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Opportunities, controversies, and challenges of extracorporeal hemoadsorption with CytoSorb during ECMO

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Abstract
Extracorporeal membrane oxygenation (ECMO) is frequently used in many centers around the globe for various indications. However, prognosis is often poor even with all supportive therapies, and in many cases, clinical deterioration is associated with inflammation. Hemoadsorption with CytoSorb is a novel approach to limit the inflammatory response, and the device can be safely and easily installed into ECMO circuits. CytoSorb has been used more than 130,000 times to date, but because randomized controlled trials are largely lacking, there is substantial debate on its use. Here, experts from critical care medicine, cardiology, cardiac surgery, and perfusion technology discuss the pros and cons of this novel therapy and outline the future aspects for its clinical application and research.

Keywords
cardiogenic shock, cytokines, CytoSorb, ECLS, extracorporeal life support, extracorporeal membrane oxygenation, ECMO, hemoadsorption, intoxication, sepsis, systemic inflammatory response syndrome

1 INTRODUCTION
The use of temporary mechanical circulatory support (MCS) has considerably increased in the last decade.1,2 Various forms of shock, refractory cardiac arrest as well as protected cardiac interventions and surgery represent the most common clinical indications for veno-arterial extracorporeal membrane oxygenation (V-A ECMO), as does acute respiratory distress syndrome (ARDS) for veno-venous ECMO (V-V ECMO).3 There are only few prospective randomized studies assessing the benefit of ECMO. Nevertheless, ECMO has emerged as a routinely used therapy in many centers. ECMO acts as a simplified and miniaturized version of cardiopulmonary bypass,
which is able to support gas exchange and the systemic circulation during intervention, or until recovery, durable MCS, or transplantation. Notwithstanding various advantages and chances of ECMO support, its use is often associated with and complicated by severe generalized hyperinflammation, which occurs due to the underlying disease as well as the ECMO circuit itself (Table 1). Hyperinflammation contributes to vasoplegia, multiple organ failure and death, but targeted interventions to limit or revert hyperinflammation have been largely unsuccessful.

In this context, extracorporeal hemoadsorption using CytoSorb (CytoSorbents, Monmouth Junction, NJ, USA) has recently gained increasing awareness in critical care medicine, cardiac surgery, and other fields. CytoSorb intends to limit a hyperinflammatory response by adsorption of circulating mediators and pathogen-associated molecular patterns. The device is approved for conditions with elevated blood levels of inflammatory mediators, myoglobin and bilirubin, irrespective of the underlying disease. Recently, CytoSorb has been proposed as adjunctive treatment in patients with the coronavirus disease 2019 (COVID-19). Currently available data on the use of CytoSorb appear promising but mostly originate from case reports, case series and small observational studies (Table 1). In addition, a large European registry collects data to generate robust evidence from clinical use of the device. However, large randomized controlled trials are lacking. So far, only one randomized trial assessed the use of CytoSorb in combination with ECMO. Thirty-four patients with COVID-19 on V-V ECMO were randomized into two groups—one with CytoSorb and one without. CytoSorb failed to reduce Interleukin-6 (IL-6)

