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SPECIAL ARTICLE

EDITOR'S CHOICE

The vascular side of COVID-19 disease

Position paper of the International Union of Angiology

Luca COSTANZO [1] *, Giacomo FAILLA [1], Pier L. ANTIGNANI [2], Jawied FAREED [3], Yongquan GU [4], Jan PITHA [5], Leonardo ALUIGI [6], Thomas KARPLUS [7], Armando MANSILHA [8]

[1]Unit of Angiology, Department of Cardio-Thoraco-Vascular, Policlinico-San Marco University Hospital, University of Catania, Catania, Italy; [2]Vascular Center, Nuova Villa Claudia Nursing Home, Rome, Italy; [3]Hemostasis and Thrombosis Research Laboratories, Loyola University Medical Center, Maywood, IL, USA; [4]Department of Vascular Surgery, XuanWu Hospital, Capital Medical University, Beijing, China; [5]Laboratory for Atherosclerosis Research, Center for Clinical and Experimental Medicine, Institute for Clinical and Experimental Medicine, Prague, Czech Republic; [6]Angiology Care Unit, Private Villalba Hospital (GVM), Bologna, Italy; [7]Department of Vascular Medicine, Sydney Local Health District, Concord Hospital, Sidney, Australia; [8]Faculty of Medicine, University of Porto, Porto, Portugal

*Corresponding author: Luca Costanzo, Unit of Angiology, Department of Cardio-Thoraco-Vascular, Policlinico-San Marco University Hospital, University of Catania, Catania, Italy. E-mail: lucacost84@gmail.com

ABSTRACT

The SARS-CoV-2 infection (COVID-19) is causing an ongoing pandemic and potentially fatal disease. Development of coagulopathy with thrombotic complications such as deep vein thrombosis and pulmonary embolism are emerging as factors for progression to severe disease and death. Also, a markedly increased level of D-dimer, a protein product of fibrin degradation, has been associated to mortality. Furthermore, activation of immune response due to virus infection may led to uncontrolled severe inflammation with damage to host cells and induction of endotheliitis and cellular apoptosis and pyroptosis. The use of low molecular weight heparin in early stage of the disease could prevent vascular complications and reduce the progression to severe stage of the disease. Aim of this paper was to summarize current evidence about vascular involvement in COVID-19 disease and potential antithrombotic therapy.

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Key words: COVID-19; Thrombosis; Blood coagulation disorders.

The Coronavirus disease of 2019 (COVID-19) is a viral illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). COVID-19 developed in the city of Wuhan, China, causing significant mortality in many countries and becoming a pandemic disease.[1]

Thromboembolic manifestation such as pulmonary embolism and disseminated intravascular coagulation (DIC) have been reported in COVID-19 disease.[2-4] Notably, the prevalence of deep vein thrombosis (DVT) in death patients for COVID-19 disease could be as high as 40%

according to the largest the largest overview of autopsies published up to date.[5]

The current manuscript summarizes the pathogenesis and available data on treatment and prevention of vascular complication in COVID-19.

Pathogenesis

SARS-CoV2 is an enveloped single-stranded RNA coronavirus of ~30 kb[6] which penetrates into human cells by binding the receptor angiotensin converting enzyme 2 (ACE2).[7] ACE2 is an integral membrane protein that is expressed in several tissues including lung alveolar cells, gastrointestinal tract, cardiac myocytes and the vascular endothelium.[8] Binding of the SARS-CoV-2 spike protein to ACE2 facilitates virus entry into lung alveolar cells.

