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Letter to the Editor

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# A Proposal for Early, Multidisciplinary and Goal-Directed Sequential Treatment in Sars Cov2/Covid-19 Infection Requiring Hospitalization and Intensive Care Unit

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## Letter to the Editor

In December 2019, a series of cases of pneumonia of unknown cause were identified in Wuhan, Hubei, China, the clinical presentation resembling that of viral pneumonia [1]. Today it is widely recognized as a SARS CoV2/COVID 19 infection declared a pandemic by the World Health Organization, causing a large number of deaths [2].

This disease is characterized in most patients by isolated respiratory tract infection where about 80% of patients will have mild or asymptomatic disease, 15% will require hospitalization, and 5% of patients will require treatment in the intensive care unit for severe disease and increased risk of death [3]. The probability of death when admitted to the intensive care unit is 50% [4].

Described immunological-clinical findings on COVID-19 cases suggest that progression to severe forms of the disease can be associated with dysfunction of follicular T helper lymphocytes. These cells are specialized in supporting B lineage on the production of antibodies and this could be associated with higher mortality rates in older patients who present more often this immune disorder [5]. In addition, the causes of death in the elderly and high risk patients could be associated with propensity to develop vascular complications, with the awareness that the virus has potential of generating coagulopathy and a thrombotic tendency. Therefore, susceptible individuals with symptoms of known endothelial dysfunction, such as patients with diabetes mellitus, prior cardiovascular disease, and cancer with or without chemotherapy, are at increased mortality risk [6]. Although cancer patients are more likely to die because they are more prone to infection and its complications, asymptomatic disease has been increasingly reported in patients with targeted immune modulator therapies, including reversal of severe cases of COVID19 when adjusted for complete anti neo-plastic dose in some cases [7].

Patients requiring hospitalization and intensive care unit are at high risk of developing two fatal complications in addition to viral infection and lung damage; cytokine release syndrome (CRS) and disseminated intravascular coagulation (DIC) [8].

Experimental models suggest that SARS CoV2 infects type II alveolar cells mediated by the angiotensin-converting enzyme (ACE2) receptor. Most patients only develop a mild inflammatory response. A smaller group of patients develop a CRS which is a severe hyper inflammatory state associated with DIC that affects lung tissue inducing acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndromes (MODS). Patients with severe respiratory failure and ARDS, develop either macrophage activation syndrome or very low human leukocyte anti-gen D related (HLA-DR) expression accompanied by depletion of CD4 lymphocytes and natural killer cells. The pattern is distinct from bacterial sepsis or influenza, produced by immune dysregulation characterized by IL-6 mediate low HLA-DR expression and lymphopenia, associated with sustained cytokine production and hyper inflammation [9]. Multiple necropsy studies have shown how fibrin and micro thrombosis are found in pulmonary and extra pulmonary blood vessels [8,10,11] and reports of preserved respiratory system mechanics despite severe hypoxemia in early small series have led to hypothesize that a significant proportion of COVID-19 respiratory failure is not the typical acute respiratory distress syndrome (ARDS) and warrants alternative management [12,13].

Several and heterogeneous treatment strategies are currently used for this disease in patients who require hospitalization in general ward or intensive care. Most of them have not shown great benefits, possibly because of implementation in the full spectrum or at advanced late stages of the disease with critical requirement of prospective trials. Infectious SARS-COV2 disease itself, CRS, and DIC are present in different degrees of severity and undoubtedly require a staged specific treatment approach [8].

Two phases of the disease (viral and inflammatory) and three stages (early infection stage, pulmonary and hyper-inflammatory stage) have been proposed [10,14]. A first reasoning is that all affected symptomatic patients are subject to assessment of severity markers at diagnosis and during the disease including those initially negative. Patients with few symptoms may have abnormal laboratory tests with an increased risk of death [15].

If hospitalization is defined, the patient should be classified into one of the three stages of the disease with an early sequential intervention, directed by clinical and laboratory objectives, preventing progression to a hyper inflammatory state. There must be an interdisciplinary collaboration of specialized doctors in each area, that is, internal medicine, hematology, infectious diseases, intensive care, rheumatology, pulmonology and radiology, not only for the diagnosis and establishment of useful and timely therapies, but also in the need for monitoring related adverse reactions [4,16].

During stage I, innate immunity cells predominate before T lymphocytes are involved, leading antiviral response by producing cytotoxic molecules with the purpose of eliminating infected cells [17]. IgM production occurs during the first week of viral infection, subsequently, high affinity IgG antibodies are produced which

presumably play a protective role, although this has not been clearly established [18]. The most reasonable therapy at this point could be antiviral drugs, convalescent plasma or high doses of polyvalent immunoglobulin. Prophylactic heparin in high risk patients is recommended [19]. Stage I patients will go to cure most of the time, although the exact underlying immune mechanisms of failure to resolve early inflammation and advance to stage II are unknown. Establishing a regimen with anti-interleukin 6 (Tocilizumab) at this time or steroids could be physiologically counterproductive by blocking immune system on early infection attack and lead to high viral replication [16].

