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

DOI: 10.34067/KID.0005242021

Marlies Ostermann and Jay Koyner

Key Points:

Abstract:

Disclosures: Jay L. Koyner reports consulting fees from NxStage Medical, Baxter; research funds Fresenius Medical and speakers fees from NxStage Medical. Marlies Ostermann reports speaker honoraria from Baxter, Fresenius Medical and Biomerieux, research funds from Fresenius Medical, Baxter, LaJolla Pharma and Biomerieux, and consulting fees from NxStage and Baxter.

Funding:

Author Contributions: Marlies Ostermann: Writing - original draft; Writing - review and editing Jay Koyner: Conceptualization; Writing - original draft; Writing - review and editing

Clinical Trials Registration: No

Registration Number:

Registration Date:

How to Cite this article: Marlies Ostermann and Jay Koyner, Extracorporeal blood purification is appropriate in critically ill patients with COVID-19 and multi-organ failure: COMMENTARY, Kidney360, Publish Ahead of Print, 10.34067/KID.0005242021

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

Marlies Ostermann¹ and Jay L. Koyner²

¹ Department of Critical Care, King's College London, Guy's & St Thomas' Hospital, London, UK
² Section of Nephrology, Department of Medicine, University of Chicago, Chicago, IL, USA

Correspondence:
Marlies Ostermann
Guy's & St Thomas Hospital
Department of Critical Care and Nephrology
East Wing
Westminster Bridge Road
London, SE1 7EH
United Kingdom
Marlies.Ostermann@gstt.nhs.uk
Substantial progress has been made in our understanding and management of Coronavirus Disease 2019 (COVID-19). Steroids and inhibitors of Interleukin-6 (IL-6) have emerged as promising therapies, when coupled with respiratory support / supplemental oxygenation to prevent progression and improve outcome. (1, 2) However, mortality remains high, in particular in patients who become critically ill and need organ support. It is therefore natural to call for more rescue strategies. Chung and Olson make a clear case for the role of extracorporeal blood purification (EBP) as a possible adjuvant therapy for critically ill patients with COVID-19 on the basis that removal of circulating inflammatory mediators and pathogenic molecules might prevent organ damage or mitigate organ failure. (3) Kashani and Forni, on the other hand, urge caution and highlight the complexity of cytokine physiology and the potential risks of unselected cytokine removal. (4)

Various EBP techniques are available that can remove some of the circulating molecules implicated in in the pathophysiology of COVID-19. (Table 1) In 2020, the United States Food and Drug Administration (FDA) decided to grant temporary emergency use authorizations for four devices (oXiris® Set, CytoSorb®, Optia Apheresis System® with the Depuro D2000® Adsorption Cartridge, and Seraph-100®). Of note, the FDA made this decision at a time when there were no pharmacological therapies for COVID-19 and the role of steroids and IL-6 inhibitors was less well established. Chung and Olson fully support the FDA's decision and add that a multi-modal EBP approach centered on pathogen reduction may have the most benefit given the dynamic pattern of mediator release in COVID-19 and the spectrum of different techniques available to clear molecules. (3) They acknowledge the need for rapid decisions in a pandemic and the obligation to continue collecting data related to EBP in COVID-19. This is particularly relevant since EBP has been studied in sepsis for more than a decade, but its role remains controversial despite several observational studies and randomized controlled trials (RCT's). Kashani and Forni urge to apply a similar level of caution in COVID-19. (4) Highlighting the complex regulation of cytokine release and interactions and the lack of tools to guide and monitor EBP therapies, they raise concerns about the risks of removing cytokines in a non-specific manner and the additional harms from potentially removing drugs and nutrients. In their opinion, more research with patient-centered outcomes is needed before EBP can be recommended for COVID-19 patients.
It has become clear that COVID-19 is not caused by a single, genetically identical RNA virus but instead from an evolving pathogen with multiple mutations, lineages and variants which have different effects on transmission and virulence. In fact, more than 60 subtypes of COVID-19 have been proposed in the last year. (5) Some forms are associated with a particularly high risk of spread and mortality. (6) In addition, not all hosts are the same. Host variability, genetic predisposition and variable comorbidities contribute to differences in the risk of infection, host immune response, disease progression and mortality. (7) As outlined in detail by Kashani and Forni, the magnitude of the innate immune response is highly variable. (4) Based on lymphocyte activation and cytokine profile, several different immunophenotypes have been described. These, together with additional pathobiological mechanisms including intravascular thrombosis and endothelial activation contribute to different sub-phenotypes of COVID-19. We believe it is this variability in phenotype and host immune response that should serve as a focus of future investigations in the setting of COVID-19 and other forms of sepsis.

