Preface

Maintaining Hemostasis and Preventing Thrombosis in Coronavirus Disease 2019 (COVID-19)—Part IV

Emmanuel J. Favaloro, PhD, FFSc, RCPA[1] Leonardo Pasalic, FRCPA, FRACP, PhD[1]
Giuseppe Lippi, MD[2]

[1] Department of Haematology, Sydney Centres for Thrombosis and Haemostasis, Institute of Clinical Pathology and Medical Research (ICPMR), Westmead Hospital, Westmead, Australia
[2] Section of Clinical Biochemistry and School of Medicine, University of Verona, Verona, Italy

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Welcome to another issue of *Seminars in Thrombosis and Hemostasis* (STH), published under the "banner" of "Maintaining hemostasis and preventing thrombosis in coronavirus disease 2019 (COVID-19)," this being Part IV, or the fourth such volume. The first three issues were, respectively, published in 2020,[1] 2021,[2] and 2022,[3] and proved very popular with the STH readership. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Believed to originate from Wuhan City in China, with the first reported case in November 2019, at the time of writing, there were over 630 million cases reported worldwide and over 6.5 million attributable deaths, thus including it among the 10 most deadly pandemics throughout recent human history.[4]

This compares with 200 million cases reported worldwide and over 4.3 million attributable deaths at the time of writing the third issue's Preface (August 11, 2021),[3] 113 million cases reported worldwide and over 2.5 million attributable deaths at the time of writing the second issue's Preface (February 27, 2021),[2] and 26 million cases reported worldwide and nearly 900,000 attributable deaths at time of writing the first COVID-19 issue Preface (August 30, 2020)[1] (►**Fig. 1**). From a smattering of reports in the scientific literature in late 2019 ($n = 228$), there are now over 300,000 publications ascribed to COVID-19 in PubMed, including over 33,000 reviews. This compares to 165,000 publications, including over 18,000 reviews, at the time of writing the third COVID-19 issue Preface,[3] 100,000 publications, including almost 12,000 reviews, at the time of writing the second COVID-19 issue Preface,[2] and 51,000 publications, including over 5,000 reviews, at the time of writing the first COVID-19 issue Preface (►**Fig. 1**).[1] Thus, cases of COVID-19 have grown 24-fold, and attributable deaths over 7-fold, since writing the first Preface. We were hopeful, at the time of writing the Preface for the third issue,[3] that these trends had finally started to show a slowdown, assisted by herd immunity and development and use of several vaccines against SARS-CoV-2 at that time.[4–7] Nevertheless, the data seem to show otherwise, mostly due to continuous incorporation of so-called (immunological) "escape" mutations within the SARS-Cov-2 genome, which make natural and vaccine-elicited immunity soon relatively obsolete and thus less efficient for preventing infections by new lineages. Although many have started to speak of "postpandemic," it is not clear to us that the pandemic is yet truly over (►**Fig. 1**), while its clinical and social consequences in terms of developing the "long-COVID" syndrome are only now becoming evident. However, the proportion of deaths per number of cases seems to be falling (►**Fig. 2**), so likely the vaccination drive has at least started to slow the death rate from COVID-19, testifying that immunity developed by natural infection or vaccination is at least efficient for preventing unfavorable disease progression.

Publications have also kept pace, and those related to COVID-19 have increased sixfold since the first issue Preface, just over 2 years ago.[1] As noted previously, this intriguing virus continues to mutate, evolves, and attempts to adapt to the host (i.e., us), and this may continue to be the state of play, at least for the immediate future, as previously mentioned. Several variants have evolved, more infectious and virulent, but not necessarily deadlier than the prototype strain sequenced in Wuhan, but notably also more seriously affecting the younger population.[5–7] SARS-CoV-2 vaccines were developed and approved for use in a previously unachievable timeframe, with the first regulatory approvals seeing vaccine

Address for correspondence Emmanuel J. Favaloro, PhD, FFSc, RCPA, Department of Haematology, Institute of Clinical Pathology and Medical Research (ICPMR), Westmead Hospital, Westmead, Australia (e-mail: emmanuel.favaloro@health.nsw.gov.au).

