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

DOI: 10.34067/KID.0006632020

Kevin Chung and Stephen Olson

Key Points:
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Abstract:

Disclosures: K. Chung reports the following: Scientific Advisor or Membership: Editorial Board of Critical Care Medicine; Editorial Board of Burns. The remaining author has nothing to disclose.

Funding:

Author Contributions: Kevin Chung: Supervision; Writing - original draft; Writing - review and editing Stephen Olson: Writing - original draft; Writing - review and editing

Clinical Trials Registration: No

Registration Number:

Registration Date:

How to Cite this article: Kevin Chung and Stephen Olson, Extracorporeal blood purification is appropriate in critically ill patients with COVID-19 and multi-organ failure: PRO, Kidney360, Publish Ahead of Print, 10.34067/KID.0006632020
Extracorporeal blood purification is appropriate in critically ill patients with COVID-19 and multi-organ failure: PRO

Kevin K. Chung¹ and Stephen W. Olson¹,²

1. Department of Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD
2. Division of Nephrology, Walter Reed National Military Medical Center, Bethesda, MD

Corresponding Author: Kevin K. Chung, MD

Address: Department of Medicine, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD, 20814 USA. Email: kevin.chung@usuhs.edu
The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has triggered a once-in-a-century global pandemic with substantial morbidity and mortality. Severe Coronavirus Disease 2019 (COVID-19) is characterized by a profound dysregulated host response resulting in excessive inflammation and coagulopathy leading to life threatening organ dysfunction and death (1). A global effort to evaluate a variety of pharmacologic targets have yielded few options to date. Remdesivir, which suppresses SARS-CoV-2 replication through inhibition of viral RNA polymerase, was shown to reduce recovery time in a double blind, randomized, placebo controlled trial (2). Recently, a large open label randomized trial evaluating four re-purposed antiviral drugs to include remdesivir failed to demonstrate any clinically meaningful benefit when compared to controls (3). Neutralizing antibody treatment with either COVID-19 convalescent plasma or monoclonal antibodies have been promising but still largely unproven (1). Of all the anti-inflammatory strategies targeting the hyper-inflammatory host response, only dexamethasone has successfully decreased mortality in randomized controlled trials for severe COVID-19 to date (1, 4). Hence, approximately a year into this pandemic, morbidity and mortality associated with severe COVID-19 has remained high with very few therapeutic options.

In the absence of abundant pharmacologic options, extracorporeal blood purification (EBP) may have a role as an adjunctive therapy in the management of critically ill COVID-19 patients. Non-pharmacologic, pathogen-agnostic therapeutic options are potentially desirable when dealing with a deadly novel pathogen without any proven therapies. As a result of potential treatment efficacy for severe COVID-19 and demonstrated device safety, the Food and Drug Administration (FDA) granted temporary emergency use authorizations (EUAs) for four EBP devices to include the oXiris® Set, CytoSorb®, the Optia Apheresis System® with the Depuro D2000® Adsorption Cartridge, and Seraph-100®(5). The FDA concluded that “Blood purification devices may be effective at treating certain patients with confirmed COVID-19 by reducing various pathogens, cytokines, and other inflammatory mediators...associated with a “cytokine storm” that may occur in some COVID-19 patients, potentially...
leading to severe inflammation, rapidly progressive shock, respiratory failure, organ failure and death.”

This bold action by the FDA has been viewed as controversial, with some suggesting that EBP should be applied only within the context of randomized clinical trials (5). In this brief review, we support our belief that the FDA made the right move at the right time with the right technologies.

First and foremost, EBP should be viewed as a medical countermeasure (MCM) available for clinical scenarios without other therapeutic options. The current pandemic that is causing an international public health emergency is one such clinical scenario. One of the functions of the FDA is to protect the United States from emerging infectious diseases by ensuring the safe implementation of MCMs (5). As such, under section 564 of the Federal Food, Drug, and Cosmetic Act, the FDA has the authority to allow unapproved medical products to “diagnose, treat, or prevent serious or life-threatening diseases”(5). This broad authority has provided the medical community with ultra-rapid access to a variety of promising MCM options for a novel and deadly virus with very few proven therapies in an attempt to save lives.

