Introduction

Synchronous or sequential failure of different organs has been termed multiorgan dysfunction syndrome (MODS) or multiorgan failure (MOF). It was first described 50 years ago as a syndrome with “respiratory failure, hypotension, sepsis and jaundice” [1]. MOF is the most frequent cause of mortality in critically ill patients [2]. An increasing number of extracorporeal organ support modalities is intriguing to provide extracorporeal organ support (ECOS) [2–6]. This review reports on recent advances in diagnosis and therapy of MOF.

History of extracorporeal organ support

In the last two decades, experimental research as well as clinical data (e.g. the SOFA database) emphasized that organ failure is rarely a “stand-alone” organ failure [7]. By contrast, combined and interacting organ failures are frequent. While humoral and cellular interaction—termed “organ crosstalk”—has been characterized more recently [3], syndromic combined organ failure has been described for a long time. For example, hepatorenal syndrome is associated with a dramatic decrease of survival compared to single organ failure of a compensated cirrhosis.

Even if the term extracorporeal organ support has been recently generalized [5], this concept was introduced about 100 years ago, when the first devices for renal replacement therapy (RRT) were investigated. Based on the theories from Grady, and the experiences from Haas and Abel, Rowntree and Turner, RRT became widely available starting in the 1950s and part of clinical routine thanks to the designs from Kolff [8]. Continuous technological improvements permitted the application of intermittent modalities for chronic patients by Scribner in 1960, the treatment of fluid overload by ultrafiltration by Silverstein in 1974, employing what is now known as slow continuous ultrafiltration (SCUF), the first continuous renal replacement therapy (CRRT) by Kramer in 1977 and newer techniques as the slow extended daily dialysis (SLEDD) introduced by Depner and Golper in 1998 [9].

In parallel, extracorporeal support for other organs was developed. Gibbon was the first to use artificial oxygenation and perfusion support for the first successful open-heart surgery in 1953 [10]. Ten years later, Kolobow described the construction and evaluation of an alveolar membrane artificial heart lung [11]. This was “the embryo” of the extracorporeal membrane oxygenation (ECMO), which was first successfully used in treatment by Hill in 1972.

Based on this previous experience, liver-support therapies using albumin dialysis as principle, and CO2 removal devices employing membrane oxygenators are now available. Moreover, other add-on devices (e.g. CytoSorb) for the removal of disease mediators during sepsis have also gained attention.

This shows a large battery of therapies available. However, as suggested by other authors [4–6], it is expected that future developments converge into a single device capable of achieving multiorgan support to cover the lung, the heart, the kidney and the liver [5]. In line with this, a landmark animal study characterized already more than 30 years ago the potential hemodynamic impairment as well as the amount of blood flow required for renal replacement, decarboxylation and oxygenation (Table 1; [12]).

Driven by the “proof of principle” of long-term organ support by chronic hemodialysis, numerous devices for extracorporeal single organ support have been introduced (Fig. 1).

Despite specific features these devices share some common principles and risks (Table 2).

Characteristics of specific organ support

Renal replacement

Up to 7% of hospitalized patients develop acute kidney injury [13] during their hospital stay. Among critically ill patients in the intensive care unit (ICU), this rate reaches even 25% [14]. What is more, a mortality rate >50% has been reported for patients with AKI and multiorgan failure [15]. In the absence of any effective pharmacologic therapies, severe AKI can only effectively be managed by RRT.

RRT can be applied with continuous or intermittent modalities. On the one hand, continuous renal replacement therapy (CRRT) refers to any device or technique aiming to replace kidney function for blood purification during an extended period of time. Intermittent therapies are conducted during up to 5h.
A successful CRRT results in a better hemodynamic stability, reduced transcellular solute shifts, and better tolerance to fluid removal. On the contrary, the need of continuous anticoagulation, patient monitoring, alarm vigilance, and experienced staff can be seen as its major disadvantages. On the other hand, during intermittent treatments, an adequate vascular access, specially trained nurses, and continuous pure water supply are demanded. Several forms of RRT can be employed [16]:

- Slow continuous ultrafiltration (SCUF) is a continuous therapy that might be used to reach a correction of fluid overload in refractory patients by applying a slow removal of plasma water.
- Continuous veno-venous hemofiltration (CVVH) provides solute clearance and volume control by convection. Replacement fluids are infused before or after the hemofilter to replace the ultrafiltrate by predilution or postdilution, respectively.
- Continuous veno-venous hemodialysis (CVVHD) uses diffusion for detoxification. This is achieved flowing dialysate into the dialysate compartment of the hemodialyzer either currently or counter-currently. IHD refers to intermittent hemodialysis.

