INTRODUCTION

Although published epidemiological data are not currently available, it is likely that despite containment measures, haemophilia patients will be exposed to SARS-CoV-2 and develop COVID-19. Here, we offer some practical guidance for persons with haemophilia (PWHs) diagnosed with COVID-19, admitted in hospital and possibly transferred to intensive care unit (ICU).

These recommendations are empirical and not validated. They are inspired by common sense and the experience gained by a group of haemophilia physicians, specialists in intensive care, internal medicine and infectious diseases from the recent management of patients with COVID-19, including patients with severe haemophilia admitted in our centre.

SOURCES OF INFORMATION ABOUT COVID-19 FOR PWHs

Several national or international haemophilia organizations (World Federation of Haemophilia, European Haemophilia Consortium, etc) have recently issued practical recommendations for PWHs or other inherited haemorrhagic diseases affected by COVID-19. It is currently impossible to evaluate the impact of these widely echoed statements on the haemophilia community and on individual PWHs. With the exception of 2 recently published case reports, no data have so far been collected about the impact, knowledge, understanding and perception of COVID-19 among PWHs. Proactively, many haemophilia treatment centres have taken the initiative to contact their patients directly to gather information on their current health status and remind them of key preventive measures.
3 | VIRUSES AND PWHs: A RECURRENT CONFRONTATION

The recent history of haemophilia is intrinsically linked to viruses, particularly hepatitis viruses B (HBV) and C (HCV) as well as human immunodeficiency virus (HIV).6 PWHs and their families are familiar with viruses and their potential dramatic consequences on health, at least those who have been exposed as a result of the contamination of intravenously administered blood products.

Compared to HIV and HCV, SARS-CoV-2 presents major differences due to its mode of transmission and the damage it causes on the lungs. Like HCV and HIV, it is a lipid enveloped virus that would be destroyed by solvents and detergents used during the production process of plasma-derived clotting factors, a concept familiar to the haemophilia community.7

Although the presence of SARS-CoV-2 RNA has been detected in blood of patients admitted in hospital with COVID-19,8 there is currently no evidence of transfusion transmission of SARS-CoV-2. In a recent study, no recipients of platelets or red blood cell transfusions from donors diagnosed with SARS-CoV-2 infection following donation developed COVID-19-related symptoms or tested positive for SARS-CoV-2 RNA.9

It seems important to explain to PWHs the fundamental differences between these viruses with respect to their mode of transmission and effects on health. PWHs should also clearly understand that they should follow the same preventive measures against SARS-CoV-2 as the rest of the population.

4 | COVID-19 IN PWHs

There is no reason to suspect that the clinical presentation of COVID-19, its severity and complications are influenced by haemophilia. It has been hypothesized that PWHs would be at greater risk of developing haemorrhagic complications of the upper or lower respiratory tract directly related to the infection or intracranial haemorrhage following coughing efforts. At present, these data are not confirmed and not supported by evidence. In the absence of published data, these patients are, however, in theory and in the absence of replacement therapy with clotting factor concentrates, more likely to develop bleeding complications following invasive procedures such as endotracheal aspiration, intubation and mechanical ventilation.

5 | HOME MANAGEMENT OF COVID-19 IN PWHs

Most PWHs with a suspicion or proven diagnosis of COVID-19 without criteria for hospital admission will be managed at home. Reasons for hospitalization should be the same as in patients without inherited bleeding diseases. Ideally, the following measures should be followed at home:

1. Information of the haemophilia treatment centre (HTC) about suspicion or confirmed diagnosis of COVID-19.
2. Regular contacts with the HTC.
3. Avoidance of paracetamol overuse (not more than 3 g/d).
4. Strict limitations of physical contacts with outside visitors. This could, however, be problematic for patients with disability and limited autonomy for intravenous infusions and self-care.
5. Continuation of regular replacement therapy with no delayed treatment in case of bleeding episode.
6. Avoidance of shortage of concentrates at home.
7. Maintenance of physical activities to avoid deterioration of joint stiffness and prevent muscle loss. Self-physiotherapy should be recommended.

6 | ADMISSION OF PWHs VIA THE EMERGENCY DEPARTMENT OR A TRIAGE CENTRE

As soon as a PWH is admitted to the hospital, it is essential that the staff be informed about his bleeding disease, regardless of its severity. The use of electronic alerts is strongly encouraged. Patients must be educated to show their haemophilia identification card on admission. Ideally and if logistically possible, PWHs should be referred to the hospital where their HTC is located. This would contribute to optimizing efficient communication between the different specialists involved, including the haemophilia physicians.