The expert group of the 25th Acute Disease Quality Initiative agreed that it was plausible that EBP therapies could have a role in the management of individual patients with COVID-19. (8) If used, the specific technique should be selected on the basis of randomized controlled data and the pathophysiology they are designed to target. They also recommended that future research should identify individuals who were likely to benefit from EBP and patients who may be harmed. Parameters for monitoring and discontinuing EBP as well as information about the impact on removal of drugs and nutrients and other complications during EBP are urgently needed. Whilst the literature contains many case reports and case series describing good outcomes with EBP in COVID-19, the need for caution was highlighted by a recent single-center open-label RCT in 34 adults with COVID-19 pneumonia. (9) Patients requiring support with extracorporeal membrane oxygenation (EMCO) were randomised to ECMO in combination with cytokine adsorption versus ECMO alone. The study showed treated with cytokine adsorption filters had insignificantly higher serum IL-6 levels after 72 hours and significantly higher 30-day mortality (82% versus 24%, p=0.0016).

We see potential parallels between the application of EBP in the setting of COVID-19 and the use of high cut-off dialyzers in multiple myeloma. Several RCTs have failed to consistently demonstrate improved patient outcomes through the removal of injurious light chains in
patients with myeloma kidney. (10, 11) In these multi-center RCTs, there were subsets who were more (or less) likely to recover renal function in the setting of severe acute kidney injury (AKI). Current work is focused on determining which patients with AKI and high light-chain levels are most likely to benefit from high-cutoff dialysis. Importantly, the protocols in these prior trials involved more than just the high-cutoff dialysis (or standard dialysis) to treat the underlying disease, in particular the use of chemotherapy (e.g. bortezomib, cyclophosphamide and corticosteroids) to help reducing the ongoing production of light-chains. (10) In the future, trials exploring the use of EBP in COVID-19 should build off these concepts, trying to identify those patients most likely to benefit as well as combine EBP with the currently validated treatments, some of which target reducing the host response.

In our opinion, there are biological and pathophysiological reasons that make EBP a plausible therapy in COVID-19 (and other forms of sepsis) but only in carefully selected and monitored individual patients. The characteristics of this cohort need to be identified first in carefully conducted research studies. We acknowledge that this path to precision medicine in COVID-19, balancing potential benefit and harm, requires an incredibly rapid pace but caution is necessary nevertheless to avoid iatrogenic harm.

**Disclosures**
Jay L. Koyner reports consulting fees from NxStage Medical, Baxter; research funds Fresenius Medical and speakers fees from NxStage Medical. Marlies Ostermann reports speaker honoraria from Baxter, Fresenius Medical and Biomerieux, research funds from Fresenius Medical, Baxter, LaJolla Pharma and Biomerieux, and consulting fees from NxStage and Baxter.

**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).
Author Contributions

Marlies Ostermann: Writing - original draft; Writing - review and editing
Jay L. Koyner: Conceptualization; Writing - original draft; Writing - review and editing

References

<table>
<thead>
<tr>
<th>Technique</th>
<th>Main clearance principle</th>
<th>Main components removed</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemofiltration</td>
<td>Extracorporeal passage of blood through a hemofilter and utilizing convective clearance (solvent drag) to remove small and middle size molecules (&lt;60kDa)</td>
<td>pro- &amp; anti-inflammatory mediators both removed at equal rates</td>
<td>loss of nutrients, trace elements, drugs and helpful anti-inflammatory mediators</td>
</tr>
<tr>
<td>Hemoperfusion</td>
<td>Extracorporeal passage of blood through hemofilter or sorbent containing cartridge where molecules / mediators are adsorbed (allowing removal of larger molecular weight molecules compared to convection alone)</td>
<td>Cytosorb®: most cytokines, myoglobin, PAMPs &amp; DAMPs but not endotoxin &amp; IL-10 Oxiris®: cytokines, endotoxin</td>
<td>adsorption of drugs, nutrients and helpful anti-inflammatory mediators</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D2000® Plasma Adsorption Column: TNF-alpha, IL-1B, IL-3, IL-6, IL-8, MCP-1, IL-10, and IFN-gamma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seraph® 100 Microbind Affinity Blood Filter®: viral particles, inflammatory mediators</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polymyxin B immobilised fibre columns: endotoxin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LPS adsorber: LPS and endotoxin</td>
<td></td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>Extracorporeal separation of blood into its components with the removal of plasma (molecules &amp; proteins) and replacement with albumin or fresh frozen plasma</td>
<td>cytokines, endotoxin and inflammatory mediators</td>
<td>loss of albumin, antibodies and immunoglobulins</td>
</tr>
</tbody>
</table>

Abbreviations: DAMPs = danger associated molecular patterns; PAMPs = pathogen associated molecular patterns; IFN = interferon; IL = interleukin 10; LPS = lipopolysaccharide; MCP-1 = Monocyte chemoattractant protein-1; TNF = tumour necrosis factor