**Continuous veno-venous hemofiltration (CVVHDF)** is a combination of the two previous techniques. The intermittent variant is known as intermittent hemodiafiltration (IHDF),

**Continuous veno-venous high-flux hemodialysis (CVVHFD) or intermittent high-flux dialysis (IHFD)** is a modified hemodialysis where high-flux membranes are applied.

### Extracorporeal lung support: oxygenation

Despite several effective approaches including prone positioning and low tidal volume ventilation, acute respiratory distress syndrome [17] still has a mortality of more than 40% and affects about 10% of ICU patients. Extracorporeal lung support was introduced more than 80 years ago with Gibbon’s heart–lung machine [18]. The first case reports on the clinical use of ECMO in ARDS and preterm infants were published in the 1970s. The first two randomized controlled trials (RCTs) provided the proof of principle with improved oxygenation, but no survival benefit. The lack of improved outcome was mainly due to unacceptably high blood losses and the absence of a lung-protective ventilation under ECMO [19, 20]. Heparin-coating of the ECMO surfaces allowed for a reduction of high-dose heparinization and reduced complication rates in the two more recent RCTs: CESAR and EOLIA [21, 22]. Both trials gave hints on a reduction of mortality by ECMO in selected patients with ARDS. Nevertheless, the improvement of the outcome was lower than assumed for the power calculation in both trials. In fact, the EOLIA trial was stopped for futility despite a nonsignificant 11% reduction in mortality. Both studies and several registries provided important subgroup analyses suggesting several approaches to improve the effect size of ECMO. Among those are a better patient selection and an optimized set-up of the extracorporeal device. Patients with ARDS should be allocated early (i.e. within about 4 days of intubation). Subtle subgroup analyses of EOLIA suggest that ECMO was more beneficial in patients with less impairment of oxygenation (pO2/FIO2 ≥66 mm Hg), but more pronounced hypercapnia (pCO2 ≥55 mm Hg).

Furthermore, outcome of patients with ECMO therapy is strongly predicted by concomitant nonpulmonary organ failure. In EOLIA, ECMO reduced mortality from 39 to 22% in patients with a SOFA score <11 but was completely ineffective in patients with SOFA ≥11.

This emphasizes the need for improved multorgan support. Interestingly, 17% of the patients randomized to ECMO in the CESAR trial (but none of the controls) were treated with the MARS liver support device.

### Extracorporeal lung support: CO₂ removal

Considering the invasiveness and risks of high-flow ECMO,Gattinoni and coworkers introduced the concept of less invasive extracorporeal lung support restricted to CO₂ removal (ECCO2R) [23].

With a more limited blood flow, ECCO2R technologies are intriguing for combination with other ECOS devices, in particular with RRT. As shown in
Options in extracorporeal support of multiple organ failure

Abstract
Multigorgan failure is among the most frequent reasons of death in critically ill patients. Based on extensive and long-term use of renal replacement therapy, extracorporeal organ support became available for other organ failures. Initially, most of these techniques (e.g. extracorporeal membrane oxygenation, extracorporeal CO2 removal [ECCO2R] and extracorporeal liver support) were used as stand-alone single organ support systems. Considering multiple interactions between native organs (“crosstalk”), combined or integrated extracorporeal organ support (ECOS) devices are intriguing. The concept of multiple organ support therapy (MOST) providing simultaneous and combined support for different failing organs was described more than 15 years ago by Ronco and Bellomo. This concept also implicates overcoming the “compartmentalized” approach provided by different single organ specialized professionals by a multidisciplinary and multiprofessional strategy. The idea of MOST is supported by the failure of several recent studies on single organ support including liver and lung support. Improvement of outcome by ECOS necessarily depends on optimized patient selection, integrated organ support and limitation of its side effects. This implicates challenges for engineers, industry and healthcare professionals. From a technical viewpoint, modular combination of pre-existing technologies such as renal replacement, albumin-dialysis, ECCO2R and potentially cytokine elimination can be considered as a first step. While this allows for stepwise and individual combination of standard organ support facilities, it carries the disadvantage of large extracorporeal blood volume and surfaces as well as additive costs. The more intriguing next step is an integrated platform providing the capacity of multiple organ support within one device. (This article is freely available.)