The primary routes of transmission are through respiratory droplets and close person-to-person contact, however other modes of transmission such as fecal-oral have been hypothesized.[1, 9]

Transmission mainly occurs through viral particles inhalation and entry in the respiratory system: in addition, the virus can survive for 24-72 hours on surfaces, depending on the type of surface, which enables fomite transmission. The viral incubation period is 2-14 days and contagion may occur during the latency period.[10] Common laboratory abnormalities found in patients with COVID-19 include lymphopenia and elevation in lactate dehydrogenase

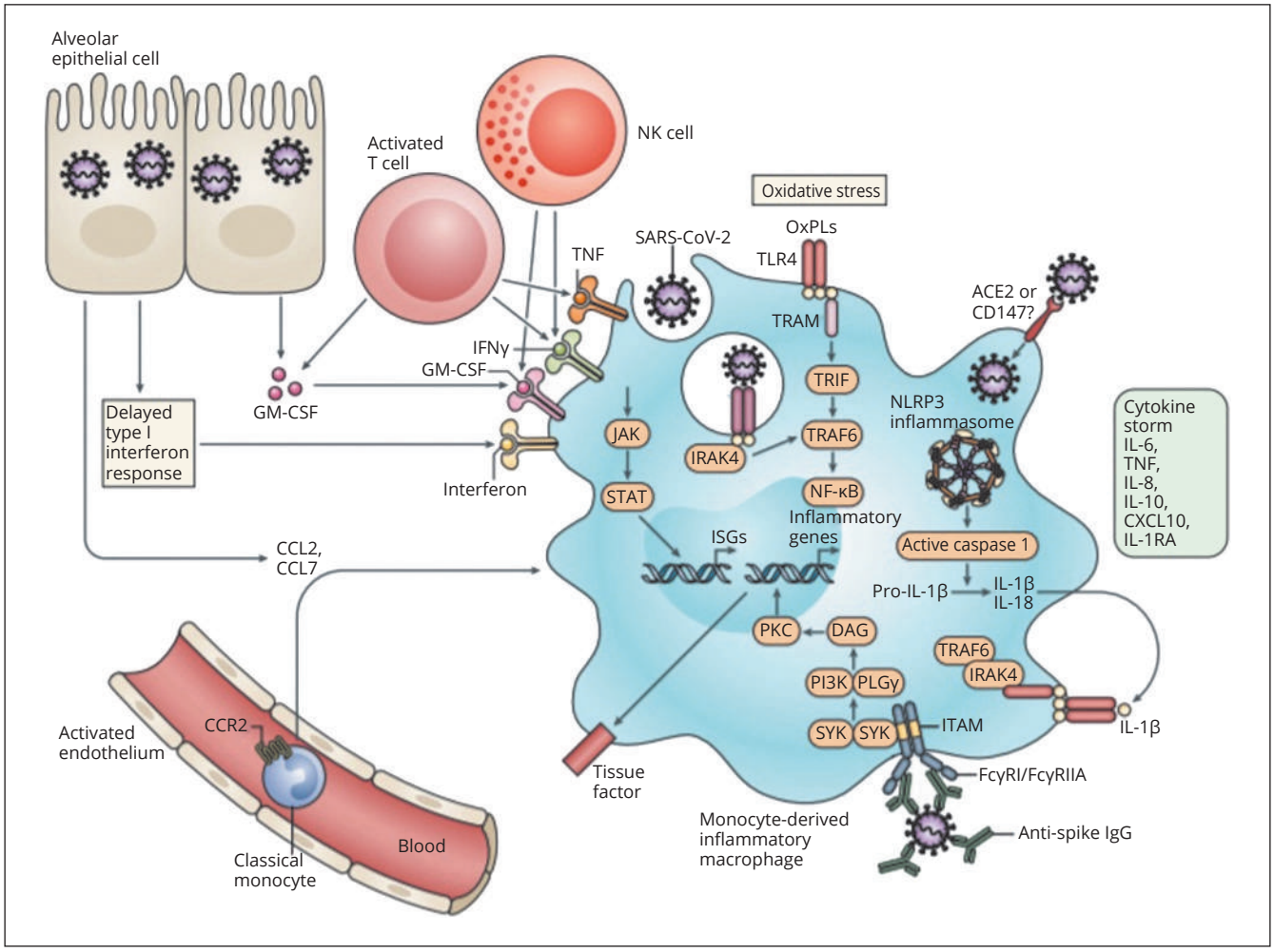

Figure 1.—Hypothesized pathways leading to hyperinflammation and activation of monocyte-derived macrophages in COVID-19. From Merad *et al.*[15] CCL: CC-chemokine ligand; CXCL10: CXC-chemokine ligand 10; ISG: interferon-stimulated gene; ITAM: immunoreceptor tyrosine-based activation motif; TRAM: TRIF-related adaptor molecule.