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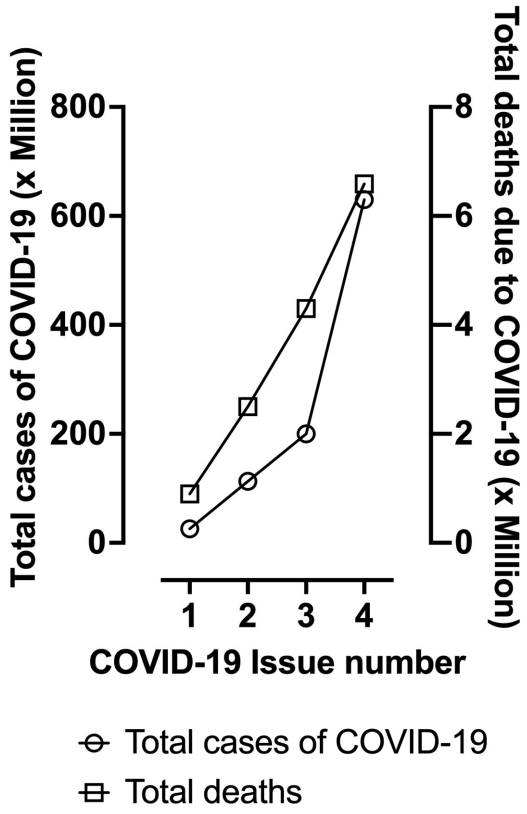

Fig. 1 Total global number of reported COVID-19 cases at the time of preparation of Prefaces for this COVID-19 issue series (left y-axis) and total global number of reported COVID-19 deaths at that same time (right y-axis).

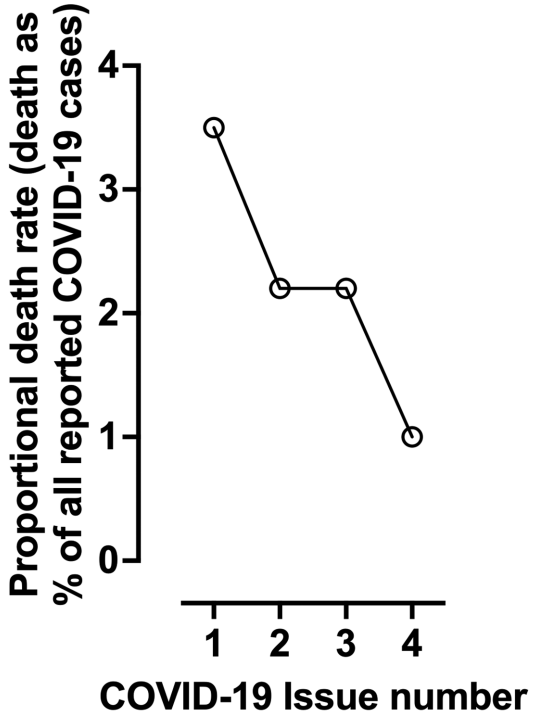

Fig. 2 Proportional death rate from ►**Fig. 1** (i.e., total deaths as percent of all reported COVID-19 cases at the time of preparation of Prefaces for this COVID-19 issue series).

use beginning at the end of 2021, basically within 1 year of the emergence of COVID-19. At the time of writing, some 20 vaccines have been authorized by at least one national regulatory authority for public use: two RNA vaccines (Pfizer–BioNTech and Moderna), four viral vector vaccines (Sputnik V, Oxford–AstraZeneca, Convidecia, and Janssen), seven conventional inactivated vaccines (Chinese CoronaVac, Sinopharm BIBP and WIBP vaccines; Indian Covaxin; pending: the Russian CoviVac; the Kazakh vaccine QazVac; and the Iranian COVIran Barekat), and four protein subunit vaccines (peptide vaccine EpiVacCorona, ZF2001, MVC-COV1901, and Corbevax; and vaccines with pending authorizations include the Novavax COVID-19 vaccine, Soberana 02 [a conjugate vaccine], and the Sanofi–GSK vaccine).[8] New bivalent vaccines (i.e., containing sequences of the ancestral SARS-CoV-2 strain combined with those of the more recent Omicron BA.1 or BA.4/5 sublineages) and heterologous vaccine administration (i.e., priming dose with one vaccine formulation, followed by a boost with another vaccine formulation) have also emerged as opportunities to improve the generation of more efficient anti–SARS-CoV-2 neutralizing antibodies, especially when lower immunogenicity is expected (i.e., older age, immune compromise, cancer, impaired renal function, etc.). In addition, according to Wikipedia,[8] a total of "353 vaccine candidates are in various stages of development, with 135 in clinical research, including 38 in phase I trials, 32 in phase I–II trials, 39 in phase III trials, and 9 in phase IV development." It may be that even these may need continuing supplementation, given the rate of mutation and variant emergence. Another concern is that despite the ongoing COVID-19 vaccination campaigns, these drives have been variably successful, mainly due to issues around vaccine supply, access, equity, and even vaccination hesitancy, in part driven by misinformation in social media and by the emergence of rare but serious adverse events such as vaccine-induced immune thrombocytopenia with thrombosis (VITT), otherwise called thrombotic thrombocytopenia syndrome (TTS) by some regulatory authorities.[9]

