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Original article

Prevention and treatment of COVID-19-associated hypercoagulability: Recommendations of the Algerian society of transfusion and hemobiology



Prévention et traitement de l'hypercoagulabilité associée à la COVID-19 : recommandations de la Société algérienne de transfusion et d'hémobiologie

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ABSTRACT

Since December 2019, an outbreak of coronavirus disease 2019 (COVID-19) in Wuhan, China, has spread throughout the world. Coagulation dysfunction is one of the major causes of death in patients with severe COVID-19. Several recent observations in Algeria and elsewhere maintain that a pulmonary embolism is frequent in patients with COVID-19 with a high incidence in intensive care. In addition, other studies have shown that many deceased patients have diagnostic criteria for disseminated intravascular coagulation (DIC) set by the International society of hemostasis and thrombosis (ISTH). The office of the Algerian society of transfusion and hemobiology composed of hemostasis and blood transfusion experts from Algerian hospitals on the epidemic front line have established a consensus on the issue through 4 axes: Indication of thromboprophylaxis, monitoring of hemostasis, indications of transfusion in the event of disseminated intravascular coagulation (DIC) and anticoagulant treatment after discharge.

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RÉSUMÉ

Depuis décembre 2019, un nouveau type de maladie à coronavirus (COVID-19) est apparu à Wuhan en Chine et s'est propagé dans le reste du monde. Les anomalies de la coagulation représentent l'une des principales causes de mortalité chez les patients atteints de la COVID-19. Plusieurs observations récentes en Algérie et ailleurs soutiennent qu'une embolie pulmonaire est fréquente chez les patients atteints de la COVID-19 avec une incidence élevée en réanimation. Aussi, d'autres études ont montré que de nombreux patients décédés avaient des critères diagnostiques de coagulation intravasculaire disséminée (CIVD) fixés par la Société internationale d'hémostase et thrombose (ISTH). Le bureau de la Société algérienne de transfusion et d'hémobiologie (SATH), composé d'experts en hémostase et en transfusion sanguine issus d'hôpitaux en ligne de front épidémique en Algérie, ont établi un consensus sur la question à travers 4 axes principaux : indication de la thromboprophylaxie, surveillance biologique de l'hémostase, indications de la transfusion en cas de coagulation intravasculaire disséminée (CIVD) et traitement anticoagulant après sortie.

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1. Introduction

Since December 2019, a new type of coronavirus disease (COVID-19) has appeared in Wuhan, China and has spread to the rest of the world [1].

The association between COVID-19 and hypercoagulability is now widely recognised. About 20% of infected patients have abnormal hemostasis results [2]. Also, these abnormalities are present in almost all patients in severe or critical conditions and represent for them one of the main causes of mortality [3].

Several recent observations in Algeria and elsewhere support that pulmonary embolism is common in patients with COVID-19 with a high incidence in intensive care.

In a recent Dutch study, in 184 critically ill patients, the cumulative incidence of venous thromboembolism (VTE) was 27% with a majority of pulmonary embolism despite all patients where under prophylactic doses of low molecular weight heparin (LMWH) [4]. Thus, the stratification of the thrombotic risk by using clinical and biological criteria becomes essential to adapt the thromboprophylaxis to each case.

Also, other studies have shown that many deceased patients had diagnostic criteria for disseminated intravascular coagulation (DIC) set by the International Society of Hemostasis and Thrombosis (ISTH) [5].

Anticoagulant treatment help prevent thromboembolic complications by maintaining a state of hypocoagulability. Among the main treatments used, we have heparins which potentiate the

action of antithrombin in inhibiting activated coagulation factors: IIa, Xa, IXa, XIa and XIIa.

In this manuscript written by the Algerian Society of Transfusion and Hemobiology (SATH), we summarise the recommendations of a few international societies, then we establish a consensus around the question by taking into consideration the local specificities including those related to the availability of certain anticoagulants and their registration in the Algerian nomenclature of drugs. The recommendations were based on 4 main axes: Indication of thromboprophylaxis, biological monitoring of hemostasis, indications for transfusion in the case of DIC and anticoagulant treatment after discharge.