and inflammatory markers such as, C reactive protein, D-dimer, ferritin and interleukin-6 (IL-6). IL-6 levels may correlate with disease severity, and a procoagulant profile.

Activation of immune system and impairment of coagulation

Activation of immune responses and inflammation at different degree with systemic increase of several cytokines have been described in COVID-19 patients.[11] Cytokines play an important role during viral infection, indeed innate immune response is the first line of defense against viral infection.[12] However, damage to the host cells may occurs in case of uncontrolled inflammatory reaction. High levels IL-1B, IFN-γ, IP-10, IL-6 and monocyte chemoattractant protein 1 (MCP-1) have been found in patients with COVID-19 especially in those with severe disease.[13] Particularly, IL-6 has been found as a predictor of mortality. Development and progression of acute respiratory distress syndrome (ARDS) and multiorgan failure are features of the end stage COVID-19 disease and are related to the cytokine storm.[11, 14, 15] Figure 1[15] summarizes possible pathways contributing to hyperinflammation and activation of monocytes in COVID-19.

The activation of the coagulation system with thromboembolic manifestations including deep vein thrombosis, pulmonary embolism, arterial thrombotic events, and disseminated intravascular coagulopathy (DIC) have been described in such stage of disease.[2, 16, 17] The impairment of coagulation in COVID-19 may be caused by several factor: dysregulated immune activation, platelet and endothelial cells dysfunction, and impaired fibrinolysis. Also, hyperactivated monocytes may contribute to coagulation in COVID-19[15] (Figure 2).[15]

Apart from the cytokine storm described above, systemic activation of complement pathways has been described in a subset of severe COVID-19. In a recent series of histological examination, extensive deposits of the terminal complement complex C5b-9, C4d and MASP2 has been found in the lungs of two death for COVID-19.[18] Therefore, a thrombotic microvascular injury syndrome mediated by activation of complement pathways can be responsible of alveolar damage in severe COVID-19 cases (Figure 3).[18]

Thrombocytopenia

Thrombocytopenia might be a risk factor for COVID-19 severe disease as shown in a recent metanalysis from 31 observational studies involving 7613 participants in which authors found a lower platelet count in patients with severe COVID-19.[19] Although pathogenesis of thrombocytopenia in COVID-19 disease has not been fully clarified, thrombocytopenia caused by autoantibodies and a reduced

