Editorial

Blood Purification

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Coronavirus Epidemic and Extracorporeal Therapies in Intensive Care: si vis pacem para bellum

Claudio Ronco[a–c] Thiago Reis[b, d] Silvia De Rosa[b, e]

[a]Department of Medicine (DIMED), University of Padova, Padova, Italy; [b]International Renal Research Institute Vicenza, Vicenza, Italy; [c]Department of Nephrology, Dialysis and Transplantation, San Bortolo Hospital, Vicenza, Italy; [d]Clinica de Doenças Renais de Brasilia, Brasilia, Brazil; [e]Intensive Care Unit, San Bortolo Hospital, Vicenza, Italy

The worldwide outbreak of coronavirus disease 2019 (COVID-19) has demonstrated that we are all part of a small world where diffusion of contagious diseases is inevitable [1]. Although the new coronavirus originated in Wuhan seems to present lower lethality compared to previous epidemic outbreaks from other coronaviruses, its capacity of diffusion has been phenomenal [2, 3]. One infected individual may transmit the virus to 2 or 3 others [4]. Of note, screening based on symptoms and signs is ineffective and asymptomatic persons can spread the disease [5]. In the very early phases, before this wide diffusion of the virus, a call to action was published in Lancet Respiratory Medicine [6] underlining the need of alertness for zoonotic virus infections crossing species and infecting human populations [7]. In particular, recommendation was made to prepare intensive care teams to deliver extracorporeal organ support (ECOS) therapies in infected patients whose pulmonary syndromes are particularly severe [8]. Once again, despite previous experiences presented higher incidence of severe complications and lethality, the current outbreak still requires intensive care for 5% of the infected population. Among those critically ill patients, the mortality rate is 49%. Even with the specific tropism for airway epithelial cells, the infection seems to be weak in humans and transmission is likely to occur only when lower respiratory tract disease develops. COVID-19 causes mild flu-like symptoms or even no symptoms in the majority of the patients [3]. Coronaviruses bind to receptors such as angiotensin-converting enzyme 2. Angiotensin-converting enzyme 2 is present in the epithelia of the lung, small intestine, colon, and biliary tract. In fact, viral nucleic acids were found in stools and anal swabs of patients diagnosed with COVID-19 infection [9]. In a cohort of COVID-19-infected patients from Singapore, half (4 out of 8) of patients tested had the virus detected in stools [10]. This might explain liver dysfunction, diarrhea, nausea, and vomiting that occurred in patients with pneumonia, namely, the gut-lung crosstalk [8, 11].

In a Chinese group of patients with pneumonia caused by COVID-19, 23% were admitted to intensive care unit (ICU), 17% had acute respiratory distress syndrome, and 11% died [11]. Major preventive measures have been undertaken in specific areas where the incidence was significantly higher, to limit the diffusion of the virus [7]. Despite those measures, the requirement of ICU services and stations still has dramatically increased. Personal communications and early reports mostly coming from China suggest that 67% of severely ill COVID-19 patients may present with additional organ dysfunction syndromes [8, 11, 12]. This has been, at least in part, related to a sepsis-like syndrome induced by high level of circulating cytokines [2, 12]. In such circumstances, while pulmonary

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E-Mail karger@karger.com
www.karger.com/bpu

Claudio Ronco, MD
Department of Nephrology, Dialysis and Transplantation
San Bortolo Hospital
Viale Rodolfi, 37, IT–36100 Vicenza (Italy)
E-Mail cronco@goldnet.it

exchanges are compromised and dominate the clinical scenario, acute kidney injury and heart and liver dysfunction may also become evident [8, 12–14]. Cytokine storm may be induced by a superimposed septic syndrome or by the direct effect of the virus on the infected host. In the past, the experience matured with H1N1 influenza, SARS, and MERS has suggested that the severity of illness depended on comorbidities and the immune-competence of the individual. In severe situations, however, an uncontrolled inflammatory state or a subsequent/simultaneous immune-paralysis is the direct consequence of endocrine effects of pro- and anti-inflammatory cytokines spilled over into the systemic circulation. Of special interest, in a retrospective analysis of a German cohort [15] of 25 critically ill H1N1-infected patients, the prevalence of virus-associated hemophagocytic syndrome (VAHS) was 36%. All patients with the syndrome had received extracorporeal membrane oxygenation (ECMO). ECMO could have been a trigger or an amplifier of cytokine activation. The pathogenesis of VAHS involves excessive production of interferon gamma and interleukin-2 [16]. VAHS itself is a prototype of a cytokine storm syndrome. In our present experience in San Bortolo Hospital, all our 4 COVID-19 critically ill patients have hyperferritinemia, raising awareness of VAHS as a differential diagnosis.