### Table 1: Publications on ECMO, inflammation and CytoSorb

<table>
<thead>
<tr>
<th>Reference</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECMO and inflammation (selection)</strong></td>
<td></td>
</tr>
<tr>
<td>Al-Fares et al 2019&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Review</td>
</tr>
<tr>
<td>Chen et al 2013&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Rapid inflammatory response in blood and brain upon ECMO support, pig model</td>
</tr>
<tr>
<td>McIlwain et al 2010&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Intestinal origin of inflammatory response during ECMO, study in piglets</td>
</tr>
<tr>
<td>Millar et al 2016&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Review</td>
</tr>
<tr>
<td>Cho et al 2021&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Cellular immune response upon V-V and V-A ECMO, rat model</td>
</tr>
<tr>
<td><strong>ECMO and CytoSorb use (selection)</strong></td>
<td></td>
</tr>
<tr>
<td>Supady et al 2021&lt;sup&gt;16&lt;/sup&gt;</td>
<td>34 patients with COVID-19 and V-V ECMO randomized to CytoSorb or control. CytoSorb had no significant effect on IL-6 levels. Mortality was higher in the CytoSorb group</td>
</tr>
<tr>
<td>Lebreton et al 2021&lt;sup&gt;18&lt;/sup&gt;</td>
<td>22 patients with COVID-19 on ECMO, of which 11 received CytoSorb. Decrease of inflammatory mediators during ECMO support with and without CytoSorb</td>
</tr>
<tr>
<td>Rieder et al 2021&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Nine patients with ARDS, V-V ECMO + CytoSorb. Reduction of vasopressor demand and decrease of lactate levels during CytoSorb, which was not observed in a historical matched control group without CytoSorb</td>
</tr>
<tr>
<td>Supady et al 2021&lt;sup&gt;20&lt;/sup&gt;</td>
<td>23 patients with ECMO for extracorporeal resuscitation and CytoSorb, compared to a propensity-matched historical control group with ECMO but without CytoSorb. No significant differences in lactate levels, need for vasopressors and fluid therapy between groups</td>
</tr>
<tr>
<td>Zickler et al 2021&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Four patients with intoxication-induced cardiac arrest and V-A ECMO + CytoSorb, strong decline of overdose drug levels</td>
</tr>
<tr>
<td>Scharf et al 2021&lt;sup&gt;22&lt;/sup&gt;</td>
<td>14 patients with V-A ECMO and 29 without ECMO. CytoSorb with RRT for rhabdomyolysis, strong decline of myoglobin</td>
</tr>
<tr>
<td>Akil et al 2021&lt;sup&gt;23&lt;/sup&gt;</td>
<td>13 patients with pneumogenic sepsis, ARDS, V-V ECMO and CytoSorb. Survival 100% and faster weaning off catecholamines, compared to 43% survival in a historical control group (N = 7)</td>
</tr>
<tr>
<td>Rieder et al 2020&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Eight patients with COVID-19 and V-V ECMO, of which four received CytoSorb. Stronger decline of IL-6 levels with CytoSorb than without.</td>
</tr>
<tr>
<td>Kogelmann et al 2020&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Seven patients with ARDS and septic shock, V-V ECMO and CytoSorb. Strong decline in vasopressor use and lactate levels</td>
</tr>
<tr>
<td>Träger et al 2020&lt;sup&gt;26&lt;/sup&gt;</td>
<td>23 patients with V-A ECMO, RRT and CytoSorb. Reduction of inflammatory mediators, catecholamine use and lactate levels</td>
</tr>
<tr>
<td>Calabro et al 2019&lt;sup&gt;27&lt;/sup&gt;</td>
<td>40 patients with cardiogenic or septic shock, ARDS or liver failure. 19 patients with ECMO. Bilirubin, lactate, CK and LDH levels decreased, and survival was higher as expected</td>
</tr>
</tbody>
</table>

**Abbreviations:** ARDS, acute respiratory distress syndrome; CK, creatine kinase; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; RRT, renal replacement therapy; V-A ECMO, veno-arterial ECMO; V-V ECMO, veno-venous ECMO.
levels beyond the reduction observed in the control group. Importantly, CytoSorb was associated with increased mortality. Interestingly, an unusual high rate of adsorber clotting was observed in this single study which demonstrate adverse clinical outcomes with CytoSorb use.

Various questions particularly on the efficacy of the device in different conditions, optimal timing and dosing, impact on drug removal, and, most importantly, its effect on morbidity and mortality remain unanswered. Several centers have already started to use CytoSorb in patients on ECMO support, as its technical implementation is easy and appears to be safe. In addition, mortality occurred rather late after treatment, the reason for which remains unclear. Overall, because prospective data are limited, there is a huge need to further discuss the application of the device and exchange experience. Here, experts from critical care medicine, cardiology, cardiac surgery, and perfusion technology discuss the current knowledge and existing concepts of CytoSorb hemoadsorption during ECMO support, with a special focus on V-A ECMO. The aim of this interdisciplinary debate is not only to provide guidance from experienced users, but even more to reflect open questions and to outline future aspects and study ideas.

2 | DEBATE

2.1 | What are potential conditions or scenarios in patients on ECMO, in which the use of CytoSorb could be considered?

Federico Pappalardo (FP): We should consider the application of CytoSorb in almost every patient requiring ECMO support. The rationale is to attenuate the hyperinflammatory response as a side effect of ECMO per se, which we can always anticipate in these patients.

Guillaume Lebreton (GL): Cardiogenic shock is a very broad indication, and at this time, it is difficult to recommend the start of CytoSorb at time 0 without evidence. Additionally, these patients are rather heterogenous in nature. Although some might already be in multiple organ failure, others might only suffer minor manifestations of the disease. Due to this heterogeneity, I would not recommend to routinely start CytoSorb together with every ECMO initiation. I think it is too early; the concept is very seductive, but we need more evidence before recommending it.

