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Management of COVID-19 associated Coagulopathy in Persons with Haemophilia

Interim Guidance on behalf of the Coagulation Products Safety, Supply and Access (CPSSA) Committee of the World Federation of Hemophilia[1]

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Abstract

Introduction: The SARS-CoV-2 coronavirus induced infection (COVID-19) can be associated with a coagulopathy mainly responsible for pulmonary microvasculature thrombosis and systemic thromboembolic manifestations. The pathophysiology and management of the COVID-19 coagulopathy are likely more complex in patients with inherited bleeding diseases such as haemophilia. These individuals might indeed present with both bleeding and thrombotic complications and require simultaneous antithrombotic and haemostatic treatments.

Objective: We propose practical guidance for the diagnosis and management of COVID-19 coagulopathy in persons with haemophilia.

Results: Continuation of regular haemostatic treatment is recommended for ambulatory patients. For patients requiring hospital admission and on replacement therapy with factors VIII or IX concentrates, prophylaxis with concentrates should be intensified according to the risk of bleeding complications and associated with prophylactic doses of LMWH. For patients on non-replacement therapy, emicizumab should be continued and possibly combined with factor VIII and prophylactic doses of LMWH depending on the risk of bleeding and thrombosis. Dose escalation of LMWH tailored to the risk of thrombosis can be employed but not supported by evidence.

Conclusions: These practical recommendations are based on the current literature on COVID-19 with its impact on haemostasis, indications and modalities for thromboprophylaxis mainly in non-haemophilic patients and how that is likely to affect persons with haemophilia in different circumstances. They will need to be tailored to each patient's clinical status and validated in future studies.

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Introduction

The coronavirus disease 2019 (COVID-19) caused by the novel coronavirus (SARS-CoV-2) is continuing its spread globally [1]. Given the absence of prior immunity to this viral infection, it is to be expected that persons with haemophilia (PWHs) will be impacted by this illness [2]. Indeed, the global haemophilia community is dealing with new challenges to ensuring continued access to haemophilia treatments including maintenance of product supply chains, impact of reduced blood and plasma donations, reduced access to health care facilities and hemophilia treatment centers, postponement of elective surgeries, and negative impacts to clinical research programs. In addition, the cancellation of many in person educational and research exchanges risks compromising the advancement and dissemination of important knowledge about the care of haemophilia and, in particular, guidance on the management of complications from COVID-19 [2].

To date, there is a paucity of publications on the clinical experience of PWHs and COVID-19 [3-7]. There is no information to suggest that PWHs, including those on prophylaxis with traditional replacement therapy or emicizumab, are at increased risk for infection or for more severe disease unless they have additional well-described co-morbidities such as older age (>65 years), pulmonary or cardiovascular disease, hypertension, obesity or diabetes mellitus.

However, we now have emerging characterization of a COVID-19 associated coagulopathy (CAC), whose management requires special consideration in PWHs. While many PWHs will develop mild or moderate symptoms of COVID-19, a proportion of those infected go on to exhibit severe inflammatory responses associated with acute lung injury, hypoxemic respiratory failure

and related mortality. Thromboinflammation describes the interplay between inflammation and coagulation and is now considered a key driver of this pathology [8-10]. Those with severe COVID-19 exhibit coagulation abnormalities including increases in procoagulant levels (especially factor VIII, von Willebrand factor, fibrinogen) and elevated D-dimer concentrations, a well-characterized biomarker for thrombotic complications [11]. The concomitant presence of this CAC at presentation and progression over the course of hospitalization has been associated with worsening respiratory status and higher mortality [12]. Notably, this coagulopathy has some features of sepsis-induced coagulopathy/disseminated intravascular coagulopathy (DIC), but the hemorrhagic phenotype typical of hyperfibrinolytic consumptive DIC, is rare. Therefore, new terminologies have been created to recognize this unique alteration in haemostasis such as CAC.