In organ dysfunction syndromes when pharmacological treatment is simply not available or efficacious, mechanical ventilation and hemodynamic support seem to be the only possible therapeutic strategy [17]. However, extracorporeal therapies such as hemofiltration or hemoperfusion (HP) offer a new possibility to support different organs in a multiple organ dysfunction condition. Using specific extracorporeal circuits and devices, heart, lungs, kidneys, and liver can be partially replaced or at least sustained during the severe phase of the syndrome. The concept is known as ECOS [18–20]. The most important technique in these cases is the ECMO mostly applied in veno-venous mode [21–23]. Furthermore, extracorporeal CO_2 removal is another option that can be performed in less severe cases to facilitate a less invasive and traumatic mechanical ventilation [24]. Although acute kidney injury in these patients is not common, continuous renal replacement therapies may offer in conditions of mild to severe kidney dysfunction a significant support for solute and fluid control. The same is true for left ventricular assist devices in case of refractory heart failure or albumin dialysis and HP in case of liver dysfunction and hyperbilirubinemia [25]. However, according to information collected from Chinese colleagues who faced a large proportion of patients with complicated COVID-19 syndromes in their ICUs, a significant benefit seems to have been obtained with the use of direct HP with cartridges containing highly biocompatible sorbents and microporous resins [26]. Such therapies, designed to remove the excess of circulating cytokines, seem to have displayed a remarkable benefit in terms of hemodynamic support and organ function recovery [2]. The suggested scheme of application of HA380 cartridges (Jafron Biomedical Co., China) was 2-1-1, that is, 2 units utilized for 12 h in the first 24 h and 1 unit per day utilized for 24 h in the following 2 days. In Europe, we had matured some experience with the use of Cytosorb© cartridges (CytoSorbents Corporation, NJ, USA), exactly for the same purpose of controlling deadly inflammation in critically ill and cardiac surgery patients [27, 28]. This approach may be just one of many others [29] utilizing extracorporeal therapies in these severe syndromes and will require scientific validation once the emergency of the current epidemic will be over. The suggested mechanism is the nonspecific removal of the peaks of the circulating cytokines both in the pro- and in the anti-inflammatory side. This is consistent with the "peak concentration hypothesis" suggested some time ago [30]. In presence of our inability to obtain instantaneous monitoring of biological levels of cytokines, the reasonable approach is to promote a nonspecific removal assuming that those cytokines with the highest concentration will be removed in higher amount (Fig. 1) [31]. This would facilitate a return to a less severe derangement of the immune system and to an improved level of the immunological response of the host. The same concept has been expressed by the "cytokinetic model." In this theory, the reduction of circulating levels of cytokines may allow the immune system of the patient to redirect the immunocompetent cells to the source or site of inflammation [32]. We warn users of these techniques that together with the removal of cytokines, some drugs and antibiotics like vancomycin are also removed. In vitro models proved that [33]. In this case, a specific adjustment of antibiotic dosage in patients with bacterial infections should be carefully planned. Another adjunctive potential extracorporeal therapy is lectin affinity plasmapheresis for coronavirus trapping. Blood runs into a plasma filter, and the filtered plasma containing viral copies passes through a matrix of lectins. There is a high affinity between the viral envelope and lectins. Likewise, some viral copies are captured and the viremia is reduced [34]. This therapy should be further explored and validated.

The main message the present editorial tries to convey is that the ICU staff and treating physicians should be familiar with the concept that extracorporeal therapies represent today an important strategy in critically ill pa-

