Extracorporeal blood purification is appropriate in critically ill patients with COVID-19 and multi-organ failure: CON

**DOI:** 10.34067/KID.0007382020

Kianoush Kashani and Lui Forni

**Key Points:**

* * *

**Abstract:**

**Disclosures:** K. Kashani reports the following: Consultancy Agreements: AM PHARMA Research Funding: La Jolla Inc.; Scientific Advisor or Membership: MediBeacon Inc., La Jolla Inc., GE. L. Forni reports the following: Consultancy Agreements: Exther Medical; Ownership Interest: Spiden; Research Funding: Baxter; Honoraria: Gambro/Baxter, Fresenius, Astute Medical, Biomerieux, Exthera Medical; Scientific Advisor or Membership: ESICM General Secretary.

**Funding:**

**Author Contributions:** Kianoush Kashani: Conceptualization; Writing - original draft Lui Forni: Writing - review and editing

**Clinical Trials Registration:** No

**Registration Number:**

**Registration Date:**

**How to Cite this article:** Kianoush Kashani and Lui Forni, Extracorporeal blood purification is appropriate in critically ill patients with COVID-19 and multi-organ failure: CON, Kidney360, Publish Ahead of Print, 10.34067/KID.0007382020

Copyright 2021 by American Society of Nephrology.
Extracorporeal blood purification is appropriate in critically ill patients with COVID-19 and multi-organ failure: CON

Kianoush Kashani¹,² and Lui G. Forni³

¹Division of Nephrology and Hypertension, Department of Medicine, Mayo Clinic, Rochester, MN
²Division of Pulmonary and Critical Care Medicine, Department of Medicine, Mayo Clinic, Rochester, MN
³Department of Clinical & Experimental Medicine, University of Surrey and Royal Surrey County Hospital NHS Foundation Trust, Guildford, United Kingdom

Corresponding author:

Kianoush Kashani, MD
Mayo Clinic
200 First Street SW
Rochester, MN  55905
E-mail: kashani.kianoush@mayo.edu
Phone: +1(507)266-7093
Fax: +1(507)266-7891
Introduction:

The National Cancer Institute defines 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, the cytokine storm is recognized as a manifestation of some acute conditions or treatments which present with high fever, other constitutional symptoms, and signs, along with inflammatory reactions which may be limited to redness, 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 was adopted for manifestations of other diseases, particularly infections, including more recently severe acute respiratory syndrome-coronavirus (SARS-CoV)[4] and coronavirus disease 2019 (COVID-19)[5]. As of the first cases of COVID-19, there has been growing evidence that it is associated with increased cytokine levels, which may explain the severity of its manifestations in some, particularly among those admitted to intensive care units[5, 6]. As 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. Whilst extracorporeal cytokine removal techniques for the management of COVID-19 may seem attractive, their impact 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 for prime time (Figure 1A).

Reductionist approach to modify a complex system

The definition of "Cytokine storm" is 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 impact the function of other cells that regulate inflammatory and repair responses. Cytokines are categorized into five groups, including interferons (antiproliferative, antiviral, and innate immune system regulation), interleukins (proinflammatory, leukocyte differentiation), chemokines (proinflammatory, chemotaxis), colony-stimulating factors (stimulation of progenitor cell proliferation and differentiation), and tumor necrosis factors (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 based on the properties of a complex system[9], which include:

1) Non-linearity: cytokines are intimately interconnected. Many of these proteins have functions related to the other cytokines classes and depend on other cytokine levels, the stage and type of primary illness, and target cells. Besides, while the cytokine system is non-linear, 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 related 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.

3) Spontaneous order: the interactions between cytokines are not random. Simultaneously, the order within the cytokine system is not static as multiple factors can impact 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) While 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, like 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\textsubscript{2} involves pneumocyte type II via ACE2 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 cytokines peak concentration, thereby mitigating their effects on affected organs, potentially improving outcomes[13]. The other suggested benefit is the cytokine response modulation through nonspecific 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 nonspecific cytokine removal potential benefits in a non-predictable fashion. Such a reductionist approach to the cytokine storm complexities may explain why the impact 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 (ADQI), the participants suggested inflammatory cytokines and pathogen-associated molecular patterns (PAMP) could contribute to the development of multiple organ failure and mortality in severe COVID-19 patients. As extracorporeal cytokine removal techniques are shown to remove PAMPs 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 role as a primary pathophysiological mechanism of multiple organ failure is far from convincing. Indeed, in a recent systematic review of 1,245 COVID-19 patients, the mean interleukin-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

Figures 1A and 1B describe 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. Like 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 impact 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 currently available techniques remove cytokines in a nonspecific manner and other potentially important substances, including medications and essential nutrients, to name but two. As a result, consistent information regarding the impact of these techniques on mortality and other hard ICU outcomes has not been regularly reported, and where they have, these tend 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. Firstly, cytokine storm needs an objectively measurable definition, which implies that we need to measure and monitor cytokine levels regularly. Secondly, cytokine removal needs to be targeted based on 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. Thirdly, 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 matching patients with appropriate personalized treatment plans. Finally, there would be a need for clinical trials to show the assumptions based on 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 ICU resources.

Disclosures:

K. Kashani reports the following: Consultancy Agreements: AM PHARMA Research Funding: La Jolla Inc.; Scientific Advisor or Membership: MediBeacon Inc., La Jolla Inc., GE. L. Forni reports the following: Consultancy Agreements: Exther Medical; Ownership Interest: Spiden; Research Funding: Baxter; Honoraria: Gambro/Baxter, Fresenius, Astute Medical, Biomerieux, Exthera Medical; Scientific Advisor or Membership: ESICM General Secretary.

Funding:

None

Acknowledgements:

The content of this article reflects the personal experience and views of the author(s) and should not be considered medical advice or recommendation. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or Kidney360. Responsibility for the information and views expressed herein lies entirely with the author(s).

Authors’ Contributions:

Kianoush Kashani: Conceptualization; Writing - original draft

Lui Forni: Writing - review and editing
References:


Figure legend:

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.
Figure 1

A) Input
- Vague CS definition
- Complexity of cytokine physiology
  -- Function of individual cytokines
  -- Interactions
  -- Dynamic changes in roles
- Unknown pathophysiology
- Lack of clarity of COVID-19 and CS relationship
- Underdeveloped monitoring tools for all involved cytokines

Intervention
- Evolving technology
- Non-specific cytokine removal
- Scarce information related to the dose and timing of treatments
- Extracorporeal circuit-related AEs
  -- Bleeding or thrombosis
  -- Acute thrombocytopenia
  -- Catheter-related complications

Output
- Uncertainty related to benefits in COVID-19 outcomes
- Drug removal
- Unpredictable loss of albumin, nutrients, and amino acids
- Electrolyte imbalances
  -- Hypophosphatemia
  -- Hypokalemia

B) Input
- CS definition should be objectively measurable
- Complex systems require complex solutions
  -- Measure and monitor tissue and blood levels of hallmark markers in each category
  -- Plan for targeted removal of dynamic cytokines
- Further studies to understand pathophysiology of CS

Intervention
- Ability to specifically remove some cytokines from blood or tissues
- Dynamic cytokine removal based on monitored levels to achieve homeostasis
  -- Engaging artificial intelligence may be necessary to optimize treatments
- Studies to determine the dose and timing of treatments
- Minimize extracorporeal circuit-related AEs

Output
- Optimizing the impact of cytokine removal to improve hemodynamics and patients' outcomes.
- Minimizing removal of drug removal
- Avoiding loss of albumin, nutrients, and amino acids
- Correcting electrolyte imbalances