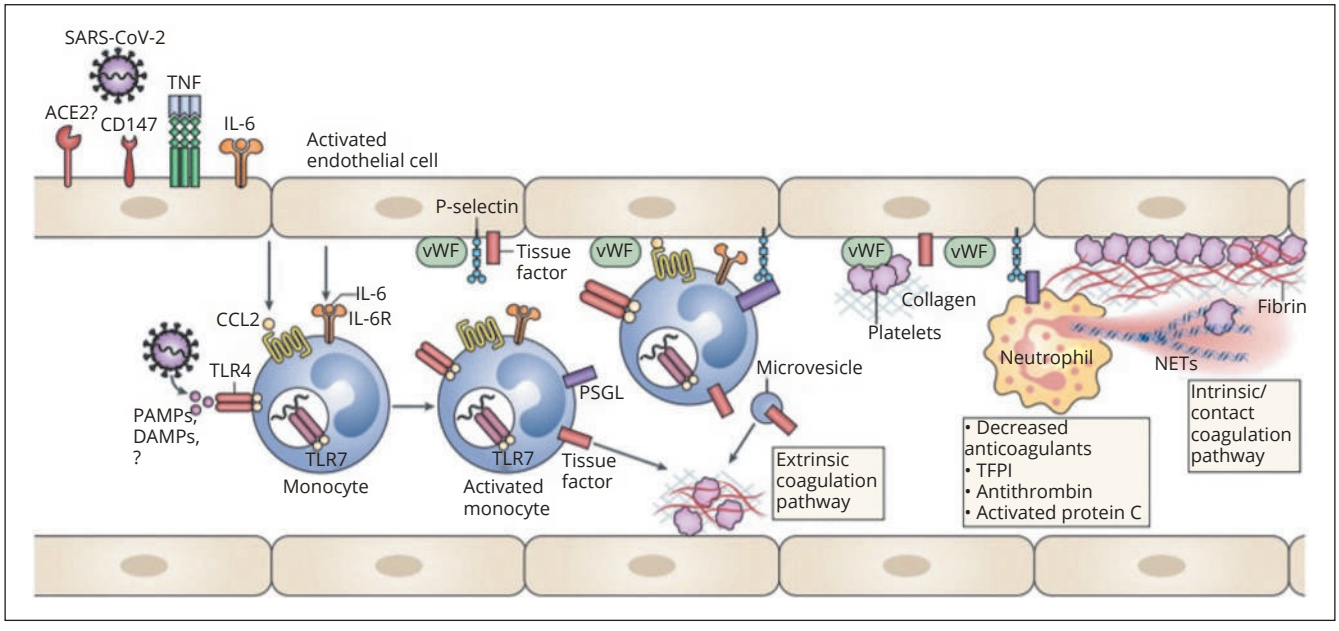

Figure 2.—Potential role of hyperactivated monocytes to coagulation in COVID-19. From Merad *et al.*[15]

