Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Moreover, it appears reasonable to formulate the hypothesis that DIC might not only be a concomitant finding, but even a pathophysiological process contributing to circulatory and organ failure, in COVID-19 particularly pulmonary damage. As well known from DIC, eg, in bacterial sepsis, disseminated fibrin deposits occur in the microvasculature, impairing the perfusion and thus performance of vital organs. In this context, it is of interest that in three patients with severe COVID-19 pneumonia induced ARDS tissue plasminogen activator (tPA) treatment resulted in documented but transient improvement of pulmonary function parameters. This would be compatible with the assumption that during tPA infusion the pulmonary microvasculature was partially reopened, but after terminating tPA the microthrombi increased again, due to the ongoing inflammatory stimulus perpetuating DIC.

If the above hypothesis is correct, it might be warranted to think about possible interventions to attenuate DIC and prevent further obstruction of organ microvasculature by fibrin deposits. The key player in the generation of fibrin deposits is thrombin. Thus, for decades several approaches of anticoagulation have been evaluated for beneficial effects in DIC, particularly in sepsis. These trials have been admittedly so far frustrating. For none of the approaches could a clear and proven survival benefit be demonstrated, as shown in a recent meta-analysis. However, some of the clinical studies conducted so far had considerable flaws. For instance, the large randomized multicenter KyberSept trial6 used exceedingly high antithrombin III (AT) doses, in many patients accompanied by effective heparin doses, resulting in excessive bleeding. In their meta-analysis, Umemura et al showed that AT nevertheless did show a small reduction of mortality (risk ratio 0.63; 95% confidence interval CI 0.45; 0.90) in the subgroup of sepsis patients with DIC. Also, a recent summary7 of systematic reviews found some evidence, albeit with low certainty, for a beneficial effect in sepsis-induced DIC, and mentioned that the Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock weakly recommended the use of antithrombin for DIC patients with reduced antithrombin activities.

Thus, it might be time for reconsidering the interaction and modulating of different connected systems, eg, coagulation, fibrinolysis, kallikrein-kinin, complement, and immunity (cytokine storm), in order to elaborate a rationale for developing strategies for attenuating DIC in COVID-19. If such efforts are successful, it might have immense benefit also for intensive care patients far beyond the current crisis.

CONFLICTS OF INTEREST
Both authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS
Rainer Seitz wrote the manuscript; both authors contributed to the concept, literature search, and conclusions.

Rainer Seitz1
Wolfgang Schramm2

1Paul-Ehrlich-Institut, Langen, Germany
2Ludwig-Maximilians University (LMU), Rudolf Marx Stiftung, Munich, Germany

Correspondence
Rainer Seitz, Paul-Ehrlich-Institut, Langen, Germany.
Email: Rainer-Seitz@t-online.de

REFERENCES
1. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-847.
2. Taylor FB, Toh CH, Hoots WK, et al. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost. 2001;86(5):1327-1330.
3. Lillicrap D. Disseminated intravascular coagulation in patients with 2019-nCoV pneumonia. J Thromb Haemost. 2020;18:786-787.
4. Wang J, Hajizadeh N, Moore EE, et al. Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): a case series. J Thromb Haemost. 2020;18:1752-1755.
5. Umemura Y, Yamakava K, Ogura H. Efficacy and safety of anticoagulant therapy in three specific populations with sepsis: a meta-analysis of randomized controlled trials. J Thromb Haemost. 2015;14:518-530.
6. Warren BL, Eid A, Singer P, et al. Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: a randomized controlled trial. JAMA. 2001;286:1869-1878.
7. Murao S, Yamakawa K. A systematic summary of systematic reviews on anticoagulant therapy in sepsis. J Clin Med. 2019;8:1869.

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Hereditary haemorrhagic telangiectasia: A disease not to be forgotten during the COVID-19 pandemic