Keywords
Extracorporeal organ support · Renal replacement therapy · Albumin dialysis · Plasma separation · Extracorporeal CO2 removal

Optionen der extrakorporalen Unterstützung bei Multiorganversagen

Zusammenfassung
Das Multiorganversagen ist eine der häufigsten Todesursachen auf der Intensivstation. Die breite Anwendung der Nierenersatztherapie bei akutem und chronischem Nierenversagen ebnete den Weg für andere extrakorporelle Organersatzverfahren. Diese wurden zunächst überwiegend als Einzelorganersatztherapien eingesetzt (extrakorporale Membranoxygenterierung, extrakorporale CO2-Entfernung [ECCO2R] sowie extrakorporaler Leberersatz). Im Hinblick auf multiple Interaktionen zwischen den Organsystemen („crosstalk“) sind kombinierte bzw. integrierte Organersatzverfahren von großem Interesse. Das Konzept der „multiple organ support therapy“ (MOST) mit kombiniertem Organersatz wurde vor über 15 Jahren von Ronco und Bellomo erstbeschrieben. Dieses Konzept ersetzt den Ansatz der „Kompartmentalisierung“ mit Ersatz einzelner Organversagen im Rahmen der jeweiligen speziellen Verfahren durch eine multidisziplinäre, multiprofessionelle Vorgehensweise. Die Strategie der MOST gewann nach dem Scheitern mehrerer jüngster Studien zum Einzelorganersatz (z. B. Leber- bzw. Lungenersatz) zunehmend an Bedeutung. Der zukünftige Erfolg dieses Konzepts des integrierten Organersatzes hängt dabei auch von einer optimierten Patientenauswahl und einer Limitierung von Nebenwirkungen des Verfahrens ab. Dies bringt zwangsläufig Herausforderungen für Ingenieure, Industrie und Heilberufe mit sich. Technisch ist eine bloße Kombination von vorbestehenden Verfahren wie Nieren- oder Leberersatz, CO2-Entfernung und ggf. Zytokinelimination nur ein erster Schritt. Auch wenn dies eine schrittweise und individualisierte Kombination von vorhandenen Organunterstützungstherapien bedeutet, ergibt sich daraus der Nachteil eines hohen extrakorporalen Blutvolumens, großer künstlicher Oberflächen und additiver Kosten für die einzelnen Verfahren. Der notwendige nächste Schritt sind integrierte Verfahren, die einen Multiorganersatz in einem Gerät ermöglichen.

Schlüsselwörter
Extrakorporaler Organersatz · Nierenersatztherapie · Albumindialyse · Plasmaseparation · Extrakorporale CO2-Entfernung

Table 3, at least five studies reported on the feasibility of low-flow ECCO2R combined with an ultraprotective ventilation aimed at tidal volumes of 4 instead of 6 ml/kg predicted bodyweight (Table 3).

Regarding multiorgan support, some of the ECCO2R devices are prepared for combined use with CVVH(D)F. However, most of these studies (Table 3) excluded patients with other organ failures (in particular liver failure). By contrast, the ongoing ADVOPROTECT trial deliberately includes patients with liver and renal failure.

Another technology of interest has been termed “respiratory electrodialysis”. This procedure combines a hemodiafilter with a membrane lung and a electrodialysis cell positioned on the hemodiaphragm. This technology regionally increases the blood chloride concentration to convert bicarbonate to CO2, thus enhancing the CO2 extraction by the membrane lung [26, 27].