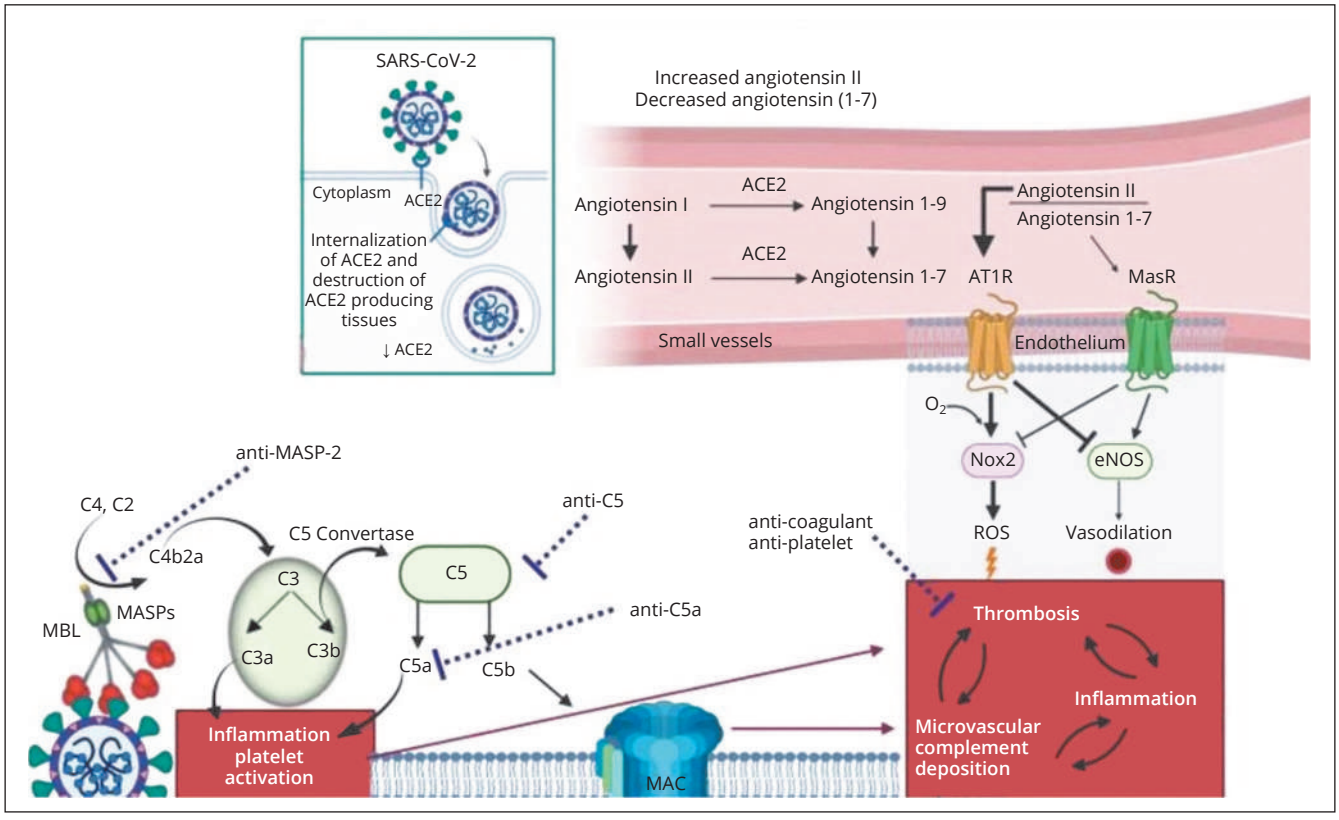

Figure 3.—Model for alternative pathway and lectin pathway of complement activation in COVID-19 and its interaction with coagulation. Modified from Magro *et al.*[18]

platelets production have been described in other respiratory infections such as SARS-CoV and influenza.[20] Furthermore, thrombocytopenia is frequently observed in patients in intensive care unit[21] and it is an indicator of the dysfunction of organs or systems. Another mechanism of platelet reduction in COVID-19 may be attributed to the damage of lung. Indeed, in severe SARS, viral damage or mechanical ventilation might lead platelet activation and aggregation, resulting in the consumption of platelet and the thrombocytopenia.[20]

Endothelial dysfunction

Endothelial cells play a crucial role in the regulation of coagulation, both producing and presenting anticoagulant markers as well as procoagulant factors. The endothelial cells involvement in COVID-19 could be hypothesized because the virus accesses host cells *via* the protein angiotensin-converting enzyme 2 (ACE2) that is also expressed by endothelial cells.[8] Evidence of direct viral infection of the endothelial cell and diffuse endothelial inflammation with cell death has been recently reported.[22] Author hypothesized that SARS-CoV-2 infection facilitates the induction of endotheliitis through direct viral damage, host inflammatory response and induction of apoptosis and pyroptosis.

Enhanced susceptibility to SARS-CoV-2 infection and fatality have been reported in elderly patients and with preexisting comorbidities including hypertension, diabetes, coronary heart disease, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), and chronic renal disease.[5, 23] All these medical conditions are associated with endothelial disfunction and impairment of plasmin/plasminogen system. Plasmin has been found to enhance the virulence and infectivity of SARS-CoV-2 virus by cleaving its spike protein augmenting its ability to bind to the host cell ACE2.[24] In the final stage of disease, high levels of D-dimer and products of the degradation of fibrinogen with possible occurrence of DIC have been reported; furthermore, markedly elevated D-dimer levels may results from plasmin-associated hyperactive fibrinolysis and