Given the continued and vast explosion of information, it is impossible for any single person to keep up with the literature on COVID-19 (nearly 300 new articles are daily indexed in PubMed). Also, given the plethora of information, it becomes increasingly difficult to determine what novel information can or should be added to the list. In the first STH issue on COVID-19,[1] the editorial team of STH contributed enormously by generating a series of Commentaries, which have indeed proved very popular.[2] One situation that was clear to us at that time was that given the great interest and initial thirst for knowledge, all journals became very interested in publishing on COVID-19 and, indeed, many papers were fast-tracked to publication, and some have since also been retracted for a variety of reasons (i.e., mistakes, flawed study design, duplication, and so forth). The STH board decided that although STH needed to publish on COVID-19, it did not want to publish just anything on COVID-19, and so a fairly rigorous stance to acceptance of papers, just because

they mentioned COVID-19, was undertaken. Clearly, STH did not want to publish misinformation or even just add other "me too" papers (e.g., reviews similar to those that had already been published elsewhere). The second issue thus took some 6 months to accumulate enough material to collate into an issue,[2] the third issue took another 8 months, and the fourth current issue another 12 months. So, unlike many other journals, we had decided to resist publishing on COVID-19 just for the sake of publishing on this captivating topic, since just adding more "noise" to the literature may hinder rather than help the cause. Indeed, we now feel it is also time to cease publishing these special COVID-19–related issues. Provided that the virus will not completely modify its biological and clinical characteristics, future accepted manuscripts related to COVID-19 will be published in the general "nonthemed" ongoing compilation series.

Given the emergence of vaccines against SARS-CoV-2, it is perhaps timely then to provide updated information on one of the rare adverse effects of immunization, namely VITT/TTS. Under the direction of Maha Othman, Zidan et al provide a minireview on the diagnostic discrepancies and global implications of VITT/TTS.[10] This rare outcome of vaccination has been reported in association with the adenovirus vector–based vaccines ChAdOx1 nCoV-19 (Oxford–AstraZeneca), Ad26.COV2.S (Janssen/Johnson & Johnson), and most recently against Sputnik V. VITT is characterized by thrombosis, typically at unusual sites,[9] low fibrinogen, and elevated plasma D-dimer, generally manifesting between 4 and 28 days following vaccination.[11] Detection of antiplatelet factor (PF4) antibodies using an enzyme-linked immunosorbent assay (ELISA) is often confirmatory. Although several similar principles subside in most diagnostic criteria for VITT,[12] the presentation of a positive ELISA assay, use of expert hematology and neurology opinion, and exclusion of possible VITT cases outside the "standard" 4- to 28-day timeframe have contributed a lack of global standardization for defining VITT. Accordingly, the global and regional incidence of VITT differs according to the diagnostic pathway and case definition used. This has influenced the public perception of VITT severity and whether or not to continue to use adenovirus vector–based vaccines for limiting SARS-CoV-2 infection. The authors thereby delineate the recognized pathogenic mechanisms, global incidence, discrepancies in diagnostic criteria, recommended treatments, and global implications to vaccine hesitancy from this serious coagulopathy.