L. Christian Napp (LCN): On the other hand, ECMO for shock is usually implemented in patients with profound shock stages, that is, when 2 or 3 catecholamine drips are in, the lactate level rises, and the shock spiral progresses. Given a mortality of 50% or higher in this population, it would make sense to consider CytoSorb on ECMO start at least in this patient population.

Alexander Supady (AS): At this time, I am also sceptical about the use of CytoSorb in every ECMO. To my impression extracorporeal cardiopulmonary resuscitation (ECPR) could be a promising indication to start CytoSorb therapy directly with ECMO. We know that many of these patients develop serious post–cardiac arrest syndrome, which is characterized by a generalized inflammatory response. The early use of CytoSorb may help to prevent further deterioration of these patients.

Filip De Somer (FDS): The PIRO concept (Textbox 1), which incorporates the domains Predisposition, Insult/Infection, Response, and Organ dysfunction, allows to draw a more differentiated picture of the clinical situation and the inflammatory burden, which may arise in a given patient. This helps to guide the decision of whether CytoSorb should be used or not.

All: For future studies, CytoSorb treatment starting with ECMO initiation would be a better defined starting point. However, as of now, we first propose a study comparing both scenarios, that is, start of CytoSorb together with ECMO versus start at a later stage in case of ongoing shock compared with a control group without CytoSorb.

2.2 | What is your recommendation concerning more technical aspects such as ECMO flow?

LCN: Integration of the adsorber as a parallel bypass introduces a shunt into the circuit (Figure 1), which equals 400-700 mL/min with the manufacturers tubing and standard

<table>
<thead>
<tr>
<th>TEXT BOX 1</th>
<th>PIRO concept</th>
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<tbody>
<tr>
<td><strong>Predisposition:</strong> defines the risk profile of a given patient</td>
<td></td>
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<tr>
<td>• Diabetes</td>
<td></td>
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<tr>
<td>• Hypertension</td>
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<tr>
<td>• Obesity</td>
<td></td>
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<tr>
<td>• Reduced renal function</td>
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<tr>
<td>• Hyperinflammation</td>
<td></td>
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<tr>
<td>• Sepsis</td>
<td></td>
</tr>
<tr>
<td><strong>Insult:</strong> extent of “Insult” will be influenced by many factors</td>
<td></td>
</tr>
<tr>
<td>• Cannula position</td>
<td></td>
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<tr>
<td>• Hemolysis</td>
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<tr>
<td>• Hypoxia</td>
<td></td>
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<tr>
<td>• Emboli</td>
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<tr>
<td><strong>Response:</strong></td>
<td></td>
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<tr>
<td>• Endothelial dysfunction</td>
<td></td>
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<tr>
<td><strong>Organ dysfunction</strong></td>
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</table>
ECMO flows of 3-5 L/min. Thus, flow values shown at the ECMO interface will not necessarily be the flow to the patient, depending on the position of the ECMO flow probe.

**FDS:** Flow through the adsorber likely has a great impact and could be much higher than expected. I would, therefore, suggest that flow should always be measured at least every...
6 hours. We all know that standard ECMO flow is around 3-5 L/min; however, in selected patients, higher flows in the range between 7 and 8 L/min can be achieved with contemporary rotors. Particularly in those situations using high flows, this should be measured with a dedicated flow sensor at best close to the CytoSorb adsorber inlet site.

**All:** If available, connection of a flowmeter to the CytoSorb tubing is recommended. The tubing of the manufacturer should be used; if not available, users should consider appropriate tubing properties and diameters.

2.3 The ECMO decision support card currently issued by the manufacturer provides a list of potential indications of the device. Does that help in daily practice?

**GL:** To my mind, it is not helpful to list potential indications (Textbox 2). We should rather aim not only to find out more about the underlying mechanisms and pathophysiology but also to define specific cutoffs when and how to use the device. Moreover, a list might be misunderstood, such as that every patient with these specific symptoms should receive CytoSorb, and it might, therefore, be dangerous (unwise) to present such lists to the controlling department or regulatory authorities. Besides that, ECMO is a symptomatic treatment in conditions of low flow, whereas CytoSorb represents a symptomatic treatment in case of hyperinflammation.