Extracorporeal liver support
In addition to the kidneys and lungs, the liver is one of three major detoxification organs. While renal failure results in the accumulation of water-soluble toxins
1950s
1854 Graham describes the diffusion between two solutions separated by a semipermeable membrane.
1913 Abel, Rowntree and Turner apply diffusion principles to remove substances from the blood of living animals.
1956 Noû, Millo and Hoit placed the first model of a biological artificial liver using a live dog’s liver in a cross-hemodialyzer in an experimental animal.
1960 IH Schotter performs the first chronic dialysis intermittent treatment using a Teflon shunt.
1964 Z Twardowski patented the first hollow-fiber dialyzer.
1970s
1971 IG reports the first successful use for prolonged life support with a heart-lung machine in an ARDS-Patient.
1980 Gattinoni describes the treatment of acute respiratory failure with low-frequency positive-pressure ventilation and extracorporeal removal of CO2.
1998 Depner and Golper introduce of slow extended daily dialysis (SLEDD) as a treatment for critically ill patients.
1999 Kreymann reports the first successful case of Single Pass Albumin Dialysis (SPAD).
1980s
1994 the endotoxin removal cartridge (Toraymyxin) containing polymyxin B immobilized receives approval in Japan.
1998 Strobl presents the Fractionated Plasma Separation and Adsorption system (FPSA).
2000 Reng reports the successful use of a pumpless extra-corporeal lung assist device (iLA) in ARDS.
2002 the HA resin Hemoperfusion Cartridge officially went on sale.
2011 Cytosorb is approved for the European market.
Fig. 1 Development of extracorporeal organ support (ECOS), ARDS, Acute Respiratory Distress Syndrome, CE, Conformité Européenne.
and fluid, liver failure reduces the elimination of protein-bound toxins and liver synthesis.

During the 1990s several extracorporeal methods to eliminate protein-bound toxins were introduced. The most common approach to date is termed albumin dialysis. It is based on the addition of 2–6% albumin to the dialysate to facilitate transport of protein-bound toxins from the blood across the semipermeable membrane into the dialysate. Single-pass albumin dialysis (SPAD) is straightforward but results in a complete waste of the albumin- and toxin-containing dialysate. The proof of principle has been shown in a patient with a serum bilirubin concentration of 102 mg/dL due to liver failure induced by Wilson disease [32]. Although the method is effective for bilirubin and copper removal, the albumin waste results in unacceptable financial burden, particularly, in case of repeated treatment. Therefore, several approaches to “regenerate” the toxin-loaded albumin in the dialysate have been introduced.

**MARS.** The molecular adsorbent recirculating system [33] has been shown to efficiently remove bilirubin as well as ammonia and creatinine. The toxin-loaded albumin in the dialysate is regenerated in a secondary circuit with two adsorption columns (charcoal and an anion-exchange resin). Initial clinical trials suggest improvement of encephalopathy, circulation, portal hypertension and major outcomes. Nevertheless, the largest RCT, the RELIEF trial [34], did not show overall improvement of survival of patients with acute on chronic liver failure (ACLF) [34]. However, a recent subgroup analysis demonstrated an improved 28-day transplant-free survival of patients with ACLF grade two or three [35]. According to the ACLF definition, these were the more severely ill subgroups with at least two or three organ failures. This suggests a potential of MARS for multi-organ support by elimination of water- and protein-bound toxins.

**Fractionized plasma separation and adsorption system (FPSA; Prometheus).** This technology combines separation of toxin-loaded albumin by an albumin-permeable membrane, and removal of the protein-bound toxins through two absorbers (a neutral resin and an anion exchanger) with hemodialysis once the purified plasma returns to the extracorporeal blood circuit. Similar to the RELIEF trial with MARS, also the HELIOS trial with the Prometheus device did not show improvement in survival by extracorporeal FPSA therapy. However,—again—there was a significant survival benefit for the more severely ill patients of the subgroup with a MELD score >30 [36].

### Table 3. Studies on ECCO2R and ultraprotective ventilation

| Reference          | Device          | Number | Main inclusion/exclusion criteria | Additional organ failures | Blood flow; catheter | Period of ECCO2R |
|--------------------|----------------|--------|----------------------------------|---------------------------|---------------------|------------------|
| Terragni et al. [28] | Decap          | 10;    | ARDS (AECC) ≤3 days              | SAPS II ca. 48            | 300–350 mL/min      | >72 h            |
| Fanelli et al. [29]  | A-Lung         | 15     | Moderate ARDS (P/F 100–200 mm Hg) | SOFA 10 ± 4               | 300–350 mL/min      | 3 days           |
| Schmidt et al. [30]  | Prisma-Lung    | 20     | Mild to moderate ARDS (P/F 100–300 mm Hg) | SOFA 9 ± 4              | 420 mL/min         | ≥1 day (mean 31 h) |
| Combes et al. [17]   | 33 A-Lung      | 95     | Moderate ARDS (P/F 100–200 mm Hg) | SOFA 7 ± 3               | 300–500 mL/min (A-Lung) | ≥1 day |
|                     | 34 ILAactive   |        |                                  |                           |                     |                  |
|                     | 28 Cardiohelp  |        |                                  |                           |                     |                  |
|                     | 800–1000(iLA;Cardiohelp) | | | | | |
|                     | 13Fr           |        |                                  |                           |                     |                  |
|                     | 15Fr           |        |                                  |                           |                     |                  |
|                     | 18.20Fr(iLA;Cardiohelp) | | | | | |
|                     | 13.5Fr         |        |                                  |                           |                     |                  |
|                     | 14Fr           |        |                                  |                           |                     |                  |
| Nentwich et al. [31] | Prisma-Lung    | 20     | Hypercapnic acidosis with a pH below 7.30 and a PaCO2 of at least 55 mm Hg under a plateau pressure of at least 25 cmH2O | SOFA 14 (8–18) | Target flow 400 mL/h | 3 days           |
| Nentwich et al. [31] | ADVOS multi    | 20     | Moderate or severe ARDS (P/F ≤200 mm Hg) | No restrictions. At least kidney or liver failure | Target flow 200 mL/h | ≥1 day |

**ARDS** Acute Respiratory Distress Syndrome, **AECC** American European Consensus Conference, **SAPS** Simplified Acute Physiology Score, **SOFA** Sequential Organ Failure Assessment, **ADVOS** Advanced Organ Support.
in those patients who did not undergo emergency liver-transplantation.

**Bioartificial liver (BAL) support.** Extra-corporeal bioartificial cellular therapies using extracorporeal liver cell bioreactors for blood purification have been investigated for decades. However, results in patients are still controversial. A recent meta-analysis on 18 clinical trials and 12 preclinical studies, suggested survival improvements are only shown in large animals, but not in humans with ALF [38]. In order to see progress in this area, alternative high-quality liver cells might be necessary, together with well-designed trials, analyzing the effects on subgroups such as primary nonfunction or fulminant hepatic failure. A phase 2 study did not show improved outcome of patients with end-stage liver disease, but demonstrated a trend to better outcome in a subgroup of patients with alcoholic steatohepatitis [39]. A RCT with 203 patients did not demonstrate an improved overall survival in patients treated with the extracorporeal liver assist device (ELAD) compared to standard therapy. Subgroup analyses suggest a potential benefit in younger patients (<47 years) with a MELD score <28 [39].

**Hemadsorption.** A few case reports and small case-series suggest that bilirubin is eliminated by the hemadsorption device CytoSorb [40]. Based on the methodology, so far no conclusions about an improved outcome can be drawn so far.

**Advanced organ support**

The advanced organ support (ADVOS) multihemodialysis device is based on the principle of albumin dialysis. The proof of principle has been shown in preclinical studies and case series [41–43]. Beyond the normal renal replacement function, it can eliminate protein-bound substances and CO₂ [44]. These properties are due to an “intelligent” dialysate: Toxins diffused from blood into the dialysate are eliminated after the application of physicochemical changes (e.g., pH) to the recirculating dialysate in a secondary circuit. This is due to conformational change occurring in albumin above a concrete pH level, which helps both to toxin removal and albumin recycling [13]. In addition, since the dialysate is formed via the on-line mixing of an acidic and an alkaline concentrate, the previously mentioned pH changes can be customized to adapt the dialysate pH. Overall, ADVOS intends to provide a multiple organ (i.e. kidney, liver, lungs) support by means of water-soluble, protein-bound toxins elimination, direct H⁺ removal (i.e. acid–base balance) and CO₂ elimination.

Serum albumin, is the main protein of human blood plasma. It binds, among others, fatty acids, hormones or bilirubin. An increase of the latter 5 times above the upper limit increases the risk to develop cholemic nephropathy [45–47]. Furthermore, new onset of acute kidney injury is associated with concomitant onset of jaundice [48]. The reduction of bilirubin levels (ideally by normalization of the hepatic function, alternatively by extra-corporeal detoxification) by the ADVOS multi device has been shown in several studies. On top of this, as already documented [43], ADVOS multi can remove creatinine, urea or ammonia, among others.