7 | DIAGNOSTIC WORKUP

Confirmation of diagnosis is based on a real-time polymerase chain reaction search for SARS-CoV-2 on a deep nasal swab. No special haemostatic precautions appear to be warranted during this procedure for PWHs. The chest X-ray is the initial imaging tool of choice. The chest CT scan can be used to better assess the extent of disease, identify complications and monitor treatment response.10

8 | HOSPITAL MANAGEMENT OF PWHs WITH COVID-19

Admission and hospitalization criteria are no different for PWHs compared to non-haemophilia patients.

8.1 | Recommended investigations on hospital admission

On top of the routine clinical examination, which should include a measurement of the respiratory rate and the non-invasive measurement of oxygen saturation by pulse oximetry, the following workup is recommended:
1. General biological assessment: CRP, full blood count, renal function, electrolytes, aPTT (activated partial thromboplastin time), prothrombin time, fibrinogen, D-dimers, FVIII or FIX assay, inhibitor screening, ferritin and troponin levels.
2. Imaging workup: chest X-ray and chest CT scan if indicated.
3. ECG to rule out any underlying cardiac disease and to measure the QTc interval if treatment with hydroxychloroquine is considered.
4. PWHs should not have arterial blood gases without correction of the FVIII or FIX deficiency (>50%).

8.2 | Review of drug treatment

It is important to collect accurate information on the current drug treatment, the recent use of paracetamol, NSAIDs or other drugs, and establish whether the patient is on immunosuppressive (IS) (steroids/other) or on any antithrombotic treatment (aspirin, etc).

8.3 | Review of comorbidities

A list of comorbidities for each patient must be rigorously established: hypertension, diabetes, obesity, cardiovascular disease, renal failure, untreated HCV infection, HIV infection, IS treatment and past history of venous or arterial thromboembolic disease. Patients with one or more comorbidities are at risk of developing more complications and adverse outcomes.

8.4 | Review of haemophilia treatment

Information on haemophilia treatment should be collected: replacement therapy (type of FVIII or FIX concentrate, treatment regimen, timing of last administration, presence of inhibitor, past history of inhibitor development, pharmacokinetic data when available, venous access)—emicizumab (treatment modalities, timing of last administration)—treatment with gene therapy (date of vectors’ administration)—treatment with gene therapy (date of vectors’ administration). It is essential to know whether the patient is participating in a clinical trial and contacts the local study coordinator for further information.

8.5 | General principles of care

Persons with haemophilia management is not fundamentally different from that of non-haemophilia patients. It is based primarily on symptomatic fever and pain control, compensation for insufficient oxygenation and careful monitoring of any deterioration in oxygenation. This management is ideally supervised by internists interacting closely with infectious diseases and intensive care specialists.

For PWHs admitted to the ICU, the following specific measures are recommended:

1. Oxygen supply: modalities not different from non-haemophilia patients.
2. Venous access: it is important not to damage the peripheral veins used by PWHs for home infusion therapy. Consider central venous access route if needed after factor concentrate administration. Assistance of an experienced operator to insert the catheter under ultrasound guidance and visualization of the internal jugular or subclavian vein is recommended.
3. Antipyretics: use paracetamol if not contraindicated.
4. Anti-infective drugs: there is no specific haemophilia-related contraindication for the use of hydroxychloroquine or antiviral agents, apart from the usual contraindications for those drugs (prolonged QTc and hydroxychloroquine for instance). Drug interference with current treatment should, however, be carefully excluded.
5. Other drugs: continuation if not contraindication.
6. Treatment of haemophilia: Maintain appropriate FVIII or FIX concentration supervised by the haemophilia specialists, ideally with continuous infusion or by bolus infusions depending on local practices, check with the pharmacy availability of the concentrate, switch concentrate if required by local availability to avoid any delayed treatment. A treatment plan should be prepared and regularly updated. For patients treated with emicizumab, relevant information should be communicated by the haemophilia team to the other specialists involved: impact of emicizumab on aPPT and factor assays results that should not be misinterpreted; regular assessment of the need for additional FVIII concentrate to correct FVIII to within the normal range; close monitoring for thrombosis as it is currently unknown how emicizumab may interact with coagulopathy caused by COVID-19; extra precautions should be taken in patients with FVIII inhibitors receiving emicizumab who require activated prothrombin complex concentrate [aPCC] due to the known drug-drug interaction between emicizumab and aPCC.
7. Rule out associated condition increasing the risk of bleeding (thrombocytopenia).
8. Blood pressure: careful monitoring of blood pressure and control of hypertension to minimize the risk of intracranial haemorrhage.
9. Biological monitoring: regular and ideally daily blood tests (CRP, full blood count, liver function tests, aPTT and FVIII or FIX assays, D-dimers) are required.
10. Thromboprophylaxis: it is not systematically contraindicated in PWHs and should be discussed with the haemophilia team, balancing the bleeding risks and the antithrombotic benefits. COVID-19 appears indeed to increase significantly the risk of arterial and venous thrombosis, especially in patients with severe inflammation, as suggested by markedly elevated D-dimer levels. Thromboprophylaxis with low molecular weight heparin (LMWH) in PWHs requires concomitant correction of FVIII or FIX with trough levels of 30% and peaks not exceeding 50%. The dosing of LMWH should be adapted according to the individual thrombotic risk, even if evidence is currently lacking.
11. For patients with HIV or untreated HCV: inform staff about risk of transmission, continue their treatment and check for drug-drug interactions.