**AS:** I do not fully agree. A list of potential indications provides a general guidance and can indeed be very helpful, particularly for less experienced users. However, this list would have to be supplemented with some information on the rationale for the use of CytoSorb in these indications, leaving enough room for individual treatment decisions for more experienced users.

**LCN:** This kind of list rather has to be considered a rough mindmap of conditions in which inflammation is present or very likely to develop, thus setting a frame of indications. Hemolysis and intoxication are two additional important conditions, which are not included in the decision support card but are potentially amenable to hemoadsorption with CytoSorb.

**FDS:** In indications like hemolysis, CytoSorb would not address the origin, just the symptom. It is, therefore, always important to also treat the cause and check all technical aspects of ECMO therapy (catheter position, flow, etc) as the basis for overall therapeutic success. Explicitly, CytoSorb should not be used to disguise self-inflicted therapy flaws.

**FP:** There is another potential indication that I would suggest to consider CytoSorb for: organ donation. CytoSorb has already been shown to protect and maintain organ function and could, therefore, help to overcome the chronic shortage of donor organs. This strategy might be beneficial during in situ and ex vivo organ perfusion.

**GL:** We agree that the conditions in this list are at least potential indications to consider CytoSorb. According to a recent randomized trial, CytoSorb should not be used uncritically in patients with COVID-19 and V-V ECMO outside of clinical trials.

2.4 To what extent does ECMO trigger inflammation by itself?

**FP:** Well, it is common knowledge that ECMO per se triggers inflammation (Table 1). This fact, plus the clinical condition by which the patient is affected, produces a “toxic milieu,” which should be considered as the rationale for CytoSorb use. Literature on inflammation triggered by cardiopulmonary bypass can further be extrapolated to support the use of CytoSorb in ECMO patients. Based not only on published evidence but also on experience, the shorter the ECMO run is used, the higher the survival rate, independent of the application of CytoSorb. However, the question is whether CytoSorb can reduce the duration of ECMO support and thereby improve patient outcome. This is, for sure, purely speculative and requires further investigation.

**FDS:** However, we should not forget that the inflammatory reaction is patient dependent. This is well explained by the PIRO concept (Textbox 1). A patient with a low predisposition (risk profile) is more likely to exert a low systemic inflammatory response and less organ damage compared with one with a high predisposition. A balanced increase between proinflammatory and antiinflammatory cytokines, independent of the absolute values, is less likely to cause damage than a predominantly proinflammatory cytokine increase.

**GL:** I personally doubt that CytoSorb can sort the major limitations of ECMO, which are for the most part due to other problems. First of all, there is an increase in ventricular afterload requiring additional MCS devices such as intra-aortic balloon pumps or Impella. Moreover, there are cannulation
issues sometimes leading to complications such as limb ischemia, bleeding, or hemolysis. Whether complications occur is, therefore, depending on how well the patient had been cannulated. For sure, we also face infections developing while ECMO is still running. I do not believe that inflammation is really the actual limitation of ECMO.

**All:** In daily practice, all common ECMO indications such as lung failure, shock, intoxication, or refractory cardiac arrest, involve substantial inflammation at the one or the other point of the cascade, be it as a trigger of the entire process or as a result of it. We concur that even though ECMO per se bears an inflammatory component, the underlying pathologic condition should be the leading decision-maker when discussing initiation of CytoSorb.

### 2.5 Which clinical markers/criteria should be used for decision making?

**All:** Finally, there needs to be a panel of parameters to achieve a full coverage with this potentially beneficial adjunctive treatment. In many centers, interleukin 6 (IL-6) assessment is not available or only with some delay. Furthermore, we perceive a substantial debate between clinicians, at which level of a given inflammatory mediator CytoSorb could or should be applied. This is, however, difficult to answer, as the cutoff for the majority of parameters depends on the underlying disease. When CytoSorb is used, some markers can be measured as a surrogate of adsorption efficacy, for example, myoglobin or IL-6. If feasible, they should be measured before and after the adsorber (i.e. at the inlet and outlet), also to detect potential saturation of the device.

**AS:** I am not convinced that measurement of a parameter just once will help us. I rather support the idea of repeated measurement, particularly in the early phase, to get an impression of how the scenario evolves. Hence, I would suggest that this issue is best to be assessed with kinetics as the trend is way more interesting than an initial value. In patients requiring ECMO for pulmonary or cardiocirculatory support, we observe a broad range of absolute levels and of kinetics of inflammatory parameters—with and without CytoSorb. Therefore, we have to come forward with randomized controlled trials to be able to better understand and differentiate the effects of the underlying pathology, the application of ECMO, and the use of CytoSorb in these patients. In the randomized controlled CYTER study (Figure 2, Cytokine Adsorption in Post-cardiac Arrest Syndrome in Patients Requiring Extracorporeal Cardiopulmonary Resuscitation, clinicaltrials.gov: NCT03685383), we assess the use of CytoSorb in patients receiving ECPR.

