

WFH Webinar: Bleeding Disorders and COVID-19

April 9, 2020

Summary of webinar and selected questions

The information presented in the webinar are accurate as of 9 April 2020. Because the facts on COVID-19 are evolving, the information presented may change over time.

THE FACTS AND RISKS TO PERSONS WITH BLEEDING DISORDERS

- Glenn Pierce, MD, PhD, WFH Vice President, Medical (La Jolla, USA)
- Flora Peyvandi, MD, PhD (Milan, Italy)
- Magdy El Ekiaby, MD, WFH Board of Director (Cairo, Egypt)
- Cedric Hermans, MD, PhD, WFH Board of Director (Brussels, Belgium)
- Radoslaw F. Kaczmarek, WFH Coagulation Product Safety, Supply, and Access Committee Chair (Indianapolis, USA)

COVID-19

- Caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first known outbreak originated in Wuhan, China, in December 2019. The virus is closely related to the original SARS coronavirus (now called SARS CoV-1) and the Middle Eastern respiratory syndrome (MERS) coronavirus, both of which occurred as epidemics in the early part of this century.
- COVID19 is mainly spread person-to-person and thought to occur mainly via respiratory droplets and close contact, resembling the spread of influenza. Transmission of COVID-19 could occur also via asymptomatic individuals including during the incubation period.
- The symptoms appear 2-14 days post-exposure. At least 20% or more are asymptomatic but infectious; about 80% recover without treatment; and about 20% need to be hospitalized, with about 5% ending up on a ventilator/in the ICU and about 2% dying.
- The symptoms of COVID-19 include high fever, tiredness, dry cough, and difficulty breathing; but the symptoms vary considerably between people and there is nothing specifically pathognomonic. In severe disease, pneumonia develops, D-dimer levels are elevated, and acute respiratory distress syndrome (ARDS) and disseminated intravascular coagulation (DIC) may develop.

Clinical presentation

- Most infections are not severe; some people have very little symptoms although many patients have had critical illness. Pneumonia appears to be the most frequent serious manifestation of infection, characterized primarily by fever, cough, dyspnea, and bilateral infiltrates on chest imaging. The overall case fatality rate is reported to be 2.3%. No deaths were reported among non-critical cases.
- As disease progresses, a series of complications tend to develop, especially in critically ill patients; high intensity treatment and intubation are needed. Pathological findings showed representative features of acute respiratory distress syndrome and involvement of multiple organs.
- Very surprisingly, those with chronic lung disease are not the first people who are the best candidates for this disease. Cardiovascular disease, diabetes mellitus, and hypertension have

particularly been associated with severe illness and mortality of COVID-19, as well as chronic lung disease, cancer, chronic kidney disease. We need to understand the common condition so favorable to this virus.

Laboratory

- Data are very similar between patients but severity could be different. The white blood cell count can vary: leukopenia, leukocytosis, and lymphopenia have been reported, although lymphopenia appears most common. Elevated liver enzyme (aminotransferase) levels have also been described.
- On admission, many patients with pneumonia have normal serum procalcitonin (PCT) levels. However, in those requiring ICU care, fibrinogen, D dimer, and aminotransferase levels are more likely to be elevated—this requires particular attention from physicians and centres. Laboratory markers indicating increased inflammation and clotting activation as high D dimer, decreased platelet count, and PT prolongation have negative prognostic value. In our experience, patients affected with COVID-19 have hypercoagulability that differs from DIC and this requires further investigation.