We continue discussion of possible vaccine-related adverse events in the next contribution Franchini and colleagues,[13] who evaluate the possibility of a signal for acquired hemophilia A (AHA) as associated with COVID-19 vaccination. AHA is a rare but life-threatening disorder, and most commonly occurs in older people or during pregnancy. During the COVID-19 vaccination campaign, an unexpected number of newly diagnosed AHA have been identified in clinical practice that were temporally related to COVID-19 vaccination. The authors therefore present the results of a signal detection analysis, aimed at exploring a possible association between COVID-19 immunization and occurrence of AHA. A disproportionality analysis on the World Health Organization (WHO) database was performed to investigate the presence of a signal of risk for AHA associated with COVID-19 vaccines. Reports of AHA associated with any COVID-19 vaccine included in the WHO database were then integrated with those available on the Food and Drug Administration (FDA) Vaccine Adverse Events Reporting System (VAERS) and those published in the medical literature. The WHO database included 146 reports of AHA. The information component (IC) was significant for the association of AHA with all COVID-19 vaccines (IC025: 1.1) and with the vaccine product BNT162b2 (IC025: 1.6). After duplicate exclusion, 96 unique cases of AHA following COVID-19 vaccines were reviewed by the authors. Median time to diagnosis was 18 days and 40% of cases documented the occurrence after the second dose. Overall, in 57% of the investigated cases, a pre-existing condition predisposing to AHA was excluded. About 22% of cases occurred in subjects with age $\leq$ 65 years and there was no case associated with pregnancy. Mortality was 11%. Although the authors could not exclude that the unexpected frequency of AHA diagnosis can be explained by a detection bias, the signal for COVID-19 vaccine–related AHA appears to be robust and therefore deserves further investigation. Of interest, and in contrast to VITT/TTS, the majority of cases of AHA were associated with the use of mRNA-based vaccines (not adenovirus-based vaccines).

Naturally, despite the devastation that rare disorders associated with vaccine use may cause, COVID-19 is by far a worse and more serious condition, and potentially affects many more people. As a pandemic, it is inevitable that all of us will be exposed to SARS-CoV-2 at some time, with a risk of death of close to 2 to 3% overall in unvaccinated people, increasing for those with comorbidities, advanced age, and extremes of body weight. In contrast, the relative risk of dying from VITT is around 1 in a million vaccinations. Accordingly, the majority of this issue, as with past issues,[1–3] is focused on COVID-19.

First, two of the Guest Editors to this issue, Lippi and Favaloro, discuss what we know (and do not know) regarding the pathogenesis of pulmonary thrombosis in COVID-19.[14] The clinical course of COVID-19 is often complicated by the onset of venous thrombosis and venous thromboembolism (VTE), encompassing also pulmonary thrombosis. Recent statistics attests that the cumulative frequency of VTE can be as high as 30% in COVID-19 hospitalized patients, increasing to nearly 40 to 70% (depending on systematic screening) in those with severe illness, mechanical ventilation, or intensive care unit admission. The risk of venous thrombosis seems mostly limited to the active phase of disease, and is directly associated with some genetic (i.e., inherited prothrombotic predisposition) and demographical factors (male sex, overweight/obesity), disease severity (risk increasing progressively from hospitalization to development of severe illness, with the highest being in patients needing mechanical ventilation and/or intensive care), presence and extent of pulmonary disease, and coexistence of multiple risk factors (immobilization, mechanical ventilation, co- or superinfections), along with increased values of inflammatory and

thrombotic biomarkers. At least three different phenotypes of pulmonary thrombosis may develop in COVID-19 patients, one caused by typical embolization from peripheral venous thrombosis (e.g., deep vein thrombosis; thereby leading to pulmonary embolism [PE]), a second type triggered by local inflammation of nearby pulmonary tissue, and a third one mostly attributable to the prothrombotic state consequent to the pronounced systemic inflammatory response (i.e., the so-called cytokine storm) that is frequently observed in COVID-19. Although the pathogenesis of these three conditions has different features, their discrimination is essential for diagnostic and therapeutic purposes. The prognosis of COVID-19 patients who develop pulmonary thrombosis is also considerably worse than those who do not, thus probably needing frequent monitoring and more aggressive therapeutic management.

