Editorial

COVID-Lung: The Battlefield

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The three horsemen of the apocalypse in COVID-lung are unrestrained inflammatory response, damaged alveolar atmosphere, and thrombotic microangiopathy. At the beginning of the pandemic, many authors believed that it would not have been a very different situation from seasonal flu. The diffusion of social media has opened up an exciting field in sharing scientific data and dramatically increased the degree of credibility of personal opinions, beliefs, and considerations allowing them to spread rapidly.[1] In fact, personal opinions were contrary to scientific facts because no experts existed at that time. To clarify the confusions on the therapeutic tactics employed in COVID-19, we need a tailored therapy, which hinges on pathophysiological wisdom.

The current hallmark of severe acute respiratory syndrome coronavirus 2 pathogenesis is the systemic cytokine storm. Cytokine storm implies that the levels of released cytokines are injurious to host cells.[2] Various inflammatory cytokines and biomarkers are significantly elevated in patients with severe disease. However, the use of anti-inflammatory therapy could provoke viral replication. It is imperative to distinguish where the viral pathogenicity is dominant versus when the host inflammatory response overtakes the pathology.[3]

Thrombocytopenia, multiorgan failure, and elevated lactate dehydrogenase are present in majority of the severe patients fulfilling the criteria of thrombocytopenia-associated multiple organ failure in which early recognition and rapid therapeutic plasma exchange (TPE) result in significantly improved outcomes.[4] Intravenous immunoglobulin (IVIg) may also play a role in modulating an immune system that is in a hyperinflammatory state. Combining TPE and IVIg regiments is a promising advanced immunomodulation technique, called the zipper method, which is a rigorous implementation of TPE and IVIg in an interpenetrating manner. This way of ranking leads to a consistency of both regimens augmenting each other's effect.[5]

Severe pneumonia is characterized by rapid viral replication, massive inflammatory cell infiltration, and cytokine storm, resulting in acute respiratory distress syndrome (ARDS). However, early stage of the disease deviates from ARDS with well-preserved lung mechanics. In this stage, lung is not recruitable and get worse with high positive end-expiratory pressures (PEEPs) because ventilation perfusion mismatch is the primary cause of hypoxemia.[6] Moreover, the low volumes normally utilized to treat ARDS deflates the COVID lungs. Most of the patients were rapidly lost at this stage because they were treated with high PEEPs and low volumes as if they were ARDS. As a result, the old-school ARDS treatment algorithms yielded devastatingly high mortality rates.

The limited number of postmortem reports currently available revealed the mechanism of pathophysiology as type-II cell damage. Significant proliferation of type-II cells and focal desquamation with coronavirus particles detected in type-II alveolar epithelia are divergent findings from a classical ARDS pattern.[7] Angiotensin-converting enzyme 2 (ACE2) is the functional receptor for COVID-19, and more than 80% of total ACE2 expression are found in type-II alveolar cells. These cells not only express viral receptors but also express more than 20 other genes closely related to virus replication and transmission. Type-II cells largely express the cellular serine protease TMRRSS2 that is required to allow the entry of coronavirus into host cells.[8] Newborn has only 3 million alveoli compared with 500 million alveoli in an adult. Less alveoli with fewer type-II cells may spare children from excessive immune reaction compared with adults. The cellular serine protease TMRRSS2 is also required to allow the entry of coronavirus into host cells and the type-II cells largely express TMPRSS2.[8] This gene was demonstrated to be upregulated by androgenic hormones. Prepubertal state may speak to the diminished entry of coronavirus into the type-II cells.[9] Type-II alveolar cells produce surfactant. The main