2. Indications for thromboprophylaxis and dosage

The summary of 3 recommendations is presented in Table 1.

The Fondaparinux is not registered in the Algerian nomenclature of drugs in date of December 31, 2019.

2.1. SATH recommendations

All hospitalised patients with COVID-19 should receive LMWH thromboprophylaxis unless the risk of bleeding is greater, such as in cases of thrombocytopenia with a blood platelet count less than $50 \times 10^9/L$, thrombopathy, history of bleeding episodes, coagulation factor deficiency or a stroke in the last 3 months.

Table 1

Anticoagulant therapy in COVID-19 according to the American, French and international hemostasis and thrombosis societies.

Recommendations	Anticoagulant therapy
American society of hematology (ASH) [6]	<ul style="list-style-type: none"> –Indication: all hospitalised patients should receive it unless the risk of bleeding outweighs the risk of thrombosis –Anticoagulant: LMWH or fondaparinux in case of a history of heparin induced thrombocytopenia (HIT) –Posology: prophylactic doses or intermediate doses in clinical trials –Dosage adjustment according to weight –Therapeutic doses for critical cases characterised by a very high D-dimer level, a marked inflammatory syndrome and/or multi-organ failure –In the event of catheter thrombosis or ECMO, the dose of anticoagulant is to be increased step by step: from the prophylactic doses to the intermediate doses and from the intermediate doses to the therapeutic doses –Adjustment in renal failure: unspecified
International society of thrombosis and hemostasis (ISTH) [7]	<ul style="list-style-type: none"> –Indication: reserved for hospitalised patients with respiratory distress or added risk factors for thrombosis, bed rest and those requiring intensive care except in the event of a proven risk of bleeding –Anticoagulant: LMWH –Posology: prophylactic doses once daily –Dosage adjustment according to weight –Therapeutic doses: recommended by a minority of the panel on a case-by-case basis
Groupe français d'études sur l'hémostase et la thrombose (GFHT) and the Groupe d'intérêt en hémostase périopératoire (GIHP) [8]	<ul style="list-style-type: none"> –Adjustment in renal failure: unspecified –Indication: all hospitalised patients should receive it –Anticoagulant: LMWH or fondaparinux –Posology: prophylactic doses once daily (e.g. Enoxaparin 4000IU/24 h by SC injection and 2000IU/24 h by SC injection if CrCl from 15 to 30 mL/min) –Dosage adjustment according to weight ($BMI > 30 \text{ kg/m}^2$): in absence of added risk factors for thrombosis: Enoxaparin 4000IU/12 h SC or 6000IU/12 h SC if weight $> 120 \text{ kg}$ and UFH 2000IU/Kg/24 h if CrCl $< 30 \text{ mL/min}$; in the presence of added risk factors for thrombosis or artificial ventilation: therapeutic doses –Therapeutic doses in case of recurrent catheter thrombosis, ECMO, obesity with added risk factors of thrombosis, D-dimers level $> 3 \mu\text{g/mL}$, fibrinogen level $> 8 \text{ g/L}$: LMWH: e.g. Enoxaparin 100IU/kg/12 h SC without exceeding 10,000 IU/12 h UFH: 500 IU/kg/24 h if creatinine clearance (CrCl) $< 30 \text{ mL/min}$ and in case of ECMO also

