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

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Substantial progress has been made in our understanding and management of coronavirus disease 2019 (COVID-19). Steroids and inhibitors of 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 patients who are critically ill 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, in contrast, 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 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 multimodal 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 because EBP has been studied in sepsis for more than a decade, but its role remains controversial despite several observational studies and randomized controlled trials (RCTs). Kashani and Forni urge the application of 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 nonspecific manner and the additional harm from potentially removing drugs and nutrients. In their opinion, more research with patient-centered outcomes is needed before EBP can be recommended for patients with COVID-19.

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 that have different effects on transmission and virulence. In fact, >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). On the basis of 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 subphenotypes 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 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 and information about the effect on removal of

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drugs and nutrients and other complications during EBP are urgently needed. Although 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 (ECMO) were randomized to ECMO in combination with cytokine adsorption, versus ECMO alone. The study showed patients treated with cytokine adsorption filters had insignificantly higher serum IL-6 levels after 72 hours, and significantly higher 30-day mortality (82% versus 24%, \( P < 0.002 \)).

We see potential parallels between the application of EBP in the setting of COVID-19 and the use of high cutoff 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 multicenter RCTs, there were subsets who were more (or less) likely to recover renal function in the setting of severe 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 reduce the ongoing production of light chains (10). In the future, trials exploring the use of EBP in COVID-19 should build on these concepts, trying to identify those patients most likely to benefit, and combine EBP with the currently validated treatments, some of which target reducing the host response.

In our opinion, there are biologic and pathophysiologic 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 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**

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**Table 1. Extracorporeal techniques in coronavirus disease 2019**

<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 medium-sized molecules (&lt;60 kDa)</td>
<td>Pro- and 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 mol wt molecules compared with convection alone)</td>
<td>Cytosorb: most cytokines, myoglobin, PAMPs and DAMPs but not endotoxin, and IL-10</td>
<td>Adsorption of drugs, nutrients and helpful anti-inflammatory mediators</td>
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<tr>
<td></td>
<td></td>
<td>Oxiris: cytokines, endotoxin</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>D2000 Plasma Adsorption Column: TNF-α, IL-1B, IL-3, IL-6, IL-8, MCP-1, IL-10, and IFN-γ</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Seraph-100 Microbind Affinity Blood Filter: viral particles, inflammatory mediators</td>
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<td></td>
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<td>Polymyxin B immobilized fiber columns: endotoxin</td>
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<td></td>
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<td>LPS adsorber: LPS and endotoxin</td>
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<tr>
<td>Plasmapheresis</td>
<td>Extracorporeal separation of blood into its components with the removal of plasma (molecules and proteins) and replacement with albumin or fresh frozen plasma</td>
<td>Cytokines, endotoxin, and inflammatory mediators</td>
<td>Loss of albumin, antibodies and Igs</td>
</tr>
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Author Contributions
M. Ostermann conceptualized the study; and all authors wrote the original draft and reviewed and edited the manuscript.

References

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