Phase II can be divided in stage IIa and IIb (depending on the presence or absence of hypoxemia). It is characterized by high viral proliferation and severe fast evolving pneumonia in which there are two enemies to attack: the virus and acute lung inflammation. Large amounts of inflammatory citokines/chemokines are produced by type II pneumocytes that lead to development of ARDS and may induce massive systemic release of acute phase reactants that are the basis of multiple organic dysfunction development [20].

Antiviral therapy remains important in phase IIa. The use of convalescent plasma is very plausible and it is important to define whether it is necessary to block the immune system or not, but in most cases, it is recommended not to implement it. Prophylactic heparin is recommended in all patients [16,19].

In phase IIb, blocking the immune system with high-dose steroids and anti-interleukin 6 therapies with tocilizumab gains importance [16]. The possible use of early mechanical ventilation is suggested because non-invasive mechanical ventilation is contraindicated in this setting [16]. Complete anticoagulation is recommended instead of prophylaxis in patients with highly elevated DIC markers [10] (Figure-1).

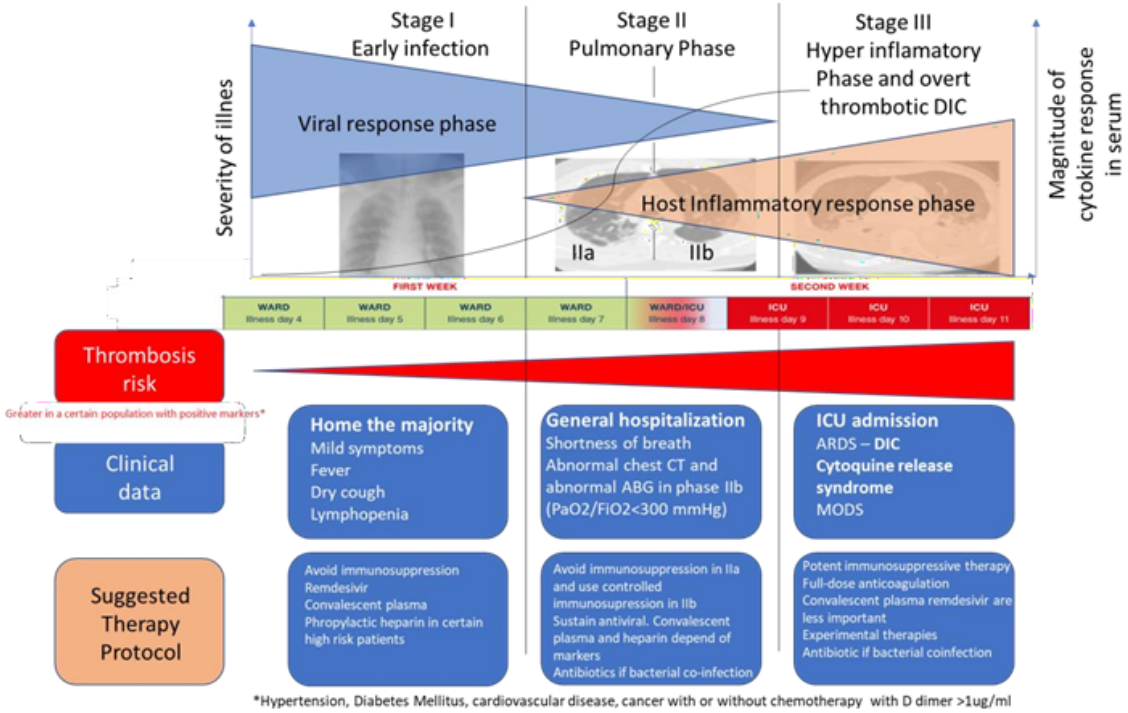


**Figure 1:** Schematic representation of phases of COVID19 with thrombosis risk, relevant clinical data and suggested protocol in each phase. HCQ, hydroxyl chloroquine; CT, computed tomography; ABG, arterial blood gases, CQ chloroquine; ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation. Modified from Siddiqi et al.

In phase III the immune system is overwhelmed and possibly is where there is the greatest risk of thrombosis; for this reason antiviral therapy and immune system modulation seem to lose importance and therapy should focus on powerful and complete blockage of the immune system and full anticoagulant therapy (especially for patients with high fibrinogen and D-dimer levels). Experimental biologically plausible treatments blocking tyrosine kinase pathway through Bruton kinase or JAK 2 inhibitors that are frequently used in oncologic hematology are showing promising results in severely ill patients [16,21,22]. Sequential early actions as conservative fluid administration are needed with the aim of reducing the rates of orotracheal intubation and thus mortality, if there is no improvement, protective mechanical ventilation should be provided (low Vt: 6 ml/kg and high PEEP in order to maintain plateau pressure less than 30 cmH2O and driving pressure less than 15 cmH2O), if despite these measures there is refractory hypoxemia, neuromuscular relaxation should be used and / or mechanical ventilation in prone [23].