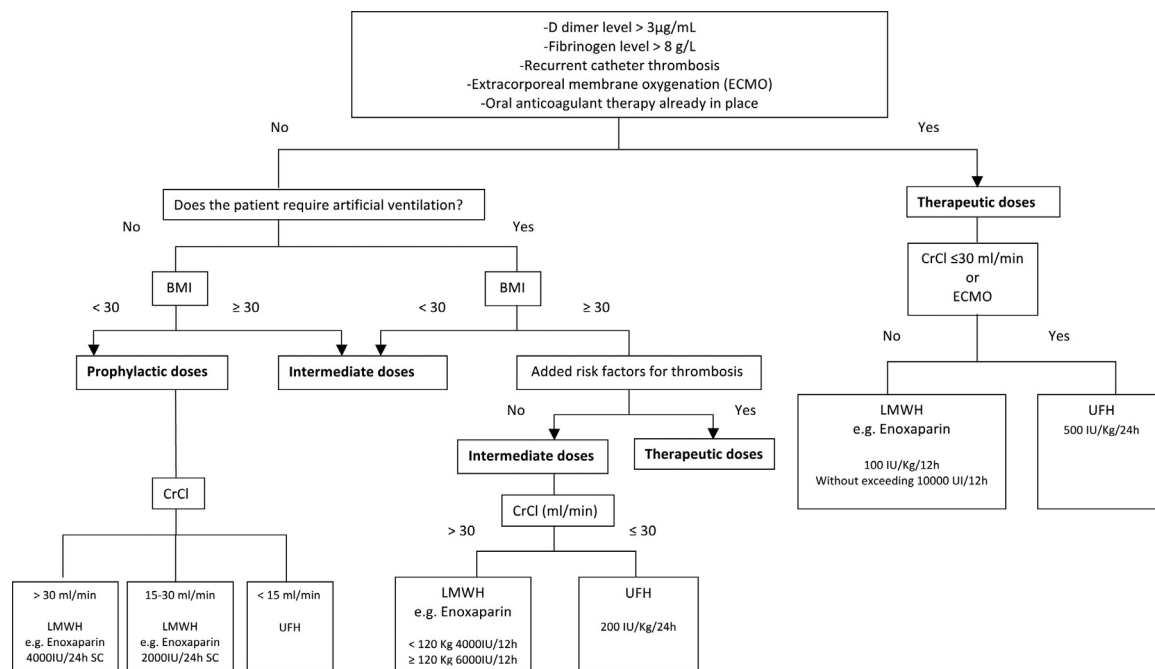


Fig. 1. Decision algorithm for the prevention of thrombotic risk in hospitalised patients with COVID-19. Recommendations of the Algerian society of transfusion and hemobiology. CrCl: creatinine clearance; LMWH: low molecular weight heparin; UFH: unfractionated heparin; BMI: body mass index.

In this situation, mechanical thromboprophylaxis should be considered by intermittent pneumatic compression.

The dosage of LMWH consists of a prophylactic dose once per day [e.g. Enoxaparin 4000 IU/24 h by subcutaneous injection (SC) and 2000 IU/24 h SC if creatinine clearance (CrCl) is 15 to 30 mL/min]. An adjustment should be made for weight when the BMI is > 30 kg/m². Thus, in the absence of an added risk factor for thrombosis, Enoxaparin 4000 IU/12 h SC or 6000 IU/12 h SC is given if the weight exceeds 120 kg or UFH 200 IU/kg/24 h in the event of CrCl < 30 mL/min.

In the event of obesity with added risk factors for thrombosis or with artificial ventilation and also in the event of catheter thrombosis, ECMO, D dimers level > 3 µg/mL, marked inflammatory syndrome (fibrinogen > 8 g/L), therapeutic doses are recommended either of LMWH (e.g. Enoxaparin 100IU/kg/12 h SC without exceeding 10,000 IU/12 h) or UFH 500IU/kg/24 h in case of ECMO or CrCl < 30 mL/min.

Also, in the event of oral anticoagulant treatment already initiated before infection, we recommend a relay with heparins at therapeutic doses.

The Fig. 1 illustrates the decision algorithm for the indications of anticoagulants and dosage adjustment according to different clinical and laboratory criteria.

3. Biological monitoring of hemostasis

The minimum admission assessment should relate to the following hemostasis parameters: the platelet count, the prothrombin time (PT), the activated partial time thromboplastin (aPTT), the fibrinogen and the D dimers. The assessment should be renewed regularly depending on the patient’s clinical condition.

In the event of elevation of D dimers at a level > 3 µg/mL, therapeutic doses of LMWH or UFH should be instituted taking into account the risk of bleeding.