Diagnosis: Test for SARS-CoV-2

- In the United States, the CDC recommends collection of specimens from the upper respiratory tract (nasopharyngeal and oropharyngeal swab) and the lower respiratory tract (sputum tracheal aspirate, or bronchoalveolar lavage). This was big issue for us at the beginning because of the limited availability of resources for swab testing.
- SARS-CoV-2 RNA is detected by reverse transcription–polymerase chain reaction (RT-PCR) tests and there are other types of tests such as the enzyme-linked immunosorbent assay (ELISA), which show the presence of COVID-19 IgG and/or IgM antibodies. A positive test result confirms the diagnosis of COVID-19.
- If initial testing is negative but the suspicion for COVID-19 remains, the WHO recommends resampling and testing from multiple respiratory tract sites. Negative RT-PCR tests on oropharyngeal swabs despite CT findings suggestive of viral pneumonia have been reported in some patients who ultimately tested positive for SARS-CoV-2.
- COVID-19 RT-PCR test performance is still unclear; it is impossible to sort out in the absence of a definitive “gold standard” diagnostic test for COVID-19. Specificity seems to be high but sensitivity may be about 60-70%, according to data from case series reports. A single negative RT-PCR does not exclude COVID-19, especially if obtained from a nasopharyngeal source and if taken relatively early in the disease course—this is very important to keep in mind. If negative, ongoing isolation and re-sampling should be considered.

COVID-19 pandemic: practical recommendations for people with hemophilia

- If you are currently being treated with a licensed product, you should continue to maintain that treatment regimen. There is no reason to fear shortage of treatment supplies, manufacturing issues, or interruption in the supply chain, particularly for those currently treated with standard or extended recombinant half-life factor VIII (FVIII) or factor IX (FIX) concentrates, FEIBA®, factor VIIa, or emicizumab.

- It's important for patients to stay in close contact with the hemophilia treatment centre (HTC); those who self-treat at home should keep track of their stock and keep a few extra doses if possible in case of delivery delays or disruptions. The goal is to minimize visits to the hospital or the hemophilia treatment centre as much as possible.

For PWH treated with plasma-derived products

- If you're treated with plasma-derived FVIII, FIX, or von Willebrand factor (VWF), one of the most important things to remember is that SARS-CoV-2 is like all the other coronaviruses. It is a lipid-enveloped virus like HIV, HCV, and HBV, and the viral inactivation and elimination procedures used during the production process are sufficient to destroy the virus instantaneously, if it is present at all.
- There have been no supply disruptions in plasma-derived products, according to the manufacturers at this point. But it is important to recognize that there has been a large decrease in plasma collections during this period which may continue, and so there may be some shortages six to nine months from now. The manufacturers are doing everything possible to avoid that but it's important for all of us in the community to recognize that the need is very high for continued blood and plasma donations in your local communities to ensure that we have supply at the end of the year as well.
- If blood-derived products are not virally inactivated (e.g., cryoprecipitate, platelets), treatment decisions need to be based on clinical risk/benefit analysis balancing safety of not treating a bleeding event and residual risk of acquiring infection.
- There have been no known transmissions at this point from any blood-derived products. However, a research letter published last week in the journal of the U.S. Centers for Disease Control and Prevention (CDC), *Emerging Infectious Diseases*, describes the detection of SARS-CoV-2 RNA in blood samples from four blood donors in Wuhan who were asymptomatic at the time of blood donation. Investigators were not able to trace active infection to any of the blood recipients but it does demonstrate that there may be a viremic phase and that this will require much more investigation.

For PWH in clinical trials

- If patients are in clinical trials or if your hemophilia treatment centre is running clinical trials, then it's all the more important for the patient and HTC to discuss the implications of the pandemic, ensure the availability of study drugs and that the treatment is not interrupted, and stay in close touch for follow-up and monitoring to the extent possible. Remote follow-up visits are strongly encouraged.
- For patients on a gene therapy trial (<12 months after infusion), making sure that scheduled liver function testing for safety and efficacy is able to continue is also very important. It's important not to discontinue or switch treatment if you're receiving a clinical trial drug unless directed the study team.
- For patients who are scheduled to be enrolled in a trial testing a new treatment, postponement should be considered and discussed with the study team. Many medical centres have stopped initiation of any new clinical trials so as not to divert resources that are needed to manage the pandemic. It's equally important for the study sponsors to be in close, constant communication with the clinical sites where patients are on clinical trials and to track any adverse events that may arise in conjunction with a COVID-19 infection.