8.6 | Management of PWHs admitted in the intensive care unit (ICU)

For PWHs admitted to the ICU, the following specific measures are recommended:

1. Haemophilia is not a contraindication to admission in ICU, assisted ventilation or any other invasive procedure deemed useful in the ICU setting. The recommendations of the Belgian Society of Intensive Care or the Swiss Academy of Medical Sciences, for example, do not mention haemophilia as an exclusion condition for ICU admission nor invasive procedure during the COVID-19 pandemic.

2. Maintain correction of the clotting factor deficiency by targeting trough and peak concentrations of 50%-100% for FVIII and 30%-60% for FIX—ideally by continuous infusion and a central venous access for FVIII and short-acting FIX and possibly by repeated bolus infusions for extended half-life FIX concentrates. Although not validated, these ranges of concentrations appear as a compromise between the risk of bleeding with invasive procedures and the risk of thrombosis with COVID-19. In patients without haemophilia and COVID-19, FVIII levels up to 369% have been reported, far above the concentrations that can be maintained in PWHs by monitored administration of exogenous FVIII.

3. Daily biological monitoring of haemophilia replacement therapy (aPTT—FVIII or FIX levels need to be monitored using a one-stage or chromogenic-based assay).

4. Presence of severe arthropathy should be taken into account when positioning the patient. Adult PWHs could be more susceptible to nerve compression because of their arthropathy. This is of particular importance in intubated patients when they are set in prone position.

5. Consider thromboprophylaxis unless contraindicated, even at higher doses (see above), ideally with regular monitoring (anti-Xa assay).

6. No contraindication to inclusion in any clinical study evaluating a new therapeutic approach, including immunomodulatory agents. Risk and benefits should be evaluated.

7. No contraindication to extracorporeal membrane oxygenation (ECMO) if required, as long as a close monitoring of coagulation parameters is performed and correction of coagulation factor deficiency is achieved. There is very limited published experience of ECMO in PWHs. However, with appropriate replacement and regular monitoring of clotting factor levels, ECMO is feasible in PWHs.

8. Monitoring of von Willebrand factor (VWF) concentrations is recommended to exclude an acquired VWF deficiency that could be induced by ECMO. Acquired deficiency of VWF could increase the risk of bleeding and alter the efficacy of replacement therapy with FVIII concentrates.

9 | END-OF-LIFE CARE, COVID-19 AND PWHs

It is likely that as for other patients, decisions will have to be made regarding resuscitation in critically ill PWHs. Haemophilia itself, irrespectively of its severity, should not influence the end-of-life directives and the 'Do Not Resuscitate' order. However, the latter must integrate possible associated comorbidities and the clinical frailty score. The guidelines developed locally to manage these situations and approved by the local ethics committee should also be considered. Members of the haemophilia team should ideally be consulted.

10 | PSYCHOLOGICAL SUPPORT

PWHs and their families usually have a close and long-standing relationship with the multidisciplinary team at their HTC. Every effort should be encouraged to provide them with the necessary support, information and emotional relief throughout this difficult period.