Discussion of pulmonary thrombosis in the form of COVID-19–associated PE continues in an original study from a team of RIETE Investigators.[15] The aim of this study was to compare the clinical characteristics, treatment, and 90-day outcomes in patients diagnosed with PE while recovering from COVID-19 in the outpatient setting versus those who were diagnosed with PE while being hospitalized with COVID-19. Data from the international RIETE registry were used. The major study outcomes were all-cause death, major bleeding, and VTE recurrences during the first 90 days after PE. Over a 1-year period from March 2020 to March 2021, 737 patients with COVID-19 experienced acute PE. Of these, 340 (46%) were recovering from COVID-19 as outpatients (267 patients who had been treated at home for COVID-19 and 73 discharged after being hospitalized with COVID-19). Compared with inpatients with COVID-19, those recovering in the outpatient setting from COVID-19 and experiencing a PE were less likely to be men (odds ratio [OR]: 0.54; 95% confidence interval [CI]: 0.40–0.72) and less likely to have hypertension (OR: 0.55; 95% CI: 0.41–0.74) or diabetes (OR: 0.51; 95% CI: 0.33–0.76). At 90-day follow-up, eight patients (none recovering from COVID-19 as outpatient vs 2.4% of inpatients with COVID-19) developed recurrent VTE, 34 (1.9% vs 7.9%) had major bleeding, and 128 (10% vs 24%) died. On multivariable analysis, inpatients with COVID-19 were at a higher risk for major bleeding (adjusted hazard ratio [HR]: 6.80; 95% CI: 1.52–30.4) or death (adjusted HR: 2.24; 95% CI: 1.40–3.58). In conclusion, using a large multinational registry of patients with COVID-19 who experienced PE, thromboembolic episodes occurring in those recovering from COVID-19 as outpatients were associated with less ominous outcomes than inpatients with COVID-19.

We move from VTE to arterial thrombosis in COVID-19 in the next contribution by Candeloro and Schulman.[16] It is well established that the risk of VTE is high in COVID-19, but the frequency of arterial thromboembolic events (ATEs) in hospitalized patients with COVID-19 is less clear, as is the magnitude of these events in comparison with other infections. The authors searched MEDLINE from February 2020 to February 2022 for prospective or retrospective cohort studies and randomized clinical trials that reported the number of acute myocardial infarction (AMI), acute ischemic stroke (AIS), acute limb ischemia (ALI), or other ATE as defined by the original authors in hospitalized patients with COVID-19. The pooled frequencies were calculated though meta-analysis using random-effects model with logit transformation and presented with relative 95% prediction intervals (95% PIs). The authors retrieved a total of 4,547 studies, 36 of which (28 retrospective cohorts, 5 prospective cohorts, and 3 randomized trials) were finally included in their analysis. The resulting cohort counted 100,949 patients, 2,641 (2.6%) of whom experienced ATE. The pooled ATE frequency was 2.0% (95% PI: 0.4–9.6). The pooled ATE frequency for AMI, AIS, ALI, and other ATE was 0.8% (95% PI: 0.1–8.1), 0.9% (95% PI: 0.3–2.9), 0.2% (95% PI: 0.0–4.2), and 0.5% (95% PI: 0.1–3.0), respectively. In comparison with ATE incidence reported in three studies on non–COVID-19 viral pneumonia, the authors did not detect a significant difference from the results in their analysis. In conclusion, the authors found a nonnegligible proportion of ATE in patients hospitalized for COVID-19, but these results were similar to those found in hospitalized patients with influenza or with non–COVID-19 viral pneumonia.

Next is a review by Iba and colleagues, who discuss platelet activation and thrombosis in COVID-19.[17] Although thrombosis frequently occurs in infectious diseases, the coagulopathy associated with COVID-19 has unique characteristics. Compared with bacterial sepsis, COVID-19–associated coagulopathy presents with minimal changes in platelet counts, prothrombin times are often normal, and D-dimer as well as fibrinogen level are increased. These differences can be explained by the distinct pathophysiology of the thromboinflammatory responses. In sepsis-induced coagulopathy, leukocytes are primarily responsible for the coagulopathy by expressing tissue factor, releasing neutrophil extracellular traps, multiple procoagulant substances, and systemic endothelial injury that is often associated with vasoplegia and shock. In COVID-19–associated coagulopathy, platelet activation is a major driver of inflammation/thrombogenesis and von Willebrand factor (VWF) and PF4 are also deeply involved in the pathogenesis. Although the initial responses are localized to the lung, they can spread systemically if the disease becomes severe. Despite platelet activation, platelet count is usually normal at presentation, but sensitive biomarkers including VWF activity, soluble P-selectin, and soluble C-type lectin-like receptor 2 are elevated, and they increase as the disease progresses. Although the role of antiplatelet therapy in COVID-19 is still unproven, current studies are ongoing to determine its potential effects.