Specific measures to reduce exposure of SARS-CoV-2 in PWH

- It's important to point out that the people at greatest risk for severe disease are those with comorbidities. That includes cardiovascular disease, hypertension, obesity, diabetes, HIV, and older age groups as well as those on steroids and immunosuppressants.
- The goal here really is to avoid exposure to everyone; or, if exposed, to make sure that you're protected when you're exposed. That includes avoiding exposure to lower risk individuals and children, a greater proportion of whom are relatively asymptomatic but yet may be infectious. That's the single-most important precaution to avoid infection. Sheltering in place and social distancing are key tools. The proportion of patients who are infectious but asymptomatic is uncertain but may be 20% or more. In close spaces, masks are essential. Minimizing visits to the hospital is also important.
- Acetaminophen/paracetamol reduces fever without inhibiting the inflammatory response needed to fight COVID-19, and is recommended for persons with bleeding disorders.
- Other safeguards to prevent COVID-19 transmission include handwashing, not touching your face, not aerosolizing your cough, and maintaining physical distance of 2 metres (6 feet).

If hospitalized with COVID-19 infection

- The most important thing is to have a good liaison with the hemophilia treatment centre if the patient is hospitalized in a hospital where the hemophilia treatment centre is not.
- The treatment centre needs to make sure that adequate amounts of replacement therapy are available. It is important to inform the COVID-19 hospital team if the patient is taking emicizumab due to the risk of misinterpretation of hemostasis lab tests with emicizumab.
- The treatment centre also needs to inform the hospital if a patient is part of an ongoing experimental treatment, especially with a rebalancing agent such as anti-TFPI or fitusiran, due to the risk of thrombosis or other clotting system imbalances; and likewise if a patient has undergone a recent treatment with gene therapy. It's very important to have the HTC involved in the management of the patient, together with the study sponsor.
- It's important to be aware that patients with severe COVID-19 infection who are hospitalized may require increased prophylaxis and clotting factor levels as precaution against bleeding from potentially severe damage inflicted by SARS-CoV-2.

Risks of acquiring SARS-CoV-2 (the virus) and COVID-19 (the disease)

- There is no increased susceptibility to infection in immune-competent people with bleeding disorders. SARS-CoV-2 is passed primarily through droplets in the air coming from infected persons and from fomites, i.e., objects.
- If infected, immunocompromised people are at greater risk for severe disease; this should be taken into consideration in the management of the patient.

Risks if COVID-19 infection with a bleeding disorder

- Risk factors include hypertension, diabetes, cardiovascular disease, and immunosuppression. As COVID-19 progresses, coagulation pathways are activated as part of the host inflammatory response to limit infection. D-dimers are elevated in many hospitalized COVID-19 patients. Further progression may lead to disseminated intravascular coagulation, which is associated with high mortality.

- Close monitoring for bleeding and thrombosis, especially for individuals with bleeding disorders, is required. Anticoagulants (e.g., low molecular weight heparin, LMWH) is recommended for some patients with elevated D-dimers and severe infection. Use of anticoagulants should be accompanied by factor replacement therapy.

COVID-19 coagulopathy

- Two articles in the *Journal of Thrombosis and Haemostasis*, both by Ning Tang et al. from Wuhan, made the initial association of significantly higher D-dimer and fibrin degradation product (FDP) levels and longer prothrombin time and activated partial thromboplastin time in non-survivors compared to survivors of COVID-19; and demonstrated that LMWH appears associated with a better prognosis. We will continue to see more articles that will more robustly describe the situation and the potential treatments.

Non-factor replacement therapies

- The risk of thrombotic complications with non-factor replacement therapies including emicizumab or other investigational agents (e.g. fitusiran, anti-TFPI) is unknown in COVID-19. It will be very important to continue to monitor patients for thrombosis. We've encountered situations where the coagulation system gets activated and the patient has a systemic infection with multiple organ systems being damaged, so it will be key for the hemophilia treatment centre to stay in touch with the hospital that the patient is in and with the manufacturers of these products to get a better understanding of how to manage the patients.

