Extracorporeal Blood Purification Is Appropriate in Critically Ill Patients with COVID-19 and Multiorgan Failure: CON

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Introduction
The National Cancer Institute defines a cytokine storm as “a severe immune reaction in which the body releases too many cytokines into the blood too quickly, as a result of an infection, autoimmune condition, or other diseases” (1). In general, a cytokine storm is recognized as a manifestation of some acute conditions or treatments that present with high fever, other constitutional symptoms, and signs, along with inflammatory reactions that may be limited to restlessness, edema, and pain, or, in the severest forms, multiple organ failure leading to death (1,2). The term cytokine storm was first reported as a consequence of graft versus host syndrome in 1993 (3), but later adopted for manifestations of other diseases, particularly infections, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (4) and coronavirus disease 2019 (COVID-19) (5). Since the first cases of COVID-19, there has been growing evidence it is associated with increased cytokine levels, which may explain the severity of its manifestations in some, particularly those admitted to intensive care units (5,6). Because the unregulated release of cytokines has been proposed as the primary pathophysiology of this syndrome, it is no surprise that immunomodulation, immunosuppression (7), or a range of extracorporeal cytokine removal techniques have been suggested as potential therapeutic options or trial protocols (8).

To expect any intervention to change the outcomes of any disease, the intervention should target its pathophysiology to enable normal homeostasis or moderate the response to the offending agent or infection. Although extracorporeal cytokine removal techniques for the management of COVID-19 may seem attractive, their effect on important clinical outcomes such as survival is questionable. We discuss why extracorporeal cytokine removal techniques for the management of COVID-19 may not be quite ready (Figure 1A).

Reductionist Approach to Modify a Complex System
The definition of a cytokine storm is an ill-defined and predominantly clinical diagnosis with assumptions that the signs and symptoms observed reflect an acute increase in cytokine levels. Cytokines are small proteins excreted by cells (autocrine, paracrine, endocrine) that affect the function of other cells that regulate inflammatory and repair responses. Cytokines are categorized into five groups, including IFNs (antiproliferative, antiviral, and innate immune system regulation), ILs (proinflammatory, leukocyte differentiation), chemokines (proinflammatory, chemotaxis), colony-stimulating factors (stimulation of progenitor cell proliferation and differentiation), and TNFs (proinflammatory, indirect cytotoxicity) (2). Unfortunately, the cytokine physiology complexity and, importantly, the interactions between cytokines in the cytokine storm are poorly understood. The physiology of cytokines is on the basis of the properties of a complex system (9), which include:

1) Nonlinearity: cytokines are intimately interconnected. Many of these proteins have functions related to the other cytokine classes and depend on other cytokine levels, the stage and type of primary illness, and target cells. Besides, although the cytokine system is nonlinear, it is only chaotic in very severe diseases where there is significant dysregulation.
2) Feedback: many feedback loops regulate the cytokine systems. For example, the systemic inflammatory response syndrome (SIRS) is often followed by compensatory anti-inflammatory response syndrome (CARS). Also, the excretion of SIRS- and CARS-related cytokines during sepsis is very dynamic. For example, TNF and IL-1 promote inflammatory cytokines such as IL-6, leading to an increase in anti-inflammatory cytokine release, including IL-10, IL-1 receptor antagonist, and soluble TNF receptor (10). Therefore, if one considers IL-6 removal as a potential therapy, it would only be effective when IL-6 is very elevated and potentially deleterious. Removal during the early response may not be required, and indeed, in the late stages of a cytokine storm may be harmful by influencing the balance between SIRS- and CARS-related cytokines leading to propagation of an inflammatory response.

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3) Spontaneous order: the interactions between cytokines are not random. Simultaneously, the order within the cytokine system is not static because multiple factors can affect the role of system components. For instance, genetic variability in toll-like receptor 1 could lead to variability within the innate system in response to gram-positive bacterial infection (11).

4) Although the cytokine system is robust (i.e., self-correction of the errors within the system), it is not centrally controlled. The cytokine system robustness is mainly due to built-in redundancies within the system, which may be disturbed by extracorporeal removal.

5) Emergence: cytokines compete and cooperate (upward and downward causalities) to create a self-organized system with properties that are not specific to individual cytokines.

6) Hierarchical organization: the cytokine system, as any other complex system, includes numerous networks. Within each network, cytokines are self-organized in hierarchies. These networks are also organized hierarchically to maintain or recover the normal homeostasis.

7) Numerosity: there are not only many components within the cytokine system, but also each cytokine participates in several overlapping networks with primary and alternative pathways (12).

8) Many infections have similar cytokine profiles. Yet, they have vastly different modes of action (e.g., SARS-CoV-2 involves pneumocyte type II via angiotensin-converting enzyme 2).