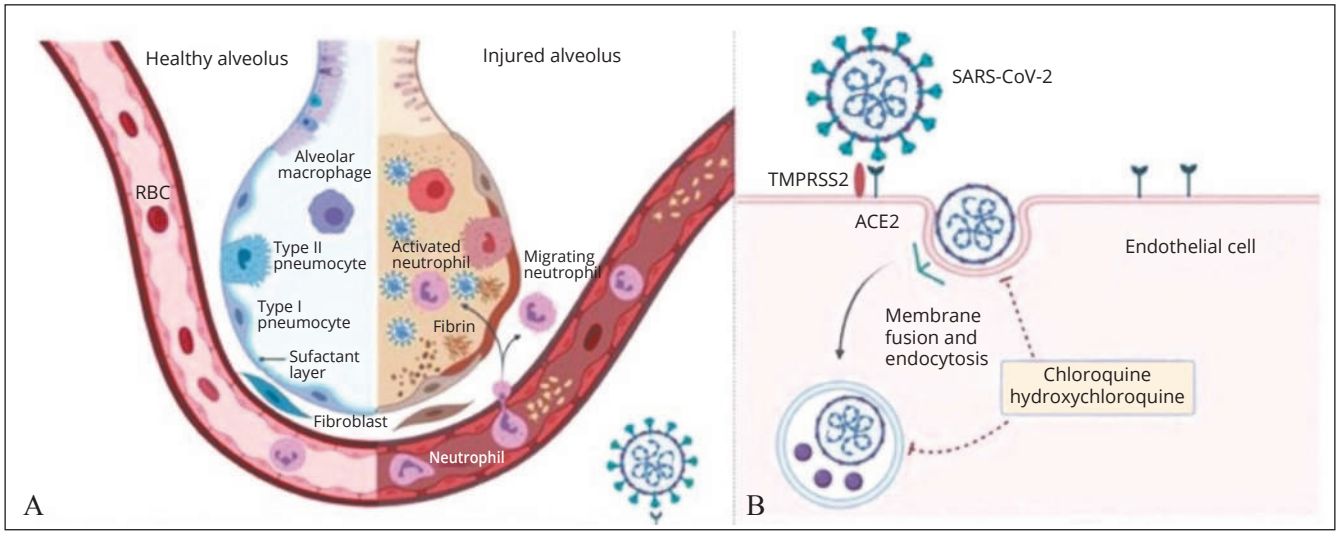

Figure 4.—Possible mechanism of thrombosis in COVID-19. A) Viral alveolar injury and inflammation, including fibrin deposition; B) viral entry into the endothelial cells and the possible protective effect of hydroxychloroquine.
Modified from Bikdeli *et al.*[36] COVID-19: Coronavirus disease 2019; tPA: tissue-type plasminogen activator.

correlated with more severe disease and mortality.[14, 23, 25] Notably, although less common than the thrombotic complications, in late stage of the disease major bleeding may occur especially in case of hemostatic defects such as thrombocytopenia or hypofibrinogenemia.[25]

Histological findings

Histological examinations confirmed the vascular inflammatory involvement at different stages of the disease. In an early phase of the lung pathology of COVID-19 pneumonia, focal hyperplasia of pneumocytes with patchy inflammatory cellular infiltration and proteinaceous exudate without prominent hyaline membranes or thrombosis have been found.[26] Conversely, in severe COVID-19, autopsy put on light a diffuse alveolar damage with fibrin exudation in alveoli, hyaline thrombi in small vessels and a thrombotic microangiopathy in lung associated with foci of alveolar hemorrhage.[27-29] Furthermore, a generalized thrombotic microvascular injury has been also documented in a series of lung and skin biopsies.[17]

Antithrombotic therapy in COVID-19

Several reports from literature discussed above emphasize the occurrence of thrombotic complications in COVID-19 patients especially in those in advanced stage of disease.

Currently, low molecular weight heparins (LMWHs) and fondaparinux, a synthetic analogue of the pentasaccharide sequence, are the gold standard treatment for the prevention of venous thromboembolism (VTE).[30] In different high-risk VTE clinical settings the selective inhibitor of activated factor X Fondaparinux has been associated with a superior efficacy than LMWH in terms of reduction of venous thromboembolism but with increased major bleeding.[31] Up to date, no report on use of Fondaparinux in COVID-19 for prevention of VTE has been published. Conversely, a favorable outcome was highlighted with the use of heparin in COVID-19 patients especially in those with markedly high D-dimer or with sepsis-induced coagulopathy.[32-34] Furthermore, LMWH seems to have anti-inflammatory actions[35] and an in-vitro interaction with SARS-CoV-2 protein receptor.[34] Although further extensive data are needed, LMWH use in COVID-19 patients can reduce the incidence of thrombotic complications and possibly decrease multi-organ damage. Timing of LMWH administration, dose and duration are the most critical questions.[35] Potential mechanism of treatments for management of COVID-19 induced thrombosis is elucidated in Figure 4.[36]