Bleeding disorders are not comorbidities in severe COVID-19

- We have an editorial that is just being publicized in *Haemophilia* journal emphasizing that patients with bleeding disorders of all severities should be eligible for all available therapies required for COVID-19 depending on their condition (e.g., ventilation support, extracorporeal membrane oxygenation [ECMO], hemofiltration). Having hemophilia or another bleeding disorder should not exclude patients from any invasive management that would be required for COVID-19. This is something to be aware of if rationing occurs.

WFH Humanitarian Aid Program

- The WFH Humanitarian Aid Program is run by our medical and humanitarian aid director Assad Haffar. We have had significant problems and have taken some immediate steps at the beginning of this week to try to address them. A number of airports in a number of countries that we ship to have closed their airports, not just to passengers but to cargo as well, so we have a number of interrupted supply lines that are challenging for countries where we were about to send donations. We are asking these countries to keep a close eye on their existing stock; and unfortunately, depending upon their supply, to stop any immune tolerance induction (ITI) therapies, elective surgeries, and prophylaxis for adults and children until further notice in order to preserve stock for emergency use to treat bleeding episodes. Where we can, we are shipping donations to countries we can get into to continue to build or maintain their stocks during this period of time. We will continue to update our website with information.

For our healthcare providers who are on the front lines, we thank you very much and ask you to continue to be as careful as possible.

SELECTED QUESTIONS & ANSWERS

Are people with hemophilia (PWH) more susceptible to COVID-19 (high-risk group)?

No, they're not.

Does COVID-19 affect PWH differently than others? What about PWH with hepatitis C?

We have a large centre with more than 300 severe cases and until now we have not yet seen any patients with COVID-19 positive, so I wouldn't be worried at this stage about any association with patients with hemophilia or those with hepatitis C.

If a PWH tests positive for COVID-19, what is the probability of internal bleeding: to the lungs or kidney? to the trachea (due to the severe dry coughing)?

I have not seen any association with hemophilia nor other bleeding disorders. EUHASS is currently trying to collect the data from all hemophilia centres in Europe and we will have more data on that. In terms of the bleeding, it seems that there is a higher tendency for clotting with COVID-19 and based on that I would not be worried about bleeding. What we have to understand is what is happening in those who have intensive treatment at the higher prophylaxis levels when they get infected with COVID-19. So I would not be worried about the bleeding. The only data on bleeding was on hemoptysis [coughing up of blood], which was reported in less than 2% of the general population.

If tested positive to COVID-19, can a PWH go to their HTC for a bleed or should they go to the ER?

This question—how a patient with a bleed should manage their bleed with regard to going to their treatment centre or the emergency room—really is a local one. That's why it's important to have contact with your hemophilia treatment centre and understand what the protocols are in your particular location.

What should PWH on emicizumab (Hemlibra) or similar products be aware of if tested positive for COVID-19?

We've had a number of questions on emicizumab (Hemlibra) and similar products. What we've said is that you should maintain your current treatment regimen with all approved products. Would any of the panelists like to comment further?

It's very important not to create any fears in our population; that's a very important issue. We do not have any reason as of now to think about stopping our treatment. We have to continue, whether we are on the regular prophylaxis with any type of product or any clinical trial. Of course, as I said, for those patients treated with those products that put them at a higher risk state of thrombin generation, if they get COVID-19 infection and they get sick and go to hospital, it is the job of the hospital and the doctor to figure out how to balance the hyper-coagulability and the good hemostasis in terms of being able to have no bleeding and no thrombogenicity. But with those who test positive but have no symptoms, I don't think there is any need to worry about that.

If you do get the signs and symptoms of COVID-19 and end up in a place that is not a hemophilia treatment centre, explain your treatment to the physicians and put them in contact with your hemophilia treatment centre. There should be communication between the specialists in the COVID-19 area and your hemophilia treatment centre—that's an important point.

In the current situation, should PWH receiving treatment at a hospital request home treatment (if possible)?