We recognize the lack of health professionals in systems that can easily collapse, for this reason it is important to establish centralized protocols that can shed light on better management and contribute to improve survival of patients with COVID-19 [24].

We are also aware that our approach has important limitations given the lack of current prospective quality evidence, especially since the drugs included in the strategy have been used indiscriminately in all phases during the pandemic era, nevertheless early interventions, goal directed strategies and highly coordinated treatment can be crucial in the treatment of this terrible disease.

## Disclosure Statement

No potential conflict of interest was reported by the author(s).

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## References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, et al. (2020) Clinical features of patients infected with 2019 novel corona virus in Wuhan, China. Lancet 395: 497-506.
2. Rudan I (2020) A cascade of causes that led to the COVID-19 tragedy in Italy and in other European Union countries. J Glob Health 10: 010335.
3. Wu Z, McGoogan JM (2020) Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases from the Chinese Center for Disease Control and Prevention. Jama.
4. Ye Z, Rochwerg B, Wang Y, Adhikari NK, Murthy S, et al. (2020) Treatment of patients with nonsevere and severe coronavirus disease 2019: an evidence-based guideline. Cmaj 192: E536-E545.
5. Lefebvre J, Masters A, Hopkins J, Laura Haynes (2016) Age-related impairment of humoral response to influenza is associated with changes in antigen specific T follicular helper cell responses. Sci Rep 6.
6. Zhou F, Yu T, Du R, Fan G, Liu Y, et al. (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395: 1054-1062.
7. Treon SP, Castillo JJ, Skarbnik AP, Soumerai JD, Ghobrial IM, et al. (2020) The BTK-inhibitor ibrutinib may protect against pulmonary injury in COVID-19 infected patients. Blood 135: 1912–1915.
8. McGonagle D, Sharif K, O'Regan A, Bridgewood C (2020) The Role of Cytokines including Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like Disease. Autoimmun Rev 19: 102537.
9. Evangelos J, Mihai GN, Nikoletta R, Akinosoglou K, Antoniadou A, et al. (2020) Complex Immune Dysregulation in COVID-19 Patients With Severe Respiratory Failure. Cell Host Microbe 27: 1-9.
10. Siddiqi H, Mehra M (2020) COVID-19 Illness in Native and Immunosuppressed States: A Clinical-Therapeutic Staging Proposal. J Heart Lung Transplant 39.
11. Magro C, Mulvey J, Berlin D, Nuovo G, Salvatore S, et al. (2020) Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. Transl Res.
12. Gattinoni L, Coppola S, Cressoni M, Busana M, Sandra Rossi S, et al. (2020) Covid-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med 201: 1299-1300.
13. Gattinoni L, Chiumello D, Caironi P, Caironi P, Busana M , Romitti F, et al. (2020) COVID-19 pneumonia: different respiratory treatment for different phenotypes? Intensive Care Med.
14. Jin Y, Cai L, Cheng Z, Cheng H, Denget T, et al. (2020) A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Mil Med Res 7.
15. Tang N, Li D, Wang X, Sun Z (2020) Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 18: 844-847.
16. de Simone G, Mancusi C (2020) COVID-19: Timing is Important. Eur J Intern Med.
17. Le Page C, Genin P, Baines M, Hiscott J (2000) Interferon activation and innate immunity. Rev Immunogenet 2: 374-86.
18. Wu F, Wang A, Liu M, Wang Q, Chen J, et al. (2020) Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. medRxiv.
19. Tang N, Bai H, Chen X, Gong J, Li D, et al. (2020) Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 18: 1094-1099.
20. Banat G, Tretyn A, Pullamsetti SS, Wilhelm J, Weigert A, et al. (2015) Immune and Inflammatory Cell Composition of Human Lung Cancer Stroma. PLoS One 10: e0139073.
21. Barrett C, Moore H, Yaffe M, Ernest E (2020) ISTH interim guidance on recognition and management of coagulopathy in COVID-19: A Comment. J Thromb Haemost.
22. Stebbing J, Phelan A, Griffin I, Tucker C, Oechsle O, et al. (2020) COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis 20: 400-402.
23. Waleed A, Morten H, Yaseen M, Loeb M, Ng Gong M, et al. (2020) Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med 46: 854-887.
24. Bouadma L, Lescure F, Lucet J, Yazdanpanah Y, Timsit J (2020) Severe SARS-CoV-2 infections: practical considerations and management strategy for intensivists. Intensive Care Med 46: 579–582.