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Letter to the Editor

COVID-19: Timing is Important

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On March 23, 2020, the Bergamo hospital team, one of the most challenged teams fighting against COVID-19 web-broadcasted a 1-hour conference on the state of their experience, seeking for discussion and suggestions (https://memorialhermann.zoom.us/j/9270060244). The attendance was about 250 contacts, with many questions raised during the conference. The presentation was very instructive and brain storming. After the conference, and based on current evidence, we developed the hypothesis that the general management of the infection of SARS-CoV-2 should be revised. The considerations that we will present are purely clinical and do not take into account the logistic setting of hospital beds [1]. We would like to raise 3 questions.

1. Time of hospital admission

In the Bergamo's experience, patients are admitted to the hospital after many days of symptoms and substantial aggravation. This delay is reported to extend up to 2 weeks. In addition, the time of permanence in the emergency rooms or in sub-intensive wards is only 4 days on average, before the patient is transferred to the intensive care unit (ICU). This indicates that often patients or their family doctors delay their decision to go to the hospital until the conditions are critical.

Thus, the first question would be: might an earlier admission to the hospital or an early aggressive therapy, at start of the viral infection and the immune response, save more lives than are now saved? We wonder whether early antiviral therapy could work better in the early phase of the disease rather than when patients are in severe condition and a massive replication of the virus is more likely [2].

2. Time of transfer to intensive care unit

Once admitted to hospital, COVID-19 patients exhibit low pO_2 and are put under non-invasive ventilation (NIV) in CPAP mode, a procedure that carries some environmental risk and is thought to be one of the reasons of in-hospital virus outbreak among health care workers [3]. NIV most often fixes the pO_2 and helps maintaining PO_2/FiO_2 ratio (P/F) in a reasonable range, but in many cases this improvement is just temporary and acute respiratory failure develops [4]. Patients are transferred to the ICU with very low P/F values.

The second question would be: is there a rationale for an earlier endo-tracheal intubation and mechanical ventilation, once a patient exhibits respiratory distress? Evidence from the H1N1 outbreak strongly suggest that in many or most cases NIV is ineffective and that early intubated patients have a better prognosis [5]. In Wuhan, 76% of a small group of critically ill patients were non-responsive to NIV [4]. It should be considered that any attempt to re-balance the respiratory function with NIV can cause a delay in intubation. Direct evidence on the consequences of delayed intubation in COVID-19 patients is not yet available. However, contacts with emergency room doctors, trained in my department at the University of Naples Federico II, who are managing patients with COVID-19 confirmed the same experience as with H1N1: early intubated patients seem to exhibit better outcome (personal communication). Analyses on retrospective data on this matter are urgently needed.

3. Management

Nobody knows exactly how to stop lung destruction caused by COVID-19. Hundreds of scientists are now working on different pharmacologic/immunologic approaches, in order to fight the viral invasion. These include specific anti-viral drugs, molecular targets to inhibit cell entry and vaccines. Another approach, which was proposed at the time of the Ebola outbreak, focuses on increasing the host resistance against the viral invasion [6]. The administration of convalescent sera [7], anti-inflammatory agents and specific cytokine-inhibition by administration of tocilizumab (a monoclonal antibody blocking IL6 and approved for the treatment of rheumatoid arthritis) were tested with some apparent success in Wuhan [8] and in Naples, Italy. A clinical trial with tocilizumab has been recently approved for COVID-19 in Italy. Several trials are on-going on all these possibilities, as reported in the COVID-19 Science Report of University of Singapore (https://sph.nus.edu.sg/wp-content/uploads/2020/03/COVID-19-Science-Report-Therapeutics-23-Mar.pdf).

The third question would be: is there a possibility that the scarce success of the drugs used so far could be, at least in part, related to the timing of administration of these compounds?

SARS-CoV-2 infection clinically presents no symptoms or symptoms of common colds until it evolves to COVID-19 pneumonia and therefore to ARDS. Siddiqi and Mehra [2] propose a 3-level stage-sequence of SARS-CoV-2 infection, based on the present knowledge. Their hypothesis is based on the assumption that, during its natural history, the

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disease switches from a viral infection to a self-maintaining hyper-inflammatory response.

During *stage I* infection, cells of the innate immunity are involved before the involvement of cytotoxic T lymphocytes (CTL), which play a major anti-viral response through the production of cytotoxic molecules with the purpose of eliminating infected cells [9]. The production of IgM anti-virus antibodies occurs during the first week of infection. Subsequently, plasma cells start producing high-affinity IgG antibodies, which presumably play a protective role.

During this initial phase of the disease (*stage I*), it would be rational to administer anti-viral medications combined with specific (convalescent sera) or even non-specific (polyvalent) high dose immunoglobulin.

Stage I can presumably evolve in most cases towards healing. Nobody knows the immunological mechanisms underlying the failure of resolution of inflammation and the progress of infection to *stage II*. An important role in the evolution toward a more severe stage could be played by T follicular helper (TFH) immune cells [10], specialized in providing help to B-lymphocytes and fundamentally required for antibody production. A dysfunction of this cell line can be found in elderly patients and contributes to the decreased antibody formation [11].

When evolved to *Stage II*, COVID-19 is characterized by virus proliferation and massive lung inflammation (viral pneumonia). In this stage, there are two enemies to fight: the virus and acute lung inflammation. Human lungs contain a plethora of immune and inflammatory cells [12], all producing inflammatory cytokines and chemokines. Massive release of these proinflammatory mediators are at the basis of the multiple organ failure. At this stage, continuation of antiviral therapy should be combined with adequate anti-inflammatory therapy (i.e. anti IL-6, chloroquine) and, especially in the elderly, potentiation of serum immunity.

In *stage III*, the main problem is hyperinflammation and therefore the main target therapy should be a very aggressive anti-inflammatory strategy including glucocorticoids [13], associated with high doses of polyvalent immunoglobulins, if convalescent serum is not available. A fulminant coronavirus myocarditis has been reported very recently in a case-report, with complete recovery using high doses glucocorticoids and high dose immunoglobulin [14]. This combination has a pathophysiologic rationale in the approach to increase host resistance [6] acting the two critical levels: inflammation and useful immune response.

We recognize that the latter approach is based on limited clinical evidence. However, the combination of aggressive anti-inflammatory therapy and support of immunological defense has a rational basis.

In this brief essay, we have tried to emphasize the importance of timing in the therapeutic approach of the different stages of COVID-19.

4. Author contribution

GdS and CM drafted the manuscript and gave final approval.

Declaration of Competing Interest

The authors declare they have no conflict of interest.

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