Dear Editor,

From November 2019 to date, almost six thousand papers have been published on COVID-19, the disease caused by SARS-CoV-2 infection. As physicians working in a multidisciplinary center for the cure of hereditary haemorrhagic telangiectasia (HHT) in a country (Italy) that has been severely affected by COVID-19, we are surprised that, among this impressive amount of publications, there is none on HHT. Indeed, we performed our last PubMed search on
22 April 2020, using the keywords “hereditary haemorrhagic telangiectasia” OR “hereditary hemorrhagic telangiectasia” OR “HHT” OR “Rendu-Osler-Weber” AND “COVID-19” OR “coronavirus,” and found no papers. This is surprising, because, although HHT is a rare disease, there are many reasons why we believe that it deserves special attention during the COVID-19 pandemic. One reason is that almost 95% of subjects with HHT have spontaneous and sudden epistaxis, which sometimes may simply require self-treatment and home remedies, but may also lead to procedural interventions in medical offices, emergency departments, hospitals, and operating rooms. The manipulation of nostrils, nasal cavity, or nasopharynx, either done at home by family members or caregivers or performed in a hospital setting by medical personnel, may expose patients to increased risk of contracting the infection. Another reason is that subjects with HHT often suffer from medical conditions that may negatively influence the clinical course of COVID-19. These include chronic anemia, heart failure, pulmonary arteriovenous malformations (AVMs), and pulmonary hypertension. All these diseases may be associated with chronic hypoxemia, which might further worsen in case of COVID-19 pneumonia. Particular attention should then be paid to the fact that subjects affected by COVID-19 seem to be at increased risk of thrombosis. This is a delicate issue for HHT patients, because it has been demonstrated that, despite the presence of an overwhelming bleeding propensity, they may also suffer from thrombotic complications. Indeed, they may develop paradoxical thromboembolic stroke from pulmonary AVMs and also possess an inherent prothrombotic state related to disturbances in the regulation of coagulation at the endothelial surface, with levels of coagulation factor VIII (FVIII) being higher in HHT subjects than the general population and the degree of FVIII elevation correlating with thrombotic risk. It should also be considered that some HHT patients are receiving treatment with medications that are either associated with an increased risk for thrombosis or interfere with the natural clot disintegration, such as thalidomide, pomalidomide, tamoxifen, pazopanib, bevacizumab, aminocaproic acid, and tranexamic acid. These people might therefore be at even higher risk of coagulopathy in case of SARS-CoV-2 infection. The other side of the coin is that antithrombotic therapy cannot be used lightly in HHT, because this disease primarily is a hemorrhagic disorder, characterized by the presence not only of epistaxis, but also of vascular malformations in the brain and gastrointestinal telangiectasia. We have recently shown that antithrombotic therapy may be well tolerated by subjects with HHT, but this certainly requires a careful evaluation by experienced physicians. Indeed, there are other studies that report significant worsening of epistaxis and increased gastrointestinal bleeding in HHT subjects treated with anticoagulants. We are not fully satisfied with the suggestions that medical societies are giving on this issue. For instance, in the International Society on Thrombosis and Haemostasis interim guidance on recognition and management of coagulopathy in COVID-19, that has been recently published in the Journal of Thrombosis and Haemostasis, the only contraindications that are mentioned, regarding the use of heparin in hospitalized COVID-19 patients, are active bleeding and reduced platelet count (less than $25 \times 10^5/L$). Additionally, many physicians around the world have the feeling that standard pharmacological thromboprophylaxis is not enough and advocate the use of higher, and even therapeutic, doses of heparin to prevent thrombotic complications in hospitalized COVID-19 patients. The risk-benefit ratio of such a therapeutic approach in HHT patients is completely unknown. Last but not least is the psychological impact that the COVID-19 pandemic may have on subjects affected by HHT. A high prevalence of depressive and post-traumatic stress disorder symptoms has been reported in HHT and we know, based on our personal experience, that subjects with HHT require particular care also at the psychological level. Isolation, social distancing, hospital restrictions, and closure of many HHT outpatient clinics may have severe deleterious effects on the mood of these patients. We call for a sustained effort by the medical and scientific HHT community to reduce the burden of COVID-19 on our patients.

CONFLICT OF INTEREST
The authors have no conflicts of interest to disclose in relation to this study.

AUTHOR CONTRIBUTIONS
All the authors contributed to conceptualization of the manuscript and provided constructive criticisms. Eleonora Gaetani also wrote the article.

Eleonora Gaetani
Passali Giulio Cesare
Maria E. Riccioni
Annalisa Tortora
Roberto Pola
Guido Costamagna
Antonio Gasbarrini
on behalf of the Multidisciplinary Gemelli Group for HHT

1Department of Medical and Surgical Sciences, Università Cattolica del Sacro Cuore School of Medicine, Rome, Italy
2Division of Otorhinolaryngology, Università Cattolica del Sacro Cuore School of Medicine, Rome, Italy
3Department of Cardiovascular Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore School of Medicine, Rome, Italy

Correspondence
Eleonora Gaetani, Istituto di Patologia Speciale Medica, 6th floor, C wing, Policlinico A. Gemelli, Lgo. A. Gemelli 8, 00168 Rome, Italy.
Email: eleonora.gaetani@unicatt.it

ORCID
Eleonora Gaetani https://orcid.org/0000-0002-78081491
Roberto Pola https://orcid.org/0000-0001-5224-2931
REFERENCES

1. Shovlin CL, Buscarini E, Kjeldsen AD, et al. European Reference Network For Rare Vascular Diseases (VASCERN) Outcome Measures For Hereditary Haemorrhagic Telangiectasia (HHT). Orphanet J Rare Dis. 2018;13:136.
2. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. J Am Coll Cardiol. 2020;75:2950-2973.
3. Shovlin CL. Circulatory contributors to the phenotype in hereditary hemorrhagic telangiectasia. Front Genet. 2015;6:101.
4. Cure HHT Official Health Updates: Coronavirus Disease (COVID-19). https://curehht.org/covid19/. Accessed April 17, 2020
5. Gaetani E, Agostini F, Porfidia A, et al. Safety of antithrombotic therapy in subjects with hereditary hemorrhagic telangiectasia: prospective data from a multidisciplinary working group. Orphanet J Rare Dis. 2019;14:298.
6. Shovlin CL, Millar CM, Droegge F, et al. VASCERN-HHT. Orphanet J Rare Dis. 2019;14:210.
7. Riera-Mestre A, Mora-Luján JM, Trujillo-Santos J, et al. Natural history of patients with venous thromboembolism and hereditary hemorrhagic telangiectasia. Findings from the RIETE registry. Orphanet J Rare Dis. 2019;14:196.
8. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost. 2020;18(5):1023-1026.
9. Barrett CD, Moore HB, Yaffe MB, Moore EE. ISTH interim guidance on recognition and management of coagulopathy in COVID-19: a comment. J Thromb Haemost. 2020. https://doi.org/10.1111/jth.14860
10. Chaturvedi S, Clancy M, Schaefer N, Oluwole O, McCrae KR. Depression and post-traumatic stress disorder in individuals with hereditary hemorrhagic telangiectasia: a cross-sectional survey. Thromb Res. 2017;153:14-18.