Nevertheless, probably, the most differentiating factor of the ADVOS therapy in comparison to other apparently similar medical devices is the possibility to adjust the pH of the dialysate (by the relation between the acidic and basic concentrates that form the dialysate) and adapt it to the needs of the patient during treatment. Going back to chemistry basics, when the pH of a solution is higher than 7.00, the concentration of OH⁻ is likewise higher than that of H⁺. The higher the pH of the dialysate, the higher the gradient of H⁺ that can be formed between blood and dialysate. Consequently, H⁺ in excess will diffuse from blood into the dialysate, providing an acidosis correction. Moreover, by removing H⁺, HCO₃⁻ will be produced in blood (Eq. 1), mimicking the mechanism used by the kidney as a metabolic response to respiratory acidosis.

**Equation 1.** Equilibrium reaction between CO₂, H⁺ and HCO₃⁻

\[
\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{HCO}_3^- + \text{H}^+
\]

The generated HCO₃⁻ provides an improvement during metabolic acidosis, but should be removed, if excessive, during respiratory acidosis. The capacity of the ADVOS system to remove CO₂ depends on blood flow, dialysate pH and the bicarbonate concentration. As demonstrated in a series of experiments using an ex vivo model for acidosis, the higher the dialysate pH, the blood flow or the accumulated HCO₃⁻, the better CO₂ removal rates are achieved [44]. In the clinical setting ADVOS is normally used with a maximum blood flow rate of 200 ml/min (to allow regional citrate anticoagulation), a maximum dialysate pH of 9 and basic concentrates containing 20 mmol/l HCO₃⁻. This allows a removal of up to 50 ml/min CO₂ with normal blood bicarbonate concentration (22–28 mmol/l). Since the HCO₃⁻ removal is the limiting factor in the ADVOS multi circuit, during a severe metabolic acidosis even more CO₂ could be removed without an increase of blood bicarbonate over 30 mmol/l. Under experimental conditions, up to 146 ml/min of CO₂ could be removed. However, this required blood flow rates of 400 ml/min and a dialysate pH >9.00 with a basic concentrate without bicarbonate [44].

In contrast to ECMO, where due to high blood flows (3–6 L/min) blood pH is normalized within minutes, it takes up to 2–4 h for ADVOS multi running at 100–200 ml/min blood flows until an acidic blood is normalized in patients. The use of elevated dialysate pH is not exempt of risks, and therefore, to avoid overcompensation, blood pH must be continuously monitored during ADVOS treatments. It is recommended that blood pH values of the samples taken at the outlet of the dialyzer (blood post-dialyzer) remain below 8.00. Above this value pH is no longer measurable in common blood gas analyzers. In case that a post-dialyzer blood pH is >8.00, dialysate pH should be reduced by 0.5 in the treatment’s settings (e.g., from 9.00 to 8.50).


**Table 4** Summary of features of clinically available devices for extracorporeal liver support

| Device      | Liver support | Renal support | ECCO2R | Acid–base modulation | Improved coagulation | Resources required | Availability | Financial burden |
|-------------|---------------|---------------|--------|-----------------------|-----------------------|--------------------|--------------|------------------|
| SPAD        | +             | +             | –      | –                     | –                     | +++                | ++           | +++              |
| MARS        | +             | +             | –      | –                     | –                     | +++                | +            | +++              |
| PROMETHEUS  | +             | +             | –      | –                     | –                     | +++                | +            | +++              |
| ADVOS       | +             | +             | +      | –                     | –                     | ++                 | +            | +++              |
| ELAD        | +             | +             | –      | –                     | –                     | +++                | –            | +++              |
| Plasma separation | +       | –             | –      | –                     | –                     | +                  | ++           | ++               |
| CytoSorb    | +             | –             | –      | –                     | –                     | ++                 | +++          | ++               |

**Table 5** Comparison of combined single organ support and multiorgan support devices

| Combination of single organ support devices | Multiorgan support devices |
|---------------------------------------------|----------------------------|
| Advantage | Disadvantage | Advantage | Disadvantage |
| Step-wise combination | Large extracorporeal volume | Limitation of extracorporeal volume | Not yet generally available |
| Use of familiar technique | Personal resources for assembling several devices | Limitation of personal resources | Little clinical data available |
| Cumulative costs of several devices | Additional features: modulation of acid–base balance | |
| Lack of “match-up” | |

Table 4 summarizes the main features of clinically available devices for extracorporeal liver support.

**Detoxification in sepsis**

Major parts of the pathophysiology of sepsis are related to microbial toxins and to the inflammatory response induced by proinflammatory cytokines. Therefore, extracorporeal elimination of toxins and cytokines is an intriguing concept to treat patients with sepsis.

