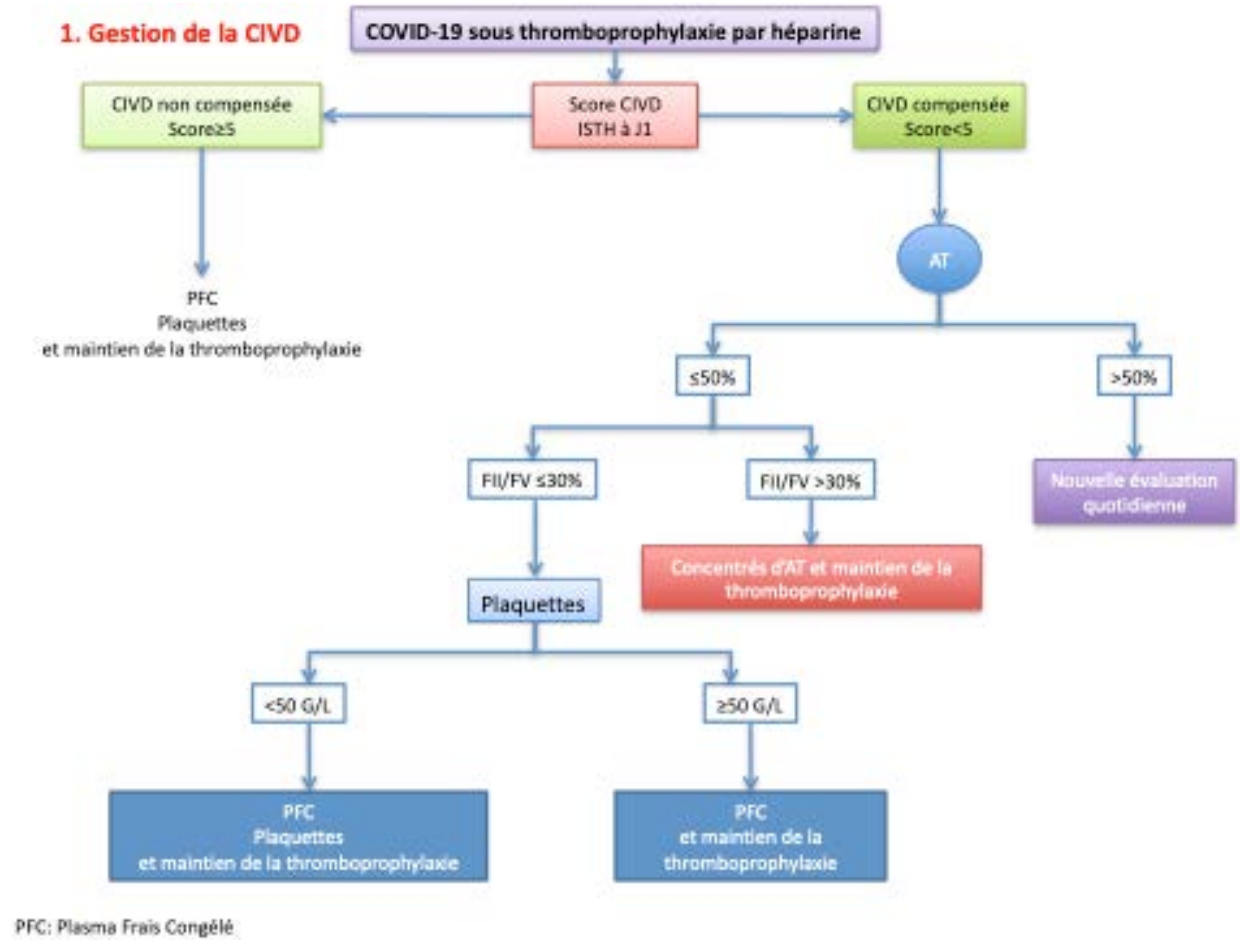


Evaluation de la probabilité de TIH - Score 4T

Nombre de points attribués	0	1	2
Thrombopénie (nadir)	Chute < 30%* ou plaquettes < 10 G/l	Chute 30-50%* ou plaquettes entre 10 et 19 G/L ou diminution de plus de 50% de la numération plaquettaire avec chirurgie récente (3 derniers jours)	Chute > 50%* Ou plaquettes nadir >20G/L sans chirurgie dans les 3 jours précédents
" Timing" Délai de survenue de la thrombopénie	Thrombopénie survenant avant 4 jours de traitement et sans héparinothérapie dans les 100 jours précédents	Chute de la numération plaquettaire après plus de 10 jours de traitement ou dans un délai de 24h si héparinothérapie semi récente (31 à 100 jours)	Thrombopénie (ou thrombose) survenue 5 à 10 jours après le début du traitement ou dans un délai de 24h s'il existe un traitement antérieur par héparine dans les 5 à 30 jours précédents
Thromboses ou autres complications	Aucun évènement	Récidive ou extension de la thrombose existanteoususpicion d'une nouvelle thrombose en attente de confirmationou un érythème cutané après injection d'héparin	Nouvelle thrombose veineuseou artérielle (confirmée)ou nécrose cutanéeou réaction systémique après injection d'héparine en bolus (HNF) ou hémorragie des surrénales
Autre cause de thrombopénie	Autres causes probables de thrombopénie: Chirurgie dans les 72h- Infection confirmée- Chimio ou radiothérapie dans les 20 jours précédents- CIVD due à une autre cause- Purpura post transfusionnel- Plaquettes <20G/L probablement d'origine médicamenteuse	Autres causes possibles de thrombopénie :- Sepsis sans confirmation microbiologique- Thrombopénie associée à une ventilation mécanique- Autres	Aucune autre cause possible de thrombopénie
Total			

* Par rapport à la numération plaquettaire avant l'administration de l'héparine

https://www.gemmat-thrombose.fr



PFC: Plasma Frais Congélé

Score ISTH CIVD compensée

Paramètre	Variation	Score
D-Dimères	Augmentation forte (x2-3)	3
	Augmentation modéré (x1.5)	2
	Pas d'augmentation	0
Plaquettes (G/L)	<50	2
	50 - 100	1
	>100	0
Fibrinogène (mg/dl)	<1.0	1
	≥1.0	0
Taux de prothrombine ou Temps de Quick (sec.)	>6 sec	2
	3 - 6 sec	1
	<3 sec	0

Aclotine (AT III) POSOLOGIE

- Une unité internationale (UI) d'antithrombine humaine est équivalente à la quantité d'antithrombine présente dans 1 mL de plasma humain normal. Le taux normal est du 70-100% (en moyenne de 100 %-VIDAL).
- L'administration de 1 UI/kg d'antithrombine humaine augmente le taux circulant d'environ 2 % dans les déficits constitutionnels, en dehors d'une période de thrombose.
- La dose administrée et la fréquence des injections seront adaptées en fonction de l'efficacité clinique et du taux d'antithrombine observés.
- **Un taux circulant d'antithrombine de 70 %** doit être maintenu pendant toute la durée du traitement.
- Déficit acquis sévère : en traitement curatif : **dose initiale de 40 à 50 UI/kg, à100 UI/kg.**
- Les doses ultérieures, la fréquence des injections et la durée du traitement seront adaptées à l'état clinique et au suivi biologique.

Equipe COAG-COVID
Disponible 24h/24h

	DECT	Portable
Grigoris Gerotziafas	15763	0648487619
Loula Papageorgiou	15482	0786211136
Ismail Elalamy	15777	0611696696

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