Second, each EBP technology has a unique mechanism of action. Therefore, negative clinical trial results for previous EBP devices should not prevent the use and study of EBP devices with different functions. The EBP field is in its infancy and evolving rapidly. Over the past decades, major technological advances have made all extracorporeal organ support modalities more biocompatible, user friendly, and safe, resulting in the adoption of various techniques for lung and renal support (6). Additionally, previous EBP techniques have largely focused on one general target. For example, conventional hemofiltration, even at high doses, is known to remove only inflammatory cytokines below a certain molecular size. More recently, Polymyxin B immobilized fiber cartridge (PMX-DHP) was designed to remove only endotoxin. As such, it is not surprising that multiple clinical trials failed to demonstrate any clinically meaningful benefit in a condition as complex as sepsis (6). The field of sepsis therapeutics is littered with negative trials of promising pharmaceutical solutions that target one molecule (7). In
contrast, newer generation EBP technologies represent novel non-pharmacologic adjunctive techniques that can modulate multiple targets to include pathogens, pathogen-associated molecular patterns (PAMPs) such as endotoxins, activated leukocytes, or cytokines in combination. While CytoSorb® targets mainly cytokines, the oXiris® filter, the Optia Apheresis System® coupled with the Depuro D2000® filter, and the Seraph-100® have introduced the concept of a multi-modal blood purification. The oXiris® and the Optia Apheresis System® are designed to remove a wider range of mediators to include endotoxins and inflammatory cytokines. The Seraph-100® is among the first to introduce pathogen removal while also binding a variety of inflammatory cytokines. Of these, Seraph-100® may have the most potential to impact outcomes in COVID-19. The Seraph-100® cartridge is composed of heparin-sulfate coated beads that mimic the protective intraluminal glycocalyx brush border of the endothelial cells (8). The Seraph-100® removes not only SARS-CoV2, but also other bacterial and fungal pathogens that cause deleterious secondary infections in COVID-19 patients. Therefore, the Seraph-100® is distinguished by the capability to help achieve intravascular source control to potentially address the trigger and potentiation of cytokine release syndrome. The Seraph-100® is the first of at least three available devices with direct pathogen binding capability. The GARNET® (BOA Biomedical, Cambridge, MA) is another hemofiltration device that directly binds pathogens and a variety of PAMPs by leveraging a genetically engineered recombinant mannose-binding lectin (MBL) linked to the Fc portion of a human immunoglobulin (FcMBL) (9). FcMBL is able to bind to mannose which is found on the surface of all pathogens. A third device called the Hemopurifier® (Aethlon Medical, San Diego, CA, USA) is a lectin affinity plasmapheresis device that specifically targets viruses and has previously been used to treat a critically ill patient with severe Ebola virus disease (10).

The current global threat of SARS-CoV-2 has underscored the necessity for the rapid evaluation and testing of non-pharmacologic, pathogen agnostic solutions such as extra-corporeal pathogen removal to counteract future novel pathogen-related threats. The ability to broadly bind and clear
bacteria, viruses and fungus would reduce the pathogen burden in the bloodstream and potentially modify disease burden and end-organ damage. Additionally, EBP could be synergistic with existing pharmacologic therapies, resulting in clearance of pathogen at more rapid rates than with pharmacologic therapeutics alone (11). Pathogen reducing EBP could therefore be a temporizing measure during the 6-24 months required to develop targeted therapies and vaccines. There are already known pathogens without (Ebola, SARS-CoV-1, MERS, and H1N1) or increasingly resistant to (CMV, ESBL/CRE, fungus, yeast, and tuberculosis) targeted therapy.

Whether EBF will be effective as an adjunct along with existing COVID-19 therapies remains to be seen. Emerging reports suggest that SARS-CoV-2 viremia contributes significantly to the pathophysiology of severe COVID-19. Various reports have confirmed the isolation of SARS-CoV-2 RNA not only in the lungs, but also in the heart, kidneys, intestines, and throughout the vascular endothelium (1). Dissemination of SARS-CoV-2 through the circulation is the best explanation for diffuse end organ damage and endothelial dysfunction contributing to hypercoagulable states. One recent report observed that 82% of severe COVID-19 cases in the ICU had SARS-CoV-2 viremia (12). Presence of viremia was highly associated with a sepsis-like biologic response and critical illness. Viremia could represent an important pathophysiologic link between SARS-CoV-2 infection and the transition from moderate illness to severe COVID-19 disease. Remdesivir can reduce viral replication and duration of hospitalization. It is clear however, that remdesivir alone is not enough. Pathogen-reducing EBP could play a significant role in further reducing viremic burden while simultaneously mitigating the early cytokine storm that is only partially suppressed by steroids.

It is vital to have a multitude of safe EBP options available via the EUA for the COVID-19 pandemic when few pharmacologic solutions exist. With the granting of the EUA, the FDA has already opined as much. Times of crisis often bring opportunity. The door is open for a major advance in this field. The host response to SARS-CoV-2 represents the most exaggerated phenotype of sepsis we have
collectively encountered in our lifetime. This is where a multi-modal EBP approach centered on pathogen reduction may have the most benefit. Hence, we believe EBP therapies demand our collective undivided attention as a nephrology and critical care community. During this EUA period, it is our obligation to carefully track and document each EBP device use and collate data to extract any efficacy and safety signals (13). An observational study is already underway to evaluate the performance of Seraph-100® during this EUA (https://clinicaltrials.gov/ct2/show/NCT04606498). In addition, the time is now to plan, fund, and execute randomized controlled trials to definitively assess the performance of these next generation EBP devices. While difficult to power, it is our duty to conclusively demonstrate clinically relevant efficacy and safety. Pathogen-reducing EBPs could not only provide therapeutic benefit for critically ill COVID-19 patients, but also represent a paradigm shift in our approach to future emerging infectious diseases and sepsis therapeutics.

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Funding: None

Acknowledgements: The views expressed in this manuscript are those of the authors and do not reflect the official policy of the Department of Army, Department of Defense, or U.S. Government.

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Author Contributions: Kevin Chung: Supervision; Writing - original draft; Writing - review and editing
Stephen Olson: Writing - original draft; Writing - review and editing
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