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**Figure 1. Issues and solutions to solve the puzzle.** (A) Why extracorporeal cytokine removal does not improve clinical outcomes. (B) How extracorporeal cytokine removal could be advanced to augment success.
enzyme 2 receptors, whereas the influenza virus infects ciliated epithelial cells and clinical manifestations (2). 9) Inflammatory cascades often occur within tissue with a relatively smaller hematogenous proportion. However, most studies focus on circulatory cytokine levels, which may not reflect the conditions within the involved tissue(s) but more a cytokine "dustbin" (2).

Extracorporeal cytokine removal is perceived to have several potential benefits in conditions associated with elevated cytokine levels. These include a decrease in peak cytokine concentrations, thereby mitigating their effects on affected organs, potentially improving outcomes (13). The other suggested benefit is the cytokine response modulation through non-specific cytokine removal with a potential promotion of appropriate immune cell trafficking to the site of inflammation (13). Although both these hypotheses are valid, they both adopt a somewhat reductionist approach in managing a very complex system, particularly during periods of "cytokine storm." The dynamic, intricate, and multifunctionality nature of cytokines and the complex interrelations between them may influence non-specific cytokine removal potential benefits in a nonpredictable fashion. Such a reductionist approach to the cytokine storm complexities may explain why the effect of these techniques on clinical outcomes has not been consistent, despite some observations relaying improved hemodynamics or oxygenation (14).

In a recent consensus conference by the Acute Disease Quality Initiative, the participants suggested inflammatory cytokines and pathogen-associated molecular patterns could contribute to the development of multiple organ failure and mortality in patients with severe COVID-19. Because extracorporeal cytokine removal techniques are shown to remove pathogen-associated molecular patterns and cytokines, they also suggested, despite the lower level of supporting evidence, these techniques to be considered in very carefully selected cases (8). However, in COVID-19, the cytokine storm's role as a primary pathophysiological mechanism of multiple organ failure is far from convincing. Indeed, in a recent systematic review of 1245 patients with COVID-19, the mean IL-6 level was 100 times less than patients with cytokine release syndrome, 27 times lower than septic patients, and 12 times less than ARDS due to other causes (15).

Solutions and Next Steps

Figure 1, A and B describes the potential reasons that benefits of extracorporeal cytokine removal in patient outcomes have not been consistently observed and provide some of the steps that need to be taken to prepare these techniques to potentially achieve routine adoption. As with any intervention, the efficacy of extracorporeal cytokine removal needs to be assessed in terms of input, intervention, and output. The lack of a verifiable and measurable definition for cytokine storm, the complexity of the cytokine system(s), the dynamic changes observed, the lack of evidence regarding the levels and effect of blood cytokines in COVID-19, and crucially, the lack of readily available routine tests that can measure and monitor cytokine levels in blood and tissues in an accurate and timely fashion make decisions related to both the commencing and continuation of these techniques very challenging. Moreover, most of the available techniques remove cytokines in a non-specific manner and other potentially important substances, including medications and essential nutrients, to name but two. As a result, consistent information regarding the effect of these techniques on mortality and other hard intensive care unit outcomes has not been regularly reported, and where it has, tends to be in uncontrolled case reports and series or small trials. In our opinion, to demonstrate any benefit from these techniques, several hurdles have to be negotiated. First, cytokine storm needs an objectively measurable definition, which implies we need to measure and monitor cytokine levels regularly. Second, cytokine removal needs to be targeted on the basis of their levels and the potential inter-relationships. To achieve this, additional studies to evaluate tissue and blood cytokine levels together with clinical manifestations of diseases are necessary. Third, new technologies should ideally be enhanced to remove specific cytokines without removing other substances. Fourth, understanding each patient's cytokine landscape using such new monitoring and measurement tools may require harnessing machine learning techniques that may be predictive in highlighting those who may benefit from treatment. Such methods may allow the matching of patients with appropriate personalized treatment plans. Finally, there would be a need for clinical trials to show the assumptions on the basis of the physiology of cytokine removal would translate into patient-level benefits in more meaningful outcomes, including mortality and quality of life and potential financial savings, in terms of consumption of intensive care unit resources.

Disclosures

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Author Contributions

K. Kashani conceptualized the study and wrote the original draft; and L.G. Forni reviewed and edited the manuscript.

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See related debate, “Extracorporeal blood purification is appropriate in critically ill patients with COVID-19 and multi-organ failure: PRO,” and commentary, “Extracorporeal blood purification is appropriate in critically ill patients with COVID-19 and multi-organ failure: COMMENTARY,” on pages 416–418 and 423–425, respectively.