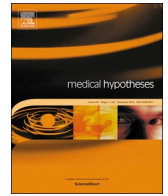




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Letter to Editors

Cytokine Storm: Is it the only major death factor in COVID-19 patients? Coagulation role



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Dear Editor,

I write to discuss the role of coagulation in severe cases of COVID-19 showing how we have previously focused too much on the inflammation, when instead the key to lower mortality rates and understanding this disease pathogenesis may very well be the coagulation disorder.

SARS-CoV, MERS-CoV and SARS-CoV-2 show a relatively higher mortality rates than other coronaviruses and are all associated with a cytokine storm, this might suggest that inflammatory responses play a role in the pathogenesis. If that is the case, targeting the coronavirus alone with antiviral therapy might not be enough to reverse highly pathogenic infections. This observation along with consideration to the cytokine storm phenomenon led to explore the use of anti-inflammatory therapy against those cytokines, an example of that is what is happening with Tocilizumab targeting Interleukin-6 (IL-6).

But is hyper-inflammatory state the sole factor responsible for acute lung injuries?

Some studies are starting to show the presence of an associated coagulopathy and, in some cases, antiphospholipid antibodies in patients with Covid-19 who showed multiple infarcts. These patients had evidence of ischemia in the lower limbs, in the hands and bilateral cerebral infarcts in multiple vascular territories. On admission their laboratory findings included leukocytosis, thrombocytopenia, and elevated prothrombin time and partial thromboplastin time, elevated levels of fibrinogen and D-dimer, and presence of anti-cardiolipin IgA antibodies, anti-beta2 glycoprotein IgA and IgG antibodies. Of note Lupus anticoagulant was not detected in those patients [1]. These results show a systemic coagulation disorder, but it is possible that the coagulopathy starts in the lungs, and only after it spreads into other organs. This might suggest that the cause of death might not be the inflammatory response itself but instead the local coagulation disorder. Coagulopathy in SARS-CoV-2 infection has been shown to be associated with high mortality, with elevated D-dimer levels and elevated fibrinogen degradation products (FDP), those being particularly important markers for the coagulopathy. A comparative analysis between survivors and non-survivors pneumonia patients revealed significantly higher D-dimers, FDP levels,

longer PT and aPTT compared to survivors on admission; more than 70% of non survivors met the criteria of disseminated intravascular coagulation (DIC) during hospitalization [2]. It has also become clear that COVID-19-related DIC is not a bleeding diathesis but rather a predominantly prothrombotic DIC with high venous thromboembolism rates, elevated D-dimer and fibrinogen levels, low anti-thrombin levels. The use of anticoagulant therapy with heparin showed to decrease mortality [3] This is especially so in patients who meet the sepsis induced coagulopathy (SIC) criteria (a score ≥ 4 is required) and in patients with markedly elevated D-dimer [3]. This suggests that Low molecular weight heparin (LMWH) at prophylactic dose should be considered in patients meeting SIC criteria and elevated D-dimer. Heparin has showed, besides its primary known use, to have also anti-inflammatory properties [4], that could be of therapeutic value in those patients with severe lung inflammation and impaired pulmonary exchange. ARDS is a common complication of COVID-19. Activation of coagulation system has been linked to ARDS onset. It has been shown that the median plasma concentrations of tissue factor and plasminogen activator inhibitor-1 were significantly higher at day seven in patients with ARDS, as compared to non-ARDS [5]. Coagulopathy arises from thrombin generation mediated by localized tissue factor, and depression of fibrinolysis usually mediated by plasminogen activator in the lungs, in accordance with an increase in PAI-1 [5]. This again points towards how heparin might be helpful in fighting this coagulopathy. Another interesting therapeutic property of heparin is its supposed antiviral role [6]. Heparin showed to inhibit infection in experimental vero cells injected with sputum from a patient with SARS-CoV pneumonia [7]. All these evidence and properties related to Heparin point toward a possible use of a low dose in the early stages of the disease to prevent the coagulation disorder from evolving and from spreading from the lungs to other organs.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2020.109829>.

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