**LCN:** At our institution, many ICUs regularly measure IL-6 in the sickest patients, as a surrogate of the systemic inflammatory burden and disease dynamics. We already know that very low levels of IL-6 (e.g., <100 ng/L) for over 24 hours are a rather good predictor of clinical stability and favorable outcome. However, there is evidence that it is the

![Figure 2: CYTER study flow chart](clinicaltrials.gov: NCT03685383)

**Primary endpoint:** Plasma IL-6 reduction

**Secondary endpoints:**
1. Reduction of: IL-2R, TNF-α, PCT, S100
2. Use of vasopressors
3. Renal function
4. Serum lactate
5. Volume resuscitation
6. PK/PD:
   1. Sulbactam/ampicillin
   2. Platelet function tests (LTA, MPA)

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**FIGURE 2** CYTER study flow chart (clinicaltrials.gov: NCT03685383)32. CPR, cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; LTA, light transmission aggregometry; MPA, maximal platelet aggregation; PCT, procalcitonin; PK/PD, pharmacokinetics/pharmacodynamics; V-A ECMO, veno-arterial extracorporeal membrane oxygenation
The persistence of IL-6 rather than the actual peak levels, which predicts a poor outcome in patients with shock. Laboratory values should further be interpreted in the context of the underlying condition: An IL-6 level of 500 ng/L may be high, for example, in a patient after cardiac arrest, or rather low, for example, in a patient with abdominal sepsis. In addition, the use of vasopressors should be considered: Patients without or with constantly low levels of vasopressors are usually not candidates for a therapy aiming at shock control. In contrast, high levels of vasopressors indicate that there is not much time for reverting the shock spiral. Therefore, I suggest to use both IL-6 levels and vasopressor levels for estimating whether CytoSorb could be initiated at a given time point (Figure 3).

**FDS:** To my impression, also other antiinflammatory mediators should always be assessed, too, and not only IL-6. Although IL-6 is superior above other parameters to correlate well with the clinical course and even outcome, inflammation is multifaceted and sometimes unpredictable. Therefore, we definitely need a panel of parameters comprising both proinflammatory and antiinflammatory markers, and this should be validated under various clinical conditions. Another commonly used parameter is lactate. The use of lactate as a marker in patients receiving CRRT is limited, as CRRT potentially results in a high lactate removal. However, if the patient receives CRRT and lactate levels do not decrease, CytoSorb might be an option to stabilize the situation.

**GL:** Lactate should not be considered for monitoring in patients on ECMO. Increasing lactate levels while on ECMO do not justify the initiation of CytoSorb therapy. It should rather trigger a dedicated check of the ECMO circuit itself from a technical side, means correct positioning of cannulas etc to ensure adequate flow conditions.

**FP:** I would add that also bilirubin, myoglobin, and markers of hemolysis such as free hemoglobin might be used for decision-making for CytoSorb application in patients on ECMO. The Vasoactive Inotropic Score is systematically reduced in all series on CytoSorb available up today: therefore, reduction of inotropes might be a clinical surrogate for the “magic biological bullet” we are searching for.

### Table: Proposed Use of CytoSorb

<table>
<thead>
<tr>
<th>Vasopressor dose</th>
<th>IL-6 level</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Low</td>
<td>No therapeutic goal for CS</td>
</tr>
<tr>
<td>None</td>
<td>High</td>
<td>Re-evaluate early (2-4 hrs)</td>
</tr>
<tr>
<td>Low</td>
<td>Low</td>
<td>No therapeutic goal for CS</td>
</tr>
<tr>
<td>Low</td>
<td>High</td>
<td>Re-evaluate early (2-4 hrs)</td>
</tr>
<tr>
<td>Low but rising</td>
<td>Low</td>
<td>Re-evaluate early (2-4 hrs)</td>
</tr>
<tr>
<td>Low</td>
<td>High</td>
<td>Consider CS</td>
</tr>
<tr>
<td>Moderate</td>
<td>Low</td>
<td>Re-evaluate early (2-4 hrs)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Consider CS</td>
</tr>
<tr>
<td>High</td>
<td>Any</td>
<td>Consider CS</td>
</tr>
<tr>
<td>Very high</td>
<td>Any</td>
<td>Consider CS</td>
</tr>
</tbody>
</table>

While decreasing serum lactate levels (‘lactate clearance’) suggest clinical improvement, persisting or increasing levels are an alarm signal and should additionally be considered during decision making.