In the event of a decrease in the level of platelets and fibrinogen, a DIC should be researched using the ISTH score of DIC based on the

PT, the level of fibrinogen, the level of D dimers or fibrin degradation products (FDP) and the platelet count. After confirmation of DIC, anticoagulant treatment must be readjusted given the risk of bleeding.

When initiating heparin therapy, the platelet count should be regular twice per week for up to 21 days and then once per week to screen for possible heparin induced thrombocytopenia (HIT) appearing most likely between the 5th and the 10th of treatment increasing the risk of thromboembolism. The diagnosis is suspected by a high 4T score and confirmed by the presence of anti PF4-heparin antibody and platelet activation in the presence of heparin by the platelet aggregation test.

Patients on prophylactic doses do not require special biological monitoring of their treatment. However, patients on intermediate doses (4000 IU or 6000 IU/12 h) and those on therapeutic doses of LMWH should be monitored with an anti-Xa activity target < 1.2 IU/mL in order to avoid overdose. Under UFH, the anti-Xa activity must be between 0.3 and 0.5 IU/mL for the intermediate doses and between 0.5 and 0.7 IU/mL for the curative doses or the TCA ratio between 2 and 3.

4. Indication for transfusion for COVID-19-associated DIC

The summary of 2 recommendations is presented in Table 2.

4.1. SATH recommendations

The diagnosis of DIC is made using the ISTH DIC score. The decision to transfuse should not be guided by biological criteria alone, but reserved for hemorrhagic syndromes or a situation at risk of bleeding.

In adult patients with COVID-19-associated DIC presenting with bleeding or candidates for an invasive procedure, platelet transfusion should be performed (3 to 6 × 10¹¹) if the platelet count is < 50 × 10⁹/L, 15 to 25 mL/kg of fresh frozen plasma (FFP) if the

Table 2
Indication of transfusion in case of COVID-19-associated DIC.

	American Society of Hematology (ASH) [6]	International Society of Thrombosis and Hemostasis (ISTH) [7]
Diagnosis of DIC	ISTH score	ISTH score
Indications	Not instituted on the basis of laboratory results alone but reserved for those with active bleeding or who are otherwise at high risk of bleeding complications	Not instituted on the basis of laboratory results alone but reserved for those with active bleeding or who are otherwise at high risk of bleeding complications
Platelet transfusion	1 Apheresis Platelet Concentrate (APC) if the platelet count is less than $50 \times 10^9/L$	1 APC if the platelet count is less than $50 \times 10^9/L$ in case of active bleeding and if less than $20 \times 10^9/L$ in case of invasive procedure
Fresh frozen plasma transfusion	4 fresh frozen plasma (FFP) if INR is above 1.8	15 to 25 mL/kg of FFP in case of bleeding with PT and/or aPTT ratio > 1.5
Transfusion in case of fibrinogen deficiency	4 g of fibrinogen concentrate or 10 units of cryoprecipitate if the fibrinogen level is less than 1.5 g/L	Fibrinogen or cryoprecipitate if the fibrinogen level is less than 1.5 g/L

PT ratio is > 1.5 and fibrinogen or cryoprecipitate if the fibrinogen level is < 1.5 g/L.

5. Anticoagulant treatment after discharge

It is recommended to continue anticoagulant treatment with LMWHs at prophylactic doses or with direct oral anticoagulants for up to 45 days in patients with added risk factors for thrombosis: e.g. prolonged immobilisation, age > 70 years, history of VTE, comorbidity (cancers +++), D dimers > 2 times the normal rate (threshold adjusted according to age [9]).

6. Conclusion

The thrombotic manifestations are particularly feared complications in patients with COVID-19. The use of anticoagulants and transfusion therapy must take into account the haemostatic balance between the risk of bleeding and the risk of thrombosis.

Close collaboration between hemobiologists and clinicians should allow effective prevention of thrombotic risk in these patients.

Disclosure of interest

The authors declare that they have no competing interest.

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