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functions of surfactant are lowering surface tension thus preventing alveolar collapse, providing a crucial first line of defense against infection by enhancing the removal of viruses facilitating their removal and preventing dissemination, and modulating immune response. Surfactant dysfunction causes alveolitis, which is characterized by influx of inflammatory cells, increased oxidative stress, and increased leakage across the blood–alveolar barrier. Alveolar exudative inflammation containing macrophages, monocytes, and CD4-positive T cells, as well as interstitial inflammation were also reported from the autopsy findings.[7] Surfactant therapy is an established treatment protocol for respiratory distress syndrome in preterm infants and COVID lung is more analogous to it than the adult with ARDS. Exogenous surfactant decreases cytokine release, DNA synthesis of inflammatory mediators, lymphocyte proliferation, immunoglobulin production, and expression of adhesion molecules. However, meta-analysis showed that administration of surfactant was not associated with improved mortality in adult with ARDS. The failure is probably due to ventilation strategies with high pressures. Surfactant is a detergent and detergents lose their properties when squished under pressure. When instilled surfactant is smashed under high positive pressure of the mechanical ventilator, it will rapidly lose its surface-active properties. A smart way of keeping instilled surfactant durable is giving it under extracorporeal membrane oxygenation (ECMO), which will prevent it from crushing under the ventilator pressure.

Other main findings of the preliminary postmortems are endotheliitis and microthrombosis. The pathological reports state that the blood vessels of alveolar septum are congested, edematous, and widened.[7] Vascular endothelium representing ACE2 receptors makes it a reasonable target for coronavirus. A feature consistently reported is a highly activated coagulation cascade, with widespread thromboses in the lung and in other organs, consistent with disseminated intravascular coagulation. Pulmonary emboli are a frequent thrombotic complication. Endothelial damage disrupts pulmonary vasoregulation and fosters thrombogenesis resulting with ventilation–perfusion mismatch. The dramatically reduced oxygenation in the presence of reasonable ventilation and increased compliance speak to pulmonary thrombosis in the COVID-lung.

Rapid recognition and deployment of therapy may well be our best strategy to win the war against COVID-19. The success of this strategy requires clarity on the therapeutic tactics and their tailored implementation. We first need to understand what we are fighting against. We have hyperinflammation in the tissue; surfactant deficiency due to the attack on the type-II cells; and microthrombosis with endothelial damage. For the sake of argument, let us make an oversimplification and acknowledge them as our three therapeutic targets. We will deploy our air force, ground force, and navy, respectively, to acquire these targets (►**Fig. 1A**).

TPE and IVIg are the ground forces, both units helping to restore extreme inflammation. We should also consider the zipper method for further immune modulation, which is basically the combined arms approach to warfare (►**Fig. 1B**).

TPE, heparin, tissue plasminogen activator, and defibrotide are the weapons employed in a navy strike. Heparin treatment appears to be associated with better prognosis in severe patients with coagulopathy (►**Fig. 1C**). Defibrotide's