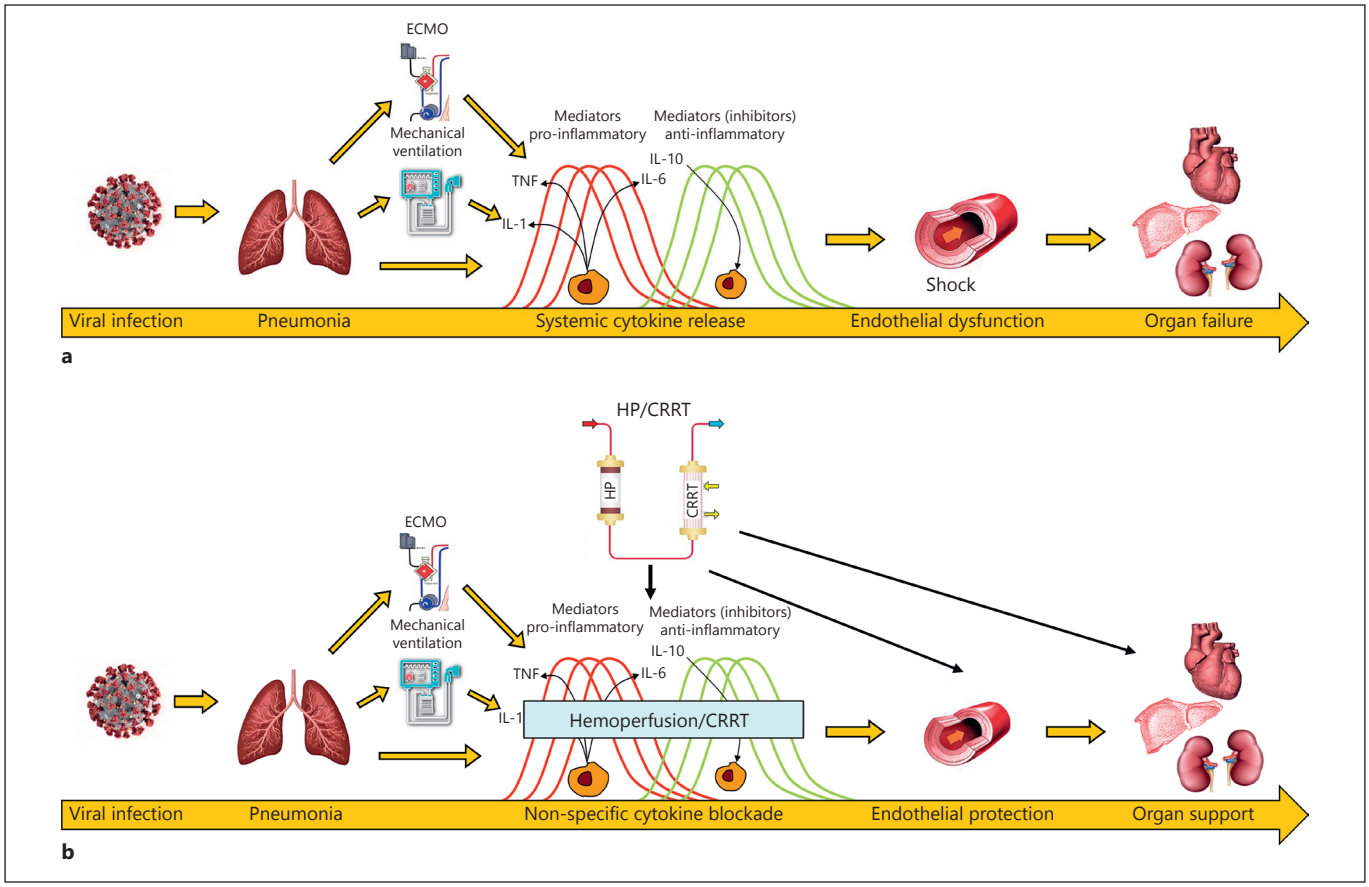

Fig. 1. a After a viral infection, a percentage of patients suffer from severe pneumonia. Such patients may have a systemic cytokine release due to the illness itself, to the mechanical ventilation-associated lung injury, and to the extracorporeal membrane oxygenation. This will induce endothelial dysfunction and consequent organ failure. **b** The application of HP may contribute to reduce the burden of cytokines cutting the peaks in a nonspecific way, restoring at least in part immune-homeostasis. When hemoperfusion is combined with continuous renal replacement therapies (HP/CRRT), the effect can be further amplified and the additional task of organ support can be accomplished. TNF, tumor necrosis factor; IL, interleukin; HP, hemoperfusion; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation.

tients with multiple organ dysfunction. Training and research should be planned to further develop skills and knowledge in this area where new membrane separation processes and adsorption techniques appear to be a new frontier in fighting the so-called "cytokine storm syndrome." We will need to increase awareness of the basic principles, to study mechanisms, to optimize prescription and delivery of different techniques. We need to stimulate research and data collection to create sufficient scientific evidence. We need to prepare for the uncertain future where the frequency of these crises will be probably increasing [4]. We must retool ourselves with new strategies and new therapies, and among those, new ECOS therapies. As the ancients used to say: "*Si vis pacem, para bellum,*" if you want peace, get prepared to war.

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