In the first case, hemoperfusion using fiber columns containing polymyxin B (an antibiotic with high affinity to endotoxins) has been used in a number of studies. However, recent results and meta-analyses did not demonstrate improved outcome by this or similar approaches [33, 49–51].

In the second case, CytoSorb provides hemoadsorption of cytokines and other midmolecular weight toxins by multiporous polymeric beads. Two larger studies in septic patients resulted in conflicting data: A RCT including 100 mechanically ventilated patients with severe sepsis or septic shock did not show a reduction in systemic IL-6 levels or in multiple organ dysfunction score, ventilation time and time course of oxygenation in the intervention group [52]. A retrospective analysis of 116 patients with septic shock demonstrated a significantly higher reduction in predicted mortality in patients with CytoSorb therapy and CRRT compared to patients with CRRT alone [53].

Similarly, the HA 330 and HA 380 cartridges (Jafron, Zhuhai, China) contain neutro-macroporous resin adsorbing beads with a pore size of 500 D–60 kD. At least two RCTs with 44 and 46 patients demonstrated significantly improved outcome (including ICU mortality) in patients treated with HA 330 hemoperfusion [54, 55].

**Modular or integrated multiorgan support?**

While there is increasing evidence for combined MOST, there is an ongoing debate about its realization. From a pragmatic viewpoint individual combination of the available devices is a first reasonable step. In particular, liver support systems such as MARS and Prometheus, and some devices for ECCO2R are usually combined with sequential RRT devices. Furthermore, the high blood flow during ECMO allows for RRT in parallel without additional vascular access [56].

Nevertheless, modular combination results in additional extracorporeal volume and potential hemodynamic impairment. Also regarding fluid balance targets, thorough monitoring of these side effects is mandatory. This starts with the observation of potential hemodynamic impairment during connection and ends with documentation of circulatory changes during disconnection. Several studies showed that transpulmonary thermodilution (TPTD) is feasible during RRT and ADVOS treatments [56]. Despite concerns on a loss of indicator into the extracorporeal circuit, a recent study demonstrated that measurement of Cardiac Index with TPTD is reliable even during ECMO [57], whereas global end-diastolic volume index (GEDVI) and extravascular lung water index (EVLWI) might be confounded.

Regarding the disadvantages and technical burdens of using combinations of pre-existing technologies (Table 5), development of procedures facilitating MOST by one single device is an intriguing next step. Although there is still a lack of data on improved outcome, ADVOS can be considered as the first integrated MOST device.

**Practical conclusion**

During the last few decades, extracorporeal organ support has become available for nearly every organ failure. All types of ECOS share the challenges of vascular access, sequestration of blood
into the device, induction of extracorporeal blood flow, anticoagulation with potential bleeding or clotting complications, a certain circulatory impairment, and finally, the attempt of extracorporeal blood purification. Based on organ-specific compensatory mechanisms and blood flow within the genuine organ(s), extracorporeal blood flow ranges from below 100 ml/min up to more than 5 l/min in ECMO. Due to the high incidence of MOF in critically ill patients, the concept of multiorgan support is intriguing. Depending on the individual organ failures, in some patients, multiorgan support can be provided by sequential and/or intermittent therapy with single-organ support systems. Another option is combined organ support (normally two organ support) using serially connected devices driven by one blood pump. Considering the additive sequestration of blood in several devices, integrated multiorgan support using one multifunctional device might be the most intriguing approach.

Corresponding address
Prof. Dr. W. Huber
Klinik und Poliklinik für Innere Medizin II
Klinikum rechts der Isar, Technische Universität München
Ismaninger Str. 22, 81675 München, Germany
wolfgang.huber@tum.de

Funding. Open Access funding provided by Projekt DEAL.

Compliance with ethical guidelines
Conflict of interest. W. Huber is member of the Medical Advisory Board of Pulson Medical systems SE (Getinge Group). W. Huber received speaker’s fees and travel reimbursement by ADVITOS GmbH, W. Huber is principal investigator of a clinical ECMO study supported by NovaLung/Xenios (Fresenius Medical Care). W. Huber is principal investigator of an animal study on ECMO and hemodynamics supported by Maquet GmbH (Getinge Group). A. F. Ruiz de Garibay is in an employment relationship with ADVITOS GmbH.