**a:** Definition of ‘low’ and ‘high’ depends on the underlying condition

**b:** regarding CS for shock control/reversal. Other indications such as rhabdomyolysis may be present independent of shock.

CS, CytoSorb®, hrs, hours; IL-6, Interleukin-6
Hemoadsorption during ECMO support

**All:** There is no single laboratory value that can be used to decide on CytoSorb use. IL-6 levels and lactate may serve useful, and their dynamics may be more important than single measurements. If CytoSorb is used in special indications such as rhabdomyolysis, then surrogate markers should be chosen accordingly. Much research is needed to characterize the inflammatory response and their prognostic value in defined conditions.

### 2.6 What is the recommended time frame for CytoSorb application and when is the time for an adsorber change?

**LCN:** The time frame for re-evaluating the application of CytoSorb should be within 2-4 hours (latest 6 hours) after ECMO initiation (Figure 3). In cases of rapid deterioration, the interval should be adapted to a re-evaluation every 2 hours. Of note, in patients on ECMO, it is even more important to define a specific therapy target (e.g., rhabdomyolysis, inflammation) that should be measured accordingly. Therefore, I recommend to use one adsorber for 6-24 hours depending on the target values (e.g., myoglobin, IL-6) measured preadsorber and postsorber. As we treat critically ill patients, clinical effects are not always seen with or after usage of the first adsorber. In such cases, I suggest not to assess the overall efficacy of CytoSorb after having used the first adsorber. My personal opinion: In patients with rapid deterioration and high loads of toxic metabolites in the blood, I propose that we need larger adsorbers containing more beads, to increase adsorption capacity and dynamics.

**FP:** That also supports my experience, while I additionally would put some more emphasis on an early start of CytoSorb treatment. A number of recently published articles support this concept. Therefore, deterioration of the patient’s status should be avoided and CytoSorb started before things are going worse. Just like ECMO, CytoSorb is also an adjunct, and the timing for application should follow the criteria for ECMO.

**AS:** I think there can be no general recommendation. We have to consider the specific pathology and evaluate this together with available laboratory parameters and additional clinical information. In rapidly evolving cardiogenic shock or ECPR, the early use of CytoSorb may be justified even though the levels of inflammatory parameters such as IL-6 may still be low at this point of time. In contrast, the use in patients with severely progressive ARDS without a relevant systemic inflammatory response may not exert an equally beneficial effect.

**All:** Currently available data do not support the general use of CytoSorb with ECMO. However, depending on the individual pathology, the clinical parameters, and the clinical course, the use of CytoSorb can be considered. Most importantly, we need more well-designed clinical trials assessing indication, timing, and duration of CytoSorb. Nevertheless, because ECMO is usually applied for medical emergency, early use of CytoSorb appears much more meaningful than use during late shock stages.

### CONCLUSIONS

CytoSorb represents a potentially useful therapeutic tool in patients on ECMO. However, there is currently not enough evidence to support the routine use of the device with every ECMO. Many open questions remain (Textbox 3). The discussants agree that CytoSorb might be started with ECMO initiation in selected conditions in the future, if more data become available. Currently, parameters for decision-making should include, but shall not be restricted to, signs of shock, vasopressor dosage, IL-6, lactate clearance, bilirubin, and myoglobin plasma levels. Based on the discussion and the clinical experience of the discussants, profound shock on ECMO, ECPR, postcardiotomy ECMO in patients with infection and ECMO in the context of organ donation represent potential indications to date.

### ETHICAL APPROVAL

Ethical approval was not necessary as this manuscript is based on an interdisciplinary discussion and does not represent a study.

### DISCLOSURES

LCN received lecture and consulting honoraria and research support from Cyotosorbs, lecture honoraria from Abbott and Maquet and lecture, proctoring and consulting honoraria and research funding from Abiomed. Other relationships beyond the topic of this work exist. GL received lecture honoraria and research support from Abiomed, Fresenius, Livanova, Abbott and proctoring honoraria from Syncardia, Medtronic,
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AUTHOR CONTRIBUTIONS
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Designed and drafted the manuscript based on the debate: Napp.

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