In asymptomatic patients LMWH prophylaxis should be considered in case of VTE risk factors (*i.e.* old age, reduced mobility, body mass index [BMI]>30, previous VTE, active cancer, etc.) balancing the hemorrhagic risk and monitoring of laboratory tests. Hypothetically, all symptomatic patients and those who required hospitalization should underwent LMWH prophylaxis unless there is an absolute contraindication. A daily dose of 40 mg of

with standard adjustments for renal insufficiency or obesity can be considered. In case of severe renal impairment (CrCl<30 mL/min) or acute kidney injury unfractionated heparin at the dosage of 5000 unit subcutaneously twice a day has to be used. Where the risk of bleeding is significant, mechanical thromboprophylaxis with anti-embolism stockings is recommended. Fondaparinux can be considered, especially in case of history or manifestation of heparin induced thrombocytopenia.

In very high VTE risk according to the clinical score adopted or in case of progressive worsening of respiratory symptoms associated with markedly increased D-dimer (*i.e.* 4-6 times the normal level), higher LMWH dosage could be considered. The use of therapeutic doses of LMWH should be considered in case of established diagnoses of VTE unless further evidence because of increased bleeding risk particularly in advanced stage of disease. If VTE is diagnosed, direct oral anticoagulant can be considered especially for extended treatment. No definitive recommendation has been published about duration of prophylaxis; in very high-risk patient LMWH prophylaxis could be considered as long as six weeks.

Finally, periodic monitoring of the coagulation parameters and reconsideration of therapy is mandatory due to the possible development of DIC and bleeding complications in severe stage of the disease. Notably, all recommendations may be susceptible to changes as evidence about COVID-19 disease are rapidly emerging.

Pediatric inflammatory multisystem syndrome temporally associated with SARS-COV-2

Associated with SARS-COV-2 is a rare condition affecting children named pediatric inflammatory multisystem syndrome temporally associated with SARS-COV-2 (PIMS-TS). It causes an acute inflammatory vasculitis associated with fever, shock, elevated inflammatory markers, abnormal coagulation studies, myocardial dysfunction, and coronary artery abnormalities.[37] Most patients with this condition showed evidence of seroconversion to the virus, but the tests were not done at the same time as the clinical episode.[38] PIMS-TS is characterized by lymphopenia, thrombocytopenia and myocarditis.[38] Twenty per cent of patients had coronary artery aneurysms in a recent study.[38] It has many of the characteristics of Kawasaki disease, another uncommon pediatric vasculitis.[39] The cause of Kawasaki disease (KD) is unknown, but it is thought to result from an excessive inflammatory response to a possible infective trigger.[40] The link between SARS-CoV-2 and PIMS-TS is unclear. The timing of SARS-COV-2 infection and clinical presentation would favor a delayed immune response to the virus. There was a 30-fold increase in cases of this KD-like disease in the Bergamo province of Italy during the peak of the SARS-COV-2 outbreak in April 2020, which is a strong temporal association.[38]

Conclusions

Shock is a feature of PIMS-TS[38] and occurs in a minority of children with KD.[41] Treatment is supportive if shock is present, with fluid resuscitation and possible inotropic support. Immunoglobulin therapy[42, 43] supplemented by steroids[38] is effective for the underlying condition. The prognosis is good, with recovery in most children.[38] A small number of deaths have been reported.[41] PIMS-TS is only reported in countries with a high incidence of SARS-COV-2 infection.[40]

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