A common finding is an elevation of the D-dimer concentrations even found in ambulant patients with no clinically obvious or investigation supported thrombosis. This elevation seems to be mainly secondary to intra-pulmonary microvascular thromboses, a frequent manifestation of CAC, initially documented in autopsy studies and more recently in antemortem imaging using the dual energy computed tomography (DECT) technology [13-16]. The clinical experience has also indicated an increased risk of more common thromboembolic complications in the outpatient setting as well as in hospitalized patients with venous thromboembolism, pulmonary emboli, ischemic limbs and stroke events [11]. This has prompted consensus guidance on coagulation test surveillance, thromboprophylaxis, choice of anticoagulants and intensity of dosing. Though these guidelines and recommendations will need to be tested and even adapted based on clinical studies, their implementation poses special challenges to PWHs.

Previous communication from the WFH COVID-19 Task Force highlighted these coagulation abnormalities with COVID-19 and directed attention toward the need for close laboratory monitoring, the need for factor replacement therapy to facilitate the use of anticoagulants for prophylaxis or treatment, and special considerations for patients on concomitant prophylaxis with emicizumab. The current guidance seeks to expand on the prior guidance based on emerging data on the mechanisms of thromboinflammation with COVID-19 and current approaches in use for the management of hospitalized non-haemophilia patients. We provide consensus recommendations on management of hospitalized PWHs with special considerations regarding hemostatic correction with concurrent anticoagulation and/or intensive care procedures, and updated details regarding management with concurrent use of emicizumab.

Current understanding of mechanisms of thrombo-inflammation with COVID-19

Review of the emerging data on the mechanisms of thrombo-inflammation with COVID-19 have identified the following [11;14]:

- Exaggerated inflammatory response to the pulmonary alveolar injury characterized by procoagulant effectors
    - inflammatory cytokines (eg. IL-6) lead to activation of vascular endothelial cells and endothelial injury
    - components of neutrophil extracellular traps (NETs), present in thrombi, activate the contact pathway and enhance procoagulant pathways resulting in increased thrombin generation
    - polyphosphates activate platelets, mast cells and factor XII in the contact pathway amplifying the intrinsic pathway of coagulation

- serine protease inhibitors (antithrombin, protein C, C1 esterase inhibitor) are decreased
- fibrinolysis is impaired due to elevated PAI-1 levels [11;14]

Another unique aspect of the pathology of this infection is an endothelialopathy that appears to contribute to the microvascular changes that occur with COVID-19 [15;17]. SARS-CoV-2 gains access to cells through the angiotensin-converting enzyme (ACE) 2 that is present on endothelial cells [18]. Ensuing inflammatory cell infiltration, endothelial cell apoptosis and microvascular prothrombotic effects lead to microcirculatory dysfunction and the subsequent clinical sequelae in patients with advancing severe disease.

Current approaches for management of hospitalized non-hemophilia patients with COVID-19

Guidance on the recognition, monitoring and management of CAC has been provided from the ISTH [19], American Society of Hematology [20], and the American College of Cardiology [21] and many others. These recommendations have been taken into account and summarized as follows:

<u>Recognition and Monitoring of COVID-19 Associated Coagulopathy</u>

1. Coagulopathy shows elevated fibrinogen, factor VIII, VWF, elevated D-dimers, with minimal change in prothrombin time (PT), activated partial thromboplastin time (aPTT), and platelet count in early stages of infection
2. Increasing IL-6 levels directly stimulate increasing fibrinogen levels

3. Coagulopathy appears to be related to severity of illness and resultant thromboinflammation and not the intrinsic viral activity
4. Increased D-dimer is the most significant change in coagulation parameters in COVID-19 patients and occurs more frequently than disturbances of other coagulation parameters (PT, aPTT)
5. Elevated D-dimer levels on admission are associated with increased mortality
6. Rising D-dimer after admission precedes multiorgan failure and overt DIC
    a. Noted to start at 4 days after admission in non-survivors
    b. Longer duration of hospital stay is associated with increasing D-dimer and development of sepsis physiology
7. A sudden marked decrease in plasma fibrinogen to concentration less than 1.0 g/L suggestive of disseminated intravascular coagulation with enhance fibrinolysis has been observed shortly before death in a number of patients with COVID-19 in China [22].
8. A significant reduction of the platelet count, fibrinogen or antithrombin levels, most frequently associated with DIC, have not been frequently described in patients with COVID-19
9. Bleeding manifestations are not common despite the coagulopathy [19-21;23]. In a recent large study, the overall and major bleeding rates were close to 5 and 2 %, respectively [23].

Suggested approaches to COVID-19 patients and coagulopathy.

All admitted patients should have baseline coagulation work-up including PT, aPTT, fibrinogen, D-dimer, and platelet count. Following changes in these values can give important information regarding status of the coagulation system and safety of using anticoagulation (Table 1). Risk for thrombosis should be assessed in all patients.

Several studies have shown among COVID-19 infected ICU patients an increased rate of venous thrombo-embolism (VTE) [24;25], the presence of pulmonary microthrombosis and a generalized inflammatory response of the endothelium possibly causing fatal organ failure.

As recommended by recent consensus guidelines, standard weight-based prophylactic anticoagulation with low molecular weight heparin (LMWH) should be offered as early as possible to prevent thrombotic events and organ damage in all patients with COVID-19 infection requiring hospital admission, including the noncritically ill, unless contra-indicated. Anticoagulant options include LMWH, unfractionated heparin (UFH) and fondaparinux. Direct oral anticoagulants should not be considered because of possible interactions with antiviral therapeutics [21]. LMWH, besides their anticoagulant properties, may exert an anti-inflammatory effect and attenuate in part the 'cytokine storm' induced by the virus [26].

Although the concept of using LMWH in hospitalized COVID-19 patients is accepted, there is a debate about the dosage to be employed. Thromboses have been reported despite low-dose prophylactic use of LMWH so that dose escalation of LMWH has been recommended either empirically or based on increasing D-dimers values.

Although there is currently limited data supporting that the dosing should be intensified in some patients, several national and scientific society guidance documents suggest therapeutic

anticoagulation in patients with respiratory compromise and features of CAC particularly if associated with highly elevated D-dimer levels based on the data available so far from uncontrolled studies showing improved outcomes with such interventions in such patients [27-29]. This approach would aim at treating 'presumed' microvascular thrombosis as suggested by correlations between coagulation markers and pulmonary pathology findings.

Several randomized control trials evaluating different anticoagulation modalities are ongoing including the RAPID COVID COAG trial that aims at determining the effect of therapeutic anticoagulation (with LMWH or UFH) compared to standard care in hospitalized patients with COVID-19 and an elevated D-dimer on the composite outcome of intensive care unit (ICU) admission, non-invasive positive pressure ventilation, invasive mechanical ventilation or death at 28 days [30].

While no data specific to COVID-19 exist, it is reasonable to consider extended thromboprophylaxis after hospital discharge for selected patients with elevated risk of VTE and low risk of bleeding [21].

While routine use in outpatients is not recommended, use in immobile infected outpatients, especially with other increased risks for VTE, can be considered on a case by case basis based on severity of illness or as incorporated into local practice.

Special considerations for PWHs

Haemophilia is characterized by a defect in thrombin generation with resultant reduced fibrin formation. In the case of haemophilia A, there are also no marked elevations of factor VIII with underlying inflammation. Therefore, it is possible that this could blunt the severity of the impact

of CAC in persons with both haemophilia A. However, many of the mechanisms described above, including the impact of endothelial injury leading to microvascular dysfunction are not solely dependent on thrombin generation. Further, the defective thrombin generation in haemophilia is modulated by prophylactic therapy with clotting factor concentrates or emicizumab, or can be transiently corrected as needed for bleeding, invasive procedures or to facilitate anticoagulation. Accordingly, a PWH and a COVID-19 infection with its risk for CAC, poses unique management challenges for those requiring admission to the hospital. PWHs with moderate to severe COVID-19 infection necessitating admission should be transferred to a haemophilia treatment center affiliated hospital capable of on-site factor assays as well as other specialized assays like bovine chromogenic factor VIII assay if on emicizumab.

The consensus guidance that follows seeks to provide recommendations on considerations for recognizing and monitoring for CAC, recommendations for hemostatic correction around invasive procedures, anticoagulation and include special considerations for those on emicizumab prophylaxis.

Considerations for recognition and monitoring for COVID-19 Associated Coagulopathy in PWHs

1. We recommend using standard laboratory assays for recognition and monitoring for CAC with these considerations (Table 2):
    a. The PT, fibrinogen and D-dimer assays are not affected by underlying haemophilia or concomitant treatment with clotting factor replacement therapy.

b. The aPTT needs to be evaluated in the context of recent replacement therapy and is typically within the normal range with most reagents, with factor VIII or IX levels above 30-40%.

c. Patients with mild haemophilia A might display increased or high FVIII levels during the inflammatory response of COVID-19. Factor VIII levels should be checked prior to start any therapy in mild haemophilia A patients and historical levels not trusted.

d. D-dimer levels are not typically increased in haemophilia except in the context of significant concurrent bleeding [31] or patients receiving intensified therapy with bypassing agents [32]). Neither are there reported observations of elevated D-dimer in patients on prophylaxis with emicizumab (G. Levy, personal communication). Therefore, we recommend that D-dimers be measured in all patients regardless of their prophylactic therapy upon admission and followed regularly during hospital admission and with any clinical deterioration.

e. The aPTT is highly sensitive to emicizumab and is consistently and erroneously within the normal range for patients on all dosing regimens and should not be utilized in this context [33].

f. When interpreting prolonged aPTT, possible interference with a lupus anticoagulant, reported to be associated with COVID-19, should be excluded [34;35].

2. Standard thromboprophylaxis

a. We do not recommend routine thromboprophylaxis in hemophilia regardless of prophylactic therapy for those with mild/moderate COVID-19 who are able to be managed in the outpatient setting (Table 3).

b. Thromboprophylaxis should be considered for PWH without inhibitor if their COVID-19 illness requires admission to hospital because of respiratory insufficiency [as per local institutional/national guidelines] after discussion of the bleeding and thrombotic risks with the patient and family. Thromboprophylaxis should be associated with replacement therapy targeting factor VIII or IX levels sufficient to prevent bleeding complications (spontaneous or related to invasive procedures) but not aggravating the risk of thrombosis.

   i. LMWH is preferred over UFH due to the reduced intensity of laboratory monitoring for quarantined patients, ease of administration and reduced risk of heparin-induced thrombocytopenia.

   ii. We recommend initiating or continuing prophylactic therapy to facilitate anticoagulation

      1. *For hemophilia A*: maintenance of factor VIII activity targeting trough levels of at least 30% while avoiding peaks above 100%
      2. *For hemophilia B*: maintenance of factor IX trough activity levels of at least 30%. Avoidance of high peak corrections of factor IX above 80% is recommended given the likelihood of markedly elevated factor VIII levels in this patient population.

   iii. We do not recommend additional factor VIII replacement therapy for patients who are at steady state prophylaxis with emicizumab as there is

anecdotal experience supporting that the level of hemostatic protection with emicizumab can at least support standard anticoagulation without significant bleeding risk [36].

c. Thromboprophylaxis should be considered for PWHs with inhibitor if on emicizumab prophylaxis (Table 4)

    i. We do not recommend regular prophylactic use of bypassing agents in order to facilitate anticoagulation for thromboprophylaxis. In particular, use of activated prothrombin complex concentrates (aPCC) with emicizumab has been associated with cases of thrombotic microangiopathy and thrombotic events, therefore the benefit/risk should be carefully considered and preferably avoided if at all possible.

    ii. We do not recommend thromboprophylaxis in haemophilia with inhibitor for those who are not on emicizumab prophylaxis

3. Escalated dose thromboprophylaxis or confirmed VTE (Tables 3 and 4)

    a. There is currently no evidence supporting that thromboprophylaxis should be intensified for PWHs if they require ICU care and particularly with clinical features of acute respiratory distress syndrome or increasing D-dimers concentrations. Given the current uncertainty, the decision to escalate thromboprophylaxis should be left to local policies until evidence provided by randomized trials appears.

    b. Full dose anticoagulation should be used if confirmed or strongly suspected VTE/PE or arterial thrombotic event or when intrapulmonary microvascular thromboses have been detected by highly specialized CT angiogram [37]. See

below for recommendations for hemostatic prophylaxis to facilitate full dose anticoagulation.

i. LWMH should be preferred over UFH because of its easier once or twice daily subcutaneous administration and reduced risk of heparin-induced thrombocytopenia. Monitoring should be conducted by anti-Xa assay. Dose adaptation is required in patients with renal insufficiency.

ii. We recommend continuing hemostatic prophylaxis with the following considerations:

1. *For hemophilia A*: maintenance of factor VIII activity within 50 and 100 %.
2. *For hemophilia B*: maintenance of factor IX activity levels between 50 and 80 %. Avoidance of high peak corrections of factor IX is recommended given the likelihood of markedly elevated factor VIII levels in this patient population.
3. *For hemophilia A on emicizumab*: consider addition of factor VIII replacement with maintenance of factor VIII activity levels (as determined by bovine chromogenic factor VIII assay) of at least 50-80%. In comparison with emicizumab, factor VIII appears to present desirable features for the management of COVID-19 coagulopathy in persons with haemophilia A (table 5).

4. There is emerging evidence for thrombotic complications in patients with COVID-19 and seemingly milder or absent pulmonary manifestations (“COVID toes”, stroke) even while under care in the community. These have not been reported in hemophilia patients to date

including those on emicizumab prophylaxis. Although we recommend continued vigilance with such symptomatology, there is no basis for which to recommend making changes to hemophilia treatment based on these reports.

Considerations for Recognition and Monitoring for COVID-19 Associated Coagulopathy in PWHs on Investigational Agents

There is a number of investigational agents that treat hemophilia by rebalancing hemostasis. These include fitusiran (RNA interference knockdown of antithrombin) [38], monoclonal antibodies that block tissue factor pathway inhibitor (TFPI) [39;40] and SerpinPC, an engineered serine protein inhibitor that targets activated protein C [41]. Some of these agents have moved to phase 3 clinical trials, so a number of subjects globally remain at risk for COVID-19 illness. Each of these clinical trial programs have a Data and Safety Monitoring Board (DSMB), pharmacovigilance teams, and medical monitors that work with the respective investigators to provide advice on management that are not covered by the study protocol.

Considering the limited available data on possible interactions between these agents and the COVID-19 coagulopathy and the small number of patients on these agents in trials, no valid recommendation can here be given on the management of PWHs with COVID-19 on these agents. It is the responsibility of the sponsors based on their accumulating data to advise on how to manage patients treated with these agents if they get COVID-19. The same recommendations would apply to patients in gene therapy trials.

Conclusions

Because of the very limited data in patients with bleeding diseases, these practical recommendations are based on our consensus interpretation of the currently available literature on the impact of COVID-19 infection on haemostasis in the non-hemophilic population and its possible effects in PWHs. These recommendations must be tailored to the specific requirements of each patient. They will also need to be tested and validated or modified based on further studies and data. To achieve this goal, inclusion of all admitted PWHs with COVID-19 in registries, as initiated in many countries, should be strongly encouraged.

Tables

TABLE 1. SUGGESTED APPROACH TO COVID-19 PATIENTS AND COAGULOPATHY

COVID-19	Coagulation tests	Standard-dose VTE prophylaxis	Escalated-dose VTE prophylaxis	Therapeutic dose anti-coagulation
Outpatient		Consider		
Inpatient	X			
Ward	X	X		
ICU	X		Could be considered in the absence of evidence	
Confirmed VTE	X			X
Presumed PE	X			X
ARDS	X		Could be considered in the absence of evidence	

Adapted from Connors et al. [20]

Table 2. Interpretation and monitoring of blood coagulation parameters of patients with COVID-19 coagulopathy		
	Non-haemophilia persons	**Persons with haemophilia**
Prothrombin Time	Slightly prolonged	Slightly prolonged
aPTT	Slightly prolonged	Prolonged in HA or HB depending on FVIII or FIX deficiency Normal if FVIII-FIX level > 30-40 % Short in patients on emicizumab Interference with a lupus anticoagulant should be excluded
Platelet Count	Decreased	Decreased
Fibrinogen	Increased	Increased Decreased in patients with DIC
D-Dimers	Markedly increased	Increased according to severity of COVID-19 coagulopathy Not intrinsically affected by haemophilia and replacement therapy with FVIII and FIX concentrates Not affected by emicizumab Increase in case of bleed and use of Bypassing agents (aPCC)
aPTT: activated partial thromboplastin time; HA: haemophilia A; HB: haemophilia B; DIC: disseminated intravascular coagulation; aPCC: activated prothrombin complex concentrate		

Table 3. Proposed modalities of substitution with clotting factor concentrates and thromboprophylaxis with LMWH in HA and HB patients with COVID-19 coagulopathy			
		FVIII and FIX substitution	**Thromboprophylaxis with LMWH**
Outpatient	**HOME**	Regular prophylaxis	None except if additional risk factors
Inpatient	**WARD**	FVIII *: maintain > 30 % (trough) while avoiding peaks > 100 %	LMWH **50** IU anti-Xa/kg OD
		FIX *: maintain above 30 % (trough) while avoiding peaks > 100 %	
	ICU / ARDS	FVIII : maintain between 50 and 100 %	LMWH **50** IU anti-Xa/kg OD or BD
		FIX : maintain between 50 and 80 %	
	PE/DVT	FVIII : maintain between 50 and 100 %	LMWH **100** IU anti-Xa/kg BD
		FIX : maintain between 50 and 80 %	
* If no invasive procedure such as arterial blood gas analysis			

Table 4. Proposed modalities of substitution with EMICIZUMAB/FVIII and thromboprophylaxis with LMWH in severe HA patients with COVID-19			
		Haemostatic treatment	**Thromboprophylaxis with LMWH**
Outpatient	**HOME**	Emicizumab alone	None except if additional risk factors
Inpatient	**WARD**	Emicizumab alone*	LMWH **50** IU anti-Xa/kg OD
	ICU / ARDS	Emicizumab + FVIII (50-80 %)	LMWH **50** IU anti-Xa/kg OD or BD
	PE/DVT	Emicizumab + FVIII (50-80 %)	LMWH **100** IU anti-Xa/kg BD
* If no invasive procedure such as arterial blood gas analysis			

Table 5. Desirable features of FVIII as haemostatic treatment in haemophilia patients with COVID-19 coagulopathy	
Flexibility	Rapid onset of action and reversibility
Measurability and predictability	FVIII can easily be titrated (APTT/FVIII assays) Specific levels can be targeted
Safety	No or limited risk of thrombosis Potential to reduce the risk of thrombosis by maintaining FVIII in the normal range (< 100 %)
Ease of use	Monotherapy
Certainty	Known effects on blood coagulation

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