Webinar

Management of hemophilia in and post era of the COVID-19 pandemic

Specific Challenges in management of Hemophilia patients with COVID-19

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The Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCoV-2), emerging toward the end of 2019 in an epidemic focused in Wuhan, China, is responsible for Coronavirus Disease 2019 (COVID-19),which spread quickly throughout China and the neighboring Asian countries, and immediately after to virtually all countries around the world, with 35,700,000 confirmed infections and more than 1,050,000 deaths, so far.

- The unexpectedly large numbers of severely affected patients have overwhelmed health care systems

- Moreover, the need for mobility restrictions is limiting access to usual standard of medical care, which is likely harmful for patients with chronic diseases and/or requiring regular clinical follow-up

- This is the case for congenital bleeding disorders (CBD), especially the most symptomatic forms, such as severe hemophilia

The challenges of health care management in the age of the COVID-19 pandemic, with focus on persons with hemophilia (PWH) by the Word Federation of Hemophilia (WFH) includes:

- Hygienic measures and information to enable reducing their exposure to SARS-CoV-2 and the associated risks of inadequate access to, or conduct of, treatment.

- Shortage of replacement product supply due to problems or restrictions in air transport can occur in low-income countries receiving aid from WFH and other humanitarian programs.

- Relevant advances in therapeutic products, that is, extended half-life (EHL) factor VIII and IX concentrates or the FVIII-mimetic bispecific monoclonal antibody emicizumab, recently introduced for prophylaxis in hemophilia A patients with and without inhibitors, may provide benefits in this emergency context, like higher bleeding protection and reduced need for treatment administration and supply

- However, switching products is not generally advised, being practically impossible to carefully follow-up patients during treatment transitions

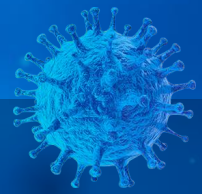
- The hemophilia community is actively confronting challenges of management of CBD in the pandemic era, but issues related to the specific impact of COVID-19 in CBD patients are largely unknown.

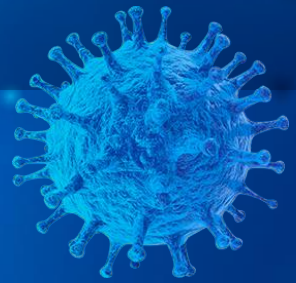
- To date a single case report has been published describing a patient with severe hemophilia A in Wuhan, China, with mild symptoms due to confirmed SARSCoV-pneumonia.

- Considering the numbers of COVID-19 infections reported in Italy, at least 30 CBD patients should have been diagnosed with COVID-19, 6 with severe or critical symptoms.

- Currently, there is no reason to think that susceptibility to SARS-CoV-2 infection or clinical course should differ in CBD patients from the general population.

An intriguing issue is the management of the coagulation defect and its management's outcome in CBD patients with COVID-19





1. Could the underlying abnormality of coagulation mitigate the prothrombotic state and the clinical course of COVID-19 in CBD patients?

2. How treat patients with inherited bleeding disorders who need anticoagulant therapy?

3. How to manage a CBD patients with COVID-19 who received Emicizumab and other non-factor replacement therapy

- Severe COVID-19 is associated with abnormalities of coagulation tests, reflecting a hypercoagulable state and hyperfibrinolysis, with mildly prolonged prothrombin time (PT) and reduced platelet count in most patients and, in particular, highly increased D-dimer, correlated with the severity of disease and risk of death

- After pulmonary viral replication and localized inflammation, the acute lung injury and hypoxia trigger a systemic hyperinflammatory state, due to activation of endothelia and cells of the monocyte/macrophage lineage, thus causing the ‘cytokine storm’ of the second stage of disease

- A vicious cycle of inflammation and coagulation activation is likely to be responsible for lung microvascular thrombosis and systemic venous thromboembolism (VTE), increasingly reported in COVID-19.

- Therefore, thromboprophylaxis with low-molecularweight or unfractionated heparin or fondaparinux at least at standard doses is advised in COVID-19 patients

- But heparin intensified-dose regimens up to therapeutic anticoagulation are being investigated in clinical trials or used according to pragmatic risk adjusted protocols, aiming at modulating thrombo-inflammatory mechanisms

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1. Could the underlying abnormality of coagulation mitigate the prothrombotic state and the clinical course of COVID-19 in CBD patients?

- This question correlates with the possible protection of CBD patients from cardiovascular and thromboembolic diseases, keenly debated in recent years, in the light of increased patients' life expectancy and the consequent higher burden of cardiovascular risk factors

- Similarly, indications and conduct of antithrombotic treatments in this setting should consider the inherent bleeding risk and the need for concomitant replacement treatment, according to the severity of coagulation defect

Arterioscler Thromb Vasc Biol. 2012 Mar;32(3):799-804. doi: 10.1161/ATVBAHA.111.238162. Epub 2011 Dec 15.

Coronary artery calcification in hemophilia A: no evidence for a protective effect of factor VIII deficiency on atherosclerosis.

Tuinenburg A[1], Rutten A, Kavousi M, Leebeek FW, Ypma PF, Laros-van Gorkom BA, Nijziel MR, Kamphuisen PW, Mauser-Bunschoten EP, Roosendaal G, Biesma DH, van der Lugt A, Hofman A, Witteman JC, Bots ML, Schutgens RE.

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J Thromb Haemost. 2012 Jan;10(1):30-7. doi: 10.1111/j.1538-7836.2011.04499.x.

Factor VIII deficiency does not protect against atherosclerosis.

Biere-Rafi S[1], Tuinenburg A, Haak BW, Peters M, Huijgen R, De Groot E, Verhamme P, Peerlinck K, Visseren FL, Kruip MJ, Laros-Van Gorkom BA, Gerdes VE, Buller HR, Schutgens RE, Kamphuisen PW.

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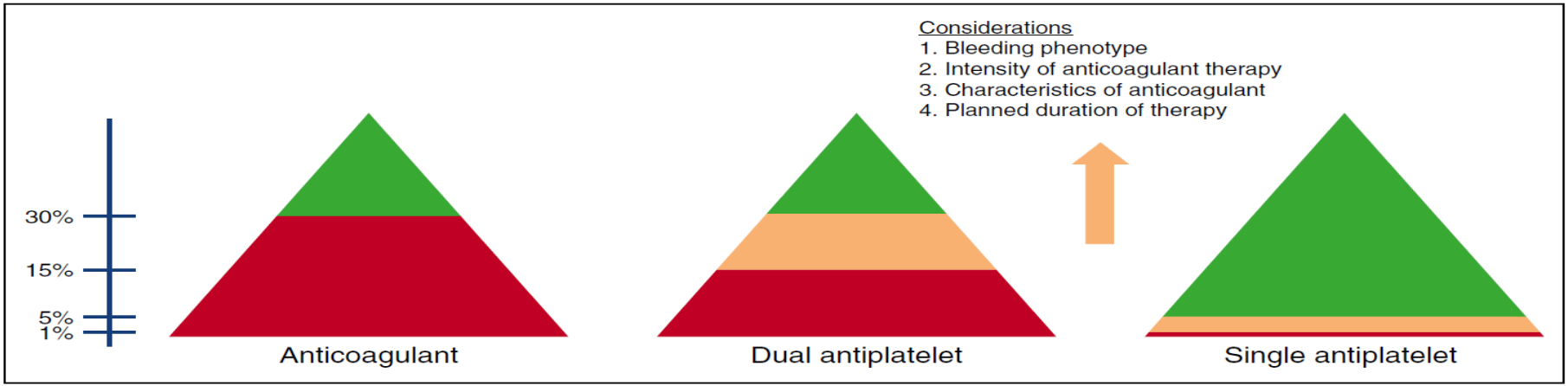
2. How treat patients with inherited bleeding disorders who need anticoagulant therapy?

Anti-coagulant treatment considerations:

1. Bleeding phenotype
2. Characteristics of anticoagulant/antiplatelet agent:
    - Intensity of anticoagulant therapy
    - Duration of antithrombotic therapy
3. Coagulation factor goals
4. Estimated Bleeding risk in the clinical course and management of COVID-19

Approach to FVIII or FIX goals for the use of anticoagulant and antiplatelet therapy in hemophilia



: avoid use
: likely okay to use
: decisions on use made after considerations

- No evidence-based guidelines are available; however, standard prophylactic doses of heparin are considered safe in PWH with (baseline or therapeutically achieved) factor levels > 5%. Higher factor levels are needed if increased doses are used, up to > 20 to 30% for full anticoagulation, as in the case of thromboembolic complications

- Antithrombotic prophylaxis/treatment is challenging in the management of CBD patients with COVID-19, as well all conditions inducing increased bleeding risk, due to the disease or to its management and treatment

- Therefore, adequate replacement treatment should be considered, aiming to achieve protective factor levels, according to the severity of risk and of the specific CBD

Table 1. Estimated Bleeding risk in the clinical course and management of COVID-19 in patients with hemophilia and congenital bleeding disorders

Condition	Setting	Low–moderate risk	High risk
Disease-related	Bleeding symptoms - Tissue injury and congestion	Nasal and throat bleeding	Hemoptysis GI bleeding
	- Trauma and predisposing conditions	Subcutaneous and muscle hematoma	Intracranial bleeding
Management and treatment-related	Invasive procedures	Arterial puncture for blood gas analysis	ECMO
		PICC or CICC insertion	
		Invasive ventilation (intubation, tracheostomy)	
		Renal replacement (dialysis and ultrafiltration)	
	Pharmacological treatment	Antiviral drugs	Corticosteroids
		Immunomodulatory agents	NSAIDs
		Antithrombotic agents at prophylactic or weight-adjusted doses	Antithrombotic agents at therapeutic doses

Abbreviations: CICC, centrally inserted central catheters; ECMO, extracorporeal membrane oxygenation; GI, gastrointestinal; NSAID, non-steroidal anti-inflammatory drugs; PICC, peripherally inserted central catheters.

DOI https://doi.org/10.1055/s-0040-1712961.