11 | ROLE OF THE HAEMOPHILIA PHYSICIANS AND NURSES DURING THE COVID-19 PANDEMIC

As detailed above, the haemophilia specialists will play an important consulting role during the pandemic for PWHs admitted with COVID-19. In our view, they should also proactively value their medical expertise as internists or haematologists by joining the medical workforce required for the daily care of hospitalized patients with COVID-19. Even if challenging, this would give them a unique opportunity to get major insights into the suspected or not yet known implications of the COVID-19 pandemic on PWHs and their management. The same is true for haemophilia nurses and other members of the haemophilia multidisciplinary teams.

12 | CONCLUSIONS

This article provides practical guidance for the management of PWHs admitted with COVID-19. These recommendations are not based on evidence, which is currently lacking. The coming months will be valued to collect data in many HTCs globally, including less developed countries, promote interactions between all stakeholders managing this crisis, update these recommendations and learn useful lessons for the future.
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The authors stated that they had no interests which might be perceived as posing a conflict or bias.

AUTHOR CONTRIBUTION
First draft was written by C. Hermans. All authors contributed to the manuscript and approved the final version.

ORCID
Cedric Hermans https://orcid.org/0000-0001-5429-8437
Catherine Lambert https://orcid.org/0000-0003-2222-0357

REFERENCES
1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-733.
2. COVID-19 (coronavirus disease 2019) pandemic caused by SARS-CoV-2: practical recommendations for people with hemophilia. 2020. https://news.wfh.org/covid-19-coronavirus-disease-2019-pandemic-caused-by-sars-cov-2-practical-recommendations-for-hemophilia-patients/. Accessed April 3, 2020
3. Updated EHC COVID-19 Position Statement. 2020. https://www.ehc.eu/updated-ehc-covid-19-statement/. Accessed May 5, 2020.
4. Cui D, Zhang A, Liu A, Hu Q. Clinical findings in a patient with haemophilia A affected by COVID-19. Haemophilia. 2020. https://doi.org/10.1111/hae.14000. [Epub ahead of print]
5. Mazza S, Sorce A, Peyvandi F, Vecchi M, Caprioli F. A fatal case of COVID-19 pneumonia occurring in a patient with severe acute ulcerative colitis. Gut. 2020;69(6):1148-1149.
6. Franchini M, Mannucci PM. The history of hemophilia. Semin Thromb Hemost. 2014;40(5):571-576.
7. Chang L, Yan Y, Wang L. Coronavirus disease 2019: coronaviruses and blood safety. Transfus Med Rev. 2020. https://doi.org/10.1016/j.tmrv.2020.02.003. [Epub ahead of print]
8. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
9. Kwon SY, Kim EJ, Jung YS, Jang JS, Cho NS. Post-donation COVID-19 identification in blood donors. Vox Sang. 2020. https://doi.org/10.1111/vox.12925. [Epub ahead of print]
10. Simpson S, Kay FU, Abbara S, et al. Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19. Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA. J Thorac Imaging. 2020. https://doi.org/10.1097/RTI.0000000000000524. [Epub ahead of print]
11. Guan WJ, Liang WH, Zhao Y, et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: a nationwide analysis. Eur Respir J. 2020. https://doi.org/10.1183/13993003.01227-2020. [Epub ahead of print]
12. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020;18(5):1094-1099. https://doi.org/10.1111/jth.14817
13. Thachil J. The versatile heparin in COVID-19. J Thromb Haemost. 2020;18(5):1020-1022.
14. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood. 2020. https://doi.org/10.1182/blood.2020006000. [Epub ahead of print]
15. Ethical principles concerning proportionality of critical care during the COVID-19 pandemic: advice by the Belgian Society of IC medicine. 2020. https://www.hartcentrumhasselt.be/professioneel/ethische-principes-concerning-proportionality-of-critical-care-during-the-covid-19-pandemic-advice-by-the-belgian-society-of-ic-medicine. Accessed May 5, 2020.
16. 2019 Novel coronavirus disease (COVID-19): articles in Swiss Medical Weekly. 2020. https://smw.ch/covid-19. Accessed May 5, 2020.
17. Escher R, Breakey N, Lammle B. Severe COVID-19 infection associated with endothelial activation. Thromb Res. 2020;190:62.
18. Frias MA, Jaraba S, Ibarra I, et al. Ventricular assist device as a bridge to transplant, and extracorporeal membrane oxygenation for primary graft failure in a child with hemophilia A. Pediatr Crit Care Med. 2011;12(6):e432-e435.
19. Malfertheiner MV, Pimenta LP, Bahr VV, et al. Acquired von Willebrand syndrome in respiratory extracorporeal life support: a systematic review of the literature. Crit Care Resusc. 2017;19(Suppl 1):45-52.

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