The last full-length paper in this STH issue is another review by Rizk and colleagues, this time on anticoagulation in COVID-19.[18] We have already established that COVID-19 is associated with a hypercoagulable state and also believed to be strongly supported by a proinflammatory state. The hypercoagulable state in turn results in increased incidence of arterial thromboembolism and VTE seen in hospitalized COVID-19 when compared with hospitalized non–COVID-19 patient cohorts. Moreover, patients with arterial thrombosis or VTE and COVID-19 have higher mortality compared with COVID-19 patients without. Prevention of arterial

thrombosis or VTE thus remains an essential question in the management of COVID-19 patients, especially because of high rates of reported microvascular and macrovascular thrombosis. This has prompted multiple randomized control trials (RCTs) evaluating different anticoagulation strategies in COVID-19 patients at various stages of disease. The authors therefore review findings from RCTs in the past 2 years of antithrombotic therapy in critically ill hospitalized patients, noncritically ill hospitalized patients, patients postdischarge from the hospital, and outpatients. RCTs in critically ill patients demonstrated therapeutic dose anticoagulation does not improve outcomes and has more bleeding than prophylaxis dose anticoagulant in these patients. Trials in noncritically ill hospitalized patients showed a therapeutic dose anticoagulation with a heparin formulation might improve clinical outcomes. Anticoagulation with a direct oral anticoagulant after hospital discharge may improve outcomes, although there is a large RCT in progress. Nonhospitalized COVID-19 patients have an insufficient burden of events to be candidates for antithrombotic therapy. Anticoagulation in pregnant and lactating patients with COVID-19, as well as antiplatelet therapy for COVID-19, is also reviewed by the authors.

The remainder of this issue contains several Commentaries as well as Letters to the Editor ("correspondence").[19–29] Such material permits publication of various "smaller" COVID-19 vignettes. First comes a Commentary related to heparin anticoagulation in COVID-19 by Lippi et al.[19] The authors discuss the benefits of heparin use from the perspectives of pleiotropic antiviral activity beyond anticoagulant and anti-inflammatory properties. Next comes a series of Commentaries on the strength of anticoagulation in various categories of COVID-19 severity.[20–22] The final commentary in this issue of the journal is managing drug–drug interactions with oral anticoagulants and nirmatrelvir/ritonavir in COVID-19 outpatients by Rizk et al. The remainder of the issue contains some correspondence (i.e., Letters to the Editor),[24–29] around the possibility of acquired thrombotic thrombocytopenic purpura (aTTP) after COVID-19 mRNA vaccination, aspirin use reducing platelet hyperreactivity and degranulation in COVID-19 patients, antiphospholipid syndrome in COVID-19, and molecular mimicry between human PF4 and SARS-CoV-2 spike protein as potential basis for autoimmune responses in vaccinated and naturally infected patients. For aTTP post-COVID-19 mRNA vaccination and antiphospholipid syndrome in COVID-19, the real questions are whether these events are caused by or coincidental to vaccination or COVID-19. A more thorough evaluation of antiphospholipid syndrome in COVID-19, or more accurately the presence of antiphospholipid antibodies or lupus anticoagulant in COVID-19 patients, was explored in the third issue on COVID-19.[3,30,31]

We thank all the authors of this fourth issue of "Maintaining hemostasis and preventing thrombosis in COVID-19" for their contributions, and we hope that the readership of STH will enjoy this latest (and possibly final) instalment in this particular series. We also continue to hope that the global vaccination program acts to dampen the pandemic scourge that is COVID-19, which provides a risk of morbidity and mortality many folds higher than the overall rare risk of VITT/TTS, even in its most severe presentation as cerebral venous thrombosis.[9]

Conflict of Interest
None declared.

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