Absolutely. There are many places where home treatment is restricted but the WFH has been advocating along with a number of other groups that home treatment is the best way to manage bleeding episodes in hemophilia because if you have to go the hospital, then you're hours away and you've got more blood accumulation in joints and muscles and more damage ensues. So if any small silver lining can come from this, I would hope that home treatment would be more universally developed and accepted amongst our global community.

If tested positive to COVID-19, what medicines (such as acetaminophen, ibuprofen) can a PWH take?

If tested positive, acetaminophen/paracetamol are recommended in hemophilia. There have been various rumours going around about ibuprofen. I don't think any of those have been established as true, but individuals with hemophilia should not be taking ibuprofen in first place.

Can the virus be transmitted through fresh frozen plasma/cryoprecipitate? Are current manufacturing processes killing the virus?

There is no evidence of transmission yet, but there is evidence that RNA for SARS-Cov-2 has been found in asymptomatic blood donors in Wuhan—this is a developing story, stayed tuned and follow it. But that involves then, if you're taking cryoprecipitate or fresh frozen plasma, assessment of the risk/benefit for that, which includes how much SARS-Cov-2 is in your community.

Do you foresee a shortage of treatment products?

Remember, it takes six to nine months in a cycle for a plasma product to be made so we will need to stay in touch with the companies that are making plasma products for what will be occurring this fall and winter and whether they envision shortages.

Could a country order a manufacturer to stop exporting their products?

Yes, that can happen.

How does COVID-19 affect other bleeding disorders (VWD, rare factor deficiencies, etc.)?

There is no association, I would say. I haven't seen any particular data regarding that but I wouldn't expect that there should be any difference.

How can PWH protect themselves from coronavirus infection? For how long should PWH quarantine themselves at home?

For quarantine, what we do here is for the patients who are symptomatic, 3 days after the fever and other symptoms have stopped completely, they start to make the first swab and if it's negative then they can come in and if it's positive then the swab is repeated. The timeline was supposed to be 14 days but unfortunately sometimes the viremia and swab test results remain positive for 3-4 weeks.

That's all the more reason to use precautions such as gloves when you're out in public. Asymptomatic people can transmit the disease, pre-symptomatic people can transmit the disease, and post-symptomatic people can still shed virus for a period of time—and it's variable. So the virus is behaving differently from SARS and MERS, each one of these is very unique in terms of its biological characteristics.

I am very worried about the situation, what can I do to worry less?

Don't watch TV and radio 24 hours out of 24 hours. Just keep one hour per day and decide which are the most serious sites where you can look for the data. And read about other things and don't follow everything on COVID-19.

There was a question about risk to children with hemophilia. Across the board, there are a higher proportion of children who are asymptomatic or who get mild disease and with each decade, the degree of serious or severe disease increases. It's been well established from Wuhan. So children can transmit but very few children get severe disease. Unfortunately, some do and we have had deaths in the greater community, not necessarily the hemophilia community. But there is no reason why children with hemophilia should be more at risk.

There was a question from somebody asking if they are more susceptible to COVID-19 if they have hypertension under control.

It's very important. There are two things. We did see in the cardiology ward especially, those patients that were having hypertension, that was hypertension that was not controlled and it was much more difficult for the physician to control and they had to intensify the treatment for the control of the hypertension.

There is a lot of discussion of the ACE receptor and its role in this disease. How much is that association, and how much is seen in the people with the hypertension who are having the higher risk. There is a lot of discussion on that. I would say please control your hypertension and try to be in pharmacological control. But for those who are COVID-19 positive, this control should be more strict and if there is any problem, contact your physician.

Related links:

<https://news.wfh.org/covid-19-coronavirus-disease-2019-pandemic-caused-by-sars-cov-2-practical-recommendations-for-hemophilia-patients/>

<https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html>

<https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/cloth-face-cover.html>

<https://www.cdc.gov/coronavirus/2019-ncov/hcp/ppe-strategy/decontamination-reuse-respirators.html>

<https://www.who.int/news-room/commentaries/detail/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations>