The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-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 ≈3,000,000 confirmed infections and more than 200,000 deaths, so far. Flu-like symptoms are the most common clinical presentation; however, 15 to 20% of patients develop a severe form of interstitial pneumonia and respiratory insufficiency, up to need for intensive care and mechanical ventilation, with significant fatal outcome, particularly in those with advanced age and comorbidities.

The unexpectedly large numbers of severely affected patients have overwhelmed health care systems, with most human and economic resources devoted to the critical epidemic emergency. 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), have been recently highlighted and the Word Federation of Hemophilia (WFH) issued specific recommendations for patients, including 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. In high-income countries, no relevant immediate impact in product delivery is expected. However, regular medical and laboratory follow-up is likely to be hampered at specialized hemophilia treatment centers (HTC), otherwise useful to enable optimized outcomes in patients on personalized regimens of primary or secondary prophylaxis to minimize bleeding and its deleterious effects, particularly on the musculoskeletal system. 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. Moreover, some patients are on investigational treatments, including non-replacement agents and gene therapy, or are scheduled to be enrolled in clinical trials, the conduct of which may be interrupted or necessarily adapted to the evolving situations. Overall, HTCs are closely meeting the specific needs for diagnostic or therapeutic consultations and follow-up of PWH and CBD patients, also using telemedicine and social media communication, and relying on the long-established trustworthy relationships with patients, their families, and key associations.

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 SARS-CoV-2 pneumonia. National and international initiatives are ongoing to collect information about CBD patients with confirmed or clinically suspected COVID-19. Considering the numbers of COVID-19 infections reported in Italy and the
incidence of CBD in our country,\textsuperscript{12} 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.\textsuperscript{13} Male and hypertensive patients more frequently experience severe up to fatal COVID-19.\textsuperscript{1} These clinical features could negatively affect PWH, almost all men and, according to some studies, suffering from hypertension with higher prevalence than age-matched subjects.\textsuperscript{14} Comorbidities in PWH possibly associated with higher risk for severe COVID-19 are human immunodeficiency (HIV) and hepatitis B and C (HBV and HCV) virus infections, frequently found in those born before mid-1980s,\textsuperscript{12} (i.e., before the introduction of virus-inactivated plasma-derived factor concentrates). However, most patients are not immunocompromised or show hepatic decompensation, thanks to currently available treatments.

An intriguing issue is represented by the possible influence of the coagulation defect in the clinical outcome of COVID-19 in CBD patients. 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.\textsuperscript{15–17} 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.\textsuperscript{18} 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.\textsuperscript{19–21} Therefore, thromboprophylaxis with low-molecular weight or unfractionated heparin or fondaparinux at least at standard doses is advised in COVID-19 patients,\textsuperscript{22} but heparin intensified-dose regimens up to therapeutic anticoagulation are being investigated in clinical trials or used according to pragmatic risk-adjusted protocols,\textsuperscript{23} aiming at modulating thrombo-inflammatory mechanisms.

On this basis, 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,\textsuperscript{24,25} 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. 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.\textsuperscript{24–26}

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.\textsuperscript{13} Therefore, adequate replacement treatment should be considered, aiming to achieve protective factor levels, according to the severity of risk and of the specific CBD (\textsuperscript{\textbullet} Table 1). The only reported PWH with COVID-19 did not experience bleeding complications, related to the disease or to treatment, performed at home with antiviral (oseltamivir) and antibiotic (cefdinir) drugs.\textsuperscript{10} Bleeding symptoms are not frequent in COVID-19. Hemoptysis, due to mucosal congestion and lung injury, is reported in 0.9% of patients, but up to 3% in severe cases.\textsuperscript{1} Nasal and throat bleeding, and rarely gastrointestinal hemorrhage also occur. Frequency and severity of symptoms are expected to be higher.

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Setting</th>
<th>Low–moderate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-related</td>
<td>Bleeding symptoms - Tissue injury and congestion</td>
<td>Nasal and throat bleeding</td>
<td>Hemothypsis GI bleeding</td>
</tr>
<tr>
<td>Management and treatment-related</td>
<td>Invasive procedures</td>
<td>Arterial puncture for blood gas analysis</td>
<td>ECMO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PICC or CICC insertion</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Invasive ventilation (intubation, tracheostomy)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal replacement (dialysis and ultrafiltration)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pharmacological treatment</td>
<td>Antiviral drugs</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immunomodulatory agents</td>
<td>NSAIDs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antithrombotic agents at prophylactic or weight-adjusted doses</td>
<td>Antithrombotic agents at therapeutic doses</td>
</tr>
</tbody>
</table>

Abbreviations: CICC, centrally inserted central catheters; ECMO, extracorporeal membrane oxygenation; GI, gastrointestinal; NSAID, non-steroidal anti-inflammatory drugs; PICC, peripherally inserted central catheters.
in CBD patients, who may experience bleeding even due to trauma or other predisposing conditions (for example, prolonged axillary and neck compression by continuous positive airway pressure helmet and straps, or persistent cough attacks or nose obstruction and vigorous blowing, causing increase of blood or abdominal pressure). Hospitalized patients are advised to carefully inform medical COVID-19 team about their CBD and replacement treatment and to provide contacts of the reference HTC. Prophylaxis regimens should be continued or implemented in all patients with severe or moderately severe CBD, aiming at maintaining factor levels higher than those in the routine practice. This will help minimize bleeding risk, even due to the frequent arterial punctures for blood gas monitoring and other invasive procedures, including those needed for vascular access, mechanical ventilation or renal replacement (Table 1). For patients requiring extracorporeal membrane oxygenation, at highest bleeding risk, achieving virtually normal factor levels has been suggested.

Bleeding threats are also related to pharmacological treatments (Table 1). Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided, because of inhibition of platelet function with increased bleeding tendency, in particular upper gastrointestinal hemorrhage. Anti-platelet effects are negligible with selective cyclo-oxygenase 2 inhibitors and corticosteroids. The latter, frequently used in the management of the second phase of COVID-19, mainly in severe cases, are known to be associated with significant risk of gastrointestinal bleeding, in particular in hospitalized patients. These risks, in addition to that of stress ulcer in this setting of critically-ill patients, highlight the role of prophylaxis with proton pump inhibitors or histamine-2 receptor antagonists.

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, umifenovir) 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 the most severe patients may develop sepsis and overt disseminated intravascular coagulopathy (DIC). 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 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.

In conclusion, HTCs and the hemophilia community are defining safe modalities for facing the COVID-19 pandemic. Clinical data in CBD patients with COVID-19 are lacking; however, they should undergo all treatment modalities available, including invasive approaches, provided that their bleeding risk is covered by adequate hemostatic prophylaxis. As our knowledge and clinical experience develop, we will learn whether the coagulation defects present in PWH and CBD may influence the epidemiologic impact and severity of COVID-19.

Conflict of Interest
Dr. Tagliaferri reports personal fees from Bayer, Novo Nordisk, and Roche, outside the submitted work. Dr. Coppola reports personal fees from Bayer, Novo Nordisk, and Werfen, outside the submitted work. Dr. Quintavalle reports personal fees from Bayer, outside the submitted work.

References
COVID-19 and Congenital Bleeding Disorders

1. Coppola et al.