- Although a specific treatment for COVID-19 is currently unavailable, an increasing series of drugs, previously used for treating other viral diseases or investigational agents with antiviral targets or immunomodulatory effects, are being evaluated in clinical practice. Many of these drugs may increase bleeding tendency because of toxicity at gastrointestinal (i.e., lopinavir/ritonavir, umfenovir) or hematologic (i.e., the interleukin-6 receptor inhibitor tocilizumab and the RNA-polymerase inhibitor favipiravir) level.

- In this respect, reduction in platelet count should be carefully considered, because of bleeding risk, but also due to the debated association with mortality in COVID-19 patients

- As mentioned earlier, coagulation laboratory testing provides crucial prognostic markers, that is, PT and, particularly, D-dimer. Their abnormalities reflect the hypercoagulable state in COVID-19 and require monitoring, as some of most severe patients may develop sepsis and overt disseminated intravascular coagulopathy

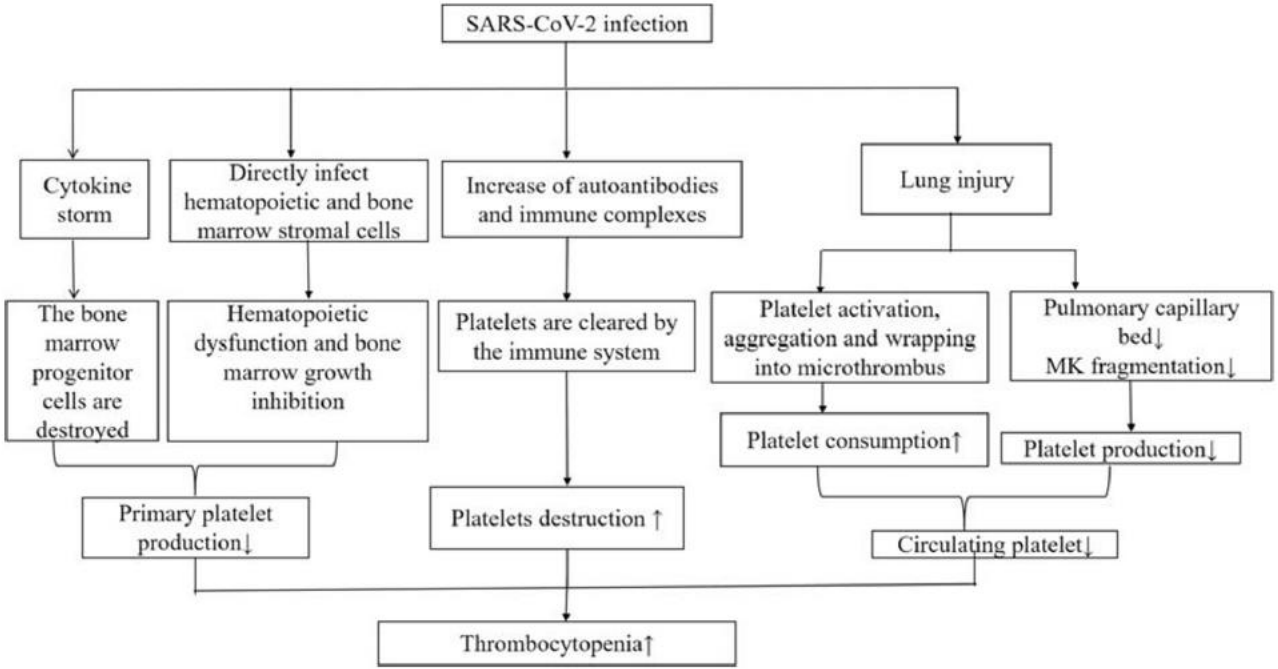


Fig. 1 The possible mechanisms of thrombocytopenia in COVID-19 patients. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019; MK, megakaryocyte; ↑, means an increase in a substance; ↓, means a decrease in a substance

https://doi.org/10.1007/s00277-020-04019-0

If coagulation laboratory abnormalities in COVID-19 are not associated with bleeding tendency, in CBD patients additional issues should be considered:

- The massive inflammatory response leads to increase of reactive proteins, including factor VIII and von Willebrand factor. This may mask mild cases of hemophilia A and von Willebrand disease

- Other CBDs with normal testing include FXIII deficiency and platelet functional defects; thus, undiagnosed patients could be missed, particularly in cases on non-referral to HTC

3. How to manage a CBD patients with COVID-19 who received Emicizumab and other non-factor replacement therapy

- In patients with hemophilia A currently on prophylaxis with emicizumab, activated partial thromboplastin time (APTT) and all clotting tests based on APTT are not reliable, overestimating coagulation and thus masking the underlying severe CBD
- Due to the prolonged half-life of emicizumab, these effects may persist for months after drug discontinuation. Patients on this and other investigational non-replacement agents (i. e., fitusiran and anti-TFPI) should be carefully monitored during COVID-19, because the risk of thrombotic complications is currently unknown

- However, treatment should not be discontinued and caution is needed if additional hemostatic therapy is administered, in particular activated prothrombin complex concentrate (APCC) in inhibitor patients

Thanks For Your Attention