Management of COVID-19 Coagulopathy in a Patient with Severe Haemophilia A

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Abstract
A 54-year-old man with a long history of severe haemophilia A treated prophylactically with efmoroctocog alpha (3,000 IU twice weekly) was diagnosed with COVID-19 infection. He had multiple risk factors for COVID-19 severity including obesity, diabetes mellitus and hypertension. He required prolonged intensive care unit (ICU) stay due to the severity of respiratory failure until his death on day 24. During his ICU stay, he received a continuous infusion of efmoroctocog alpha in order to maintain factor VIII activity between 80 and 100%, together with therapeutic doses of low-molecular-weight heparin targeting anti-Xa activity above 0.5 IU/mol. He tolerated numerous invasive procedures without bleeding. At post-mortem examination, there was no evidence for thrombosis or haemorrhage in the different organs.

Introduction
During the recent COVID-19 pandemic, the difficulties to maintain an accurate balance between thrombotic and haemorrhagic risks have been outlined. As illustrated by the following observation, this would be more particularly the case for patients with severe haemophilia requiring intensive care and invasive procedures.
Medication (propofol, sufentanil, clonidine, ketamine) and neuromuscular blockade. Inhaled nitric oxide therapy was also applied. The patient had received a last bolus of efmoroctocog alpha 48 h before ICU admission. Coagulation tests on ICU admission revealed: aPTT 47 s (27–36) and PT 12.3 s (9.3–14.3). In the ICU, a continuous infusion of efmoroctocog alpha was started by a bolus infusion and maintained at a rate of 200 IU/h in order to obtain a factor VIII activity between 80 and 100% [1]. The patient received subcutaneous low-molecular-weight heparin (LMWH) (nadroparine) targeting anti-Xa activity above 0.5 (initially 3,800 anti-Xa IU once a day, then twice a day, and 9,500 anti-Xa IU twice a day from day 9 after the recurrence of numerous episodes of atrial fibrillation).

During the ICU stay, he did not experience any clinically patent haemorrhagic or thrombotic event and tolerated invasive procedures (insertion of central venous line, arterial lines, orotracheal intubation, insertion of nasogastric feeding tube and bladder catheter) and postural changes for ventilation in prone position. The level of D-dimers never exceeded 7,118 ng/mL (normal < 500), with normal platelet count. Anti-Xa activity ranged from 0.40 to 0.53 U/mL, aPTT from 29.6 to 36.6 s, and PT from 12.3 to 16.8 s. Among inflammatory parameters, the peak level of CRP was 348 mg/dL and maintained at a rate of 200 IU/h in order to obtain a factor VIII activity between 80 and 100% [1]. The patient received subcutaneous low-molecular-weight heparin (LMWH) (nadroparine) targeting anti-Xa activity above 0.5 (initially 3,800 anti-Xa IU once a day, then twice a day, and 9,500 anti-Xa IU twice a day from day 9 after the recurrence of numerous episodes of atrial fibrillation).

The patient died on day 24 from refractory septic shock caused by *Pseudomonas aeruginosa* septicaemia as the primary cause of death. A post-mortem examination was obtained. The macroscopic examination of the lungs failed to reveal significant thrombi in the different arterial segments. There was no evidence of thrombosis or recent bleeding in the other organs. The ultrastructural examination of the lung was well consistent with diffuse alveolar damage, consisting of the presence of hyaline membranes and “acute fibrinous and organizing pneumonia-like” intra-alveolar fibrin deposition [2]. There was no sign of fibrinoid vessel wall necrosis, vasculitis/capillaritis or haemorrhage.

### Discussion

With a medical history of obesity, diabetes mellitus and hypertension, our patient was particularly illustrative of the population at risk for COVID-19 infection, independently from his history of bleeding disorder [3]. Not surprisingly, haemophilic patients were also affected at variable degree of severity by the recent COVID-19 pandemic. In most of them, the severity was comparable to that of the general population. Few data are currently available regarding haemophilic patients requiring invasive procedures following ICU admission for COVID-19 severe infection, with a difficult balance between thromboprophylaxis and prevention of bleeding complications.

Among other complications, COVID-19 infection has been strongly associated with coagulopathy with a high prothrombotic risk secondary to the intense inflammatory response to the viral infection. Although its mechanism remains rather obscure, its occurrence seems to be associated with higher mortality rates [4]. Anticoagulation has been suggested to reduce the thrombotic events related to the COVID-19 infection and higher anticoagulation targets have been proposed in critically ill patients [5, 6]. The beneficial effect of heparin has been linked with its potential effects on inflammation, endothelial protection, thrombus formation, etc. [7].

In some reports, the incidence of venous thromboembolic events in patients with a severe coronavirus disease can be as high as 31% and seems to be correlated with the D-dimer increase [8]. Of particular interest is the more specific finding in the lungs of some patients of widespread vascular thrombosis with micro-angiopathy and occlusion of alveolar capillaries [9, 10]. On the other hand, haemorrhagic symptoms seem far less commonly associated with the COVID-19 infection [11, 12]. Exceptionally, acquired haemophilia A has been reported to be triggered by COVID-19 infection [13]. Additionally, there is a theoretical risk of bleeding tendency with some drugs used in specific protocols for COVID-19 [14].

As illustrated by the present case, permanent correction of factor VIII deficiency by continuous infusion of a factor VIII concentrate combined with intensified thromboprophylaxis with LMWH proved to be effective in preventing bleeding and thrombotic complications. Such treatment required a close collaboration between the haemophilia-treating physicians and the ICU team as well as regular monitoring of several haemostatic parameters (D-dimers, factor VIII level and anti-Xa) [1].

More experience on the complex management of COVID-19 coagulopathy in patients with haemophilia treated with non-replacement therapies such as emicizumab should be collected [15]. Our case illustrates that factor VIII concentrates present several desirable features to correct the haemostatic defect in haemophilia A patients with severe COVID-19 infection. These are the rapid onset of action, rapid reversibility, titration of effect by measuring the factor VIII level, the safety of use and well-known effects on blood coagulation.

Ongoing registries should provide more information on the optimal combined haemostatic and antithrombotic managements of the complex COVID-19 coagulopathy in patients with severe haemophilia.

Finally, there are no definitive recommendations for the adaptation of LMWH in patients with augmented renal clearance [16].

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Statement of Ethics
Informed consent was obtained from the relatives.

Conflict of Interest Statement
The authors have no conflict of interest.

Author Contributions
João Pinto Pereira, Ludovic Gerard, Xavier Wittebole: conception of the manuscript; Catherine Lambert, Cédric Hermans: literature review; Philippe Hantson, Pierre-François Laterre: supervision and approval of the final version.

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