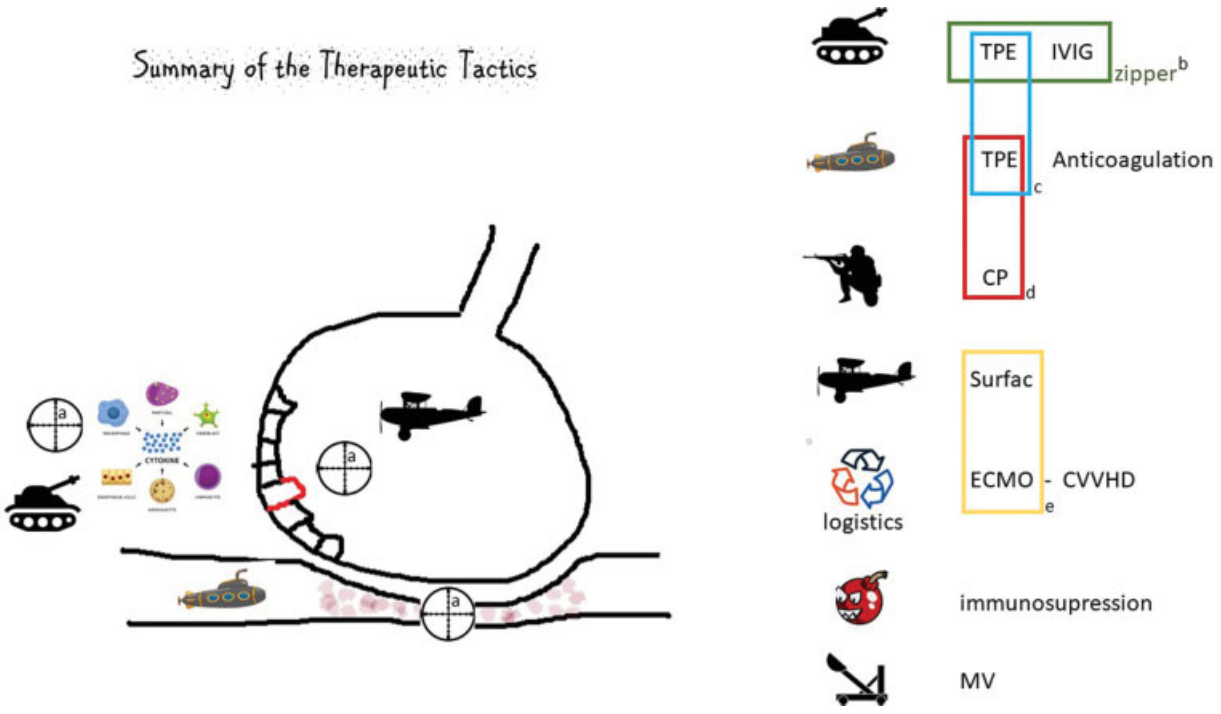

Fig. 1 Battlefield of the COVID-lung. (A) Targets. (B) Zipper method of immunomodulation. (C) TPE acting in both anti-inflammation and anticoagulation sides. (D) TPE with CP. (E) Surfactant instillation under ECMO. CP, convalescent plasma; CVVHD, continuous venovenous hemofiltration; ECMO, extracorporeal membrane oxygenation; IVIg, intravenous immune globulin; MV, mechanical ventilator; Surfac, surfactant; TPE, therapeutic plasma exchange.

antithrombotic and anti-inflammatory activities with protective effects on the endothelium make it a promising drug for the treatment of thrombotic microangiopathy in various scenarios. Defibrotide has a potential to restore the established endothelial damage in COVID-lung. Actually, TPE acts like an amphibious commando serving as a military vehicle on the ground for inflammation and in the water for coagulation.

Antiviral agents are like rookie snipers. They only occasionally hit the bullseye. The only scout sniper with precision marksmanship available to us today is the convalescent plasma (CP). It has recently been shown that CP with a high concentration of neutralizing antibodies can rapidly reduce the viral load and tends to improve clinical outcomes. If we consider combining TPE with CP, we can provide our scout sniper an amphibious commando guard (►**Fig. 1D**).

Surfactant is instilled via airway and can be considered as the air force. Logistics is the lifeblood of military power, and ECMO and continuous venovenous hemofiltration (CVVHD) are the logistic forces needed to sustain the battle. CVVHD also helps immunomodulation by removing cytokines. Giving surfactant under ECMO will help prevent smashing it under pressure (►**Fig. 1C**).

Beware of immunosuppression as it may have a barrel bomb effect, destroying the good along with the bad.

Positive-pressure ventilators are like the antiquated catapults from medieval times. They require a lot of oversight and micromanagement, which can be quite taxing. Consider negative-pressure ventilators instead.

Modern warfare requires contemporary tools such as mesenchymal stem cell treatment as an emerging force promising immunomodulatory effects with calming down the hyperactive immune response and promoting tissue repair.

Timing is crucial, whatever you do, you have to do it timely and tactically. COVID situation is not restricted to lung solely, so we have to show regard to the entire body in order not to win a battle but the war.

Conflict of Interest
None declared.

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