For this article no studies with human participants or animals were performed by any of the authors. All studies performed were in accordance with the ethical standards indicated in each case.

The supplement containing this article is not sponsored by industry.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References
1. Skillman JJ et al (1969) Respiratory failure, hypotension, sepsis, and jaundice. A clinical syndrome associated with lethal hemorrhage from acute stress ulceration of the stomach. Am J Surg 117(4):523–530
2. Ronco C, Bellomo R (2002) Acute renal failure and multiple organ dysfunction in the ICU: from renal replacement therapy (RRT) to multiple organ support therapy (MOST). Int J Artif Organs 25(8):73–74
3. Husain-Syed F et al (2018) Extracorporeal organ support (ECSO) in critical illness and acute kidney injury: from native to artificial organ crosstalk. Intensive Care Med 44(1):1447–1459
4. Ronco C, Ricci Z, Husain-Syed F (2019) From multiple organ support therapy to extracorporeal organ support in critically ill patients. Blood Purif 48(2):99–105
5. Ranieri VM, Brodie D, Vincent JL (2017) Extracorporeal organ support: from technological tool to clinical strategy supporting severe organ failure. JAMA 318(12):1105–1106
6. Vincent JL (2019) Introduction to extracorporeal multiple organ support. Blood Purif 48(2):97–98
7. Vincent JL et al (1998) Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on “sepsis-related problems” of the European society of intensive care medicine. Crit Care Med 26(11):1793–1800
8. Gottschalk CW, Fellner SK (1997) History of the science of dialysis. Am J Nephrol 17(3–4):289–298
9. Twardowski ZJ (2008) History of hemodialyzers’ designs. Hemodial Int 12(2):173–210
10. Boettcher W, Merkle F, Weitkemper HH (2003) History of extracorporeal circulation: the conceptional and developmental period. J Extra Corporeal Technol 35(3):172–183
11. Kolobow T, Bowman RL (1963) Construction and evaluation of an alveolar membrane artificial heart-lung. Trans Am Soc Artif Intern Organs 9:238–243
12. Gattinoni L et al (1978) Control of intermittent positive pressure breathing (IPPB) by extracorporeal removal of carbon dioxide. Br J Anaesth 50(8):753–758
13. Yamasaki K et al (1999) Interactive binding to the two principal ligand binding sites of human serum albumin: effect of the neutral-to-base transition. Biochim Biophys Acta 1432(2):313–323
14. Tolvani A (2012) Continuous renal-replacement therapy for acute kidney injury. N Engl J Med 367(26):2505–2514
15. Uchino S et al (2005) Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 294(7):813–818
16. Villa G et al (2016) Nomenclature for renal replacement therapy and blood purification techniques in critically ill patients: practical applications. Crit Care 20(1):283
17. Combes A et al (2019) Feasibility and safety of extracorporeal CO2 removal to enhance protective ventilation in acute respiratory distress syndrome: the SUPERNOVA study. Intensive Care Med 45(5):592–600
18. Passaroni AC, Silva MA, Yoshida WB (2015) Cardiopulmonary bypass: development of John Gibbon’s heart-lung machine. Rev Bras Cir Cardiovasc 30(2):235–245
19. Morris AH et al (1994) Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO2 removal for adult respiratory distress syndrome. Am J Respir Crit Care Med 149(2 Pt 1):295–305
20. Zapol WM et al (1979) Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. JAMA 242(20):2193–2196
21. Combes A, Slutsky AS, Brodie D (2018) ECMO for severe acute respiratory distress syndrome. N Engl J Med 379(11):1091–1092
22. Peek GJ et al (2009) Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet 374(9698):1351–1363
23. Gattinoni L et al (1986) Low-frequency positive-pressure ventilation with extracorporeal CO2 removal in severe acute respiratory failure. JAMA 256(7):881–886
24. Bein T et al (2013) Lower tidal volume strategy (approximately 3 ml/kg) combined with extracorporeal CO2 removal versus ‘conventional’ protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study. Intensive Care Med 39(5):847–853
25. Kluge S et al (2012) Avoiding invasive mechanical ventilation by extracorporeal carbon dioxide removal in patients failing noninvasive ventilation. Intensive Care Med 38(10):1632–1639
26. Zanella A et al (2019) Extracorporeal carbon dioxide removal by electrodialysis (Cre-ED): a novel approach to correct acidemia. Am J Respir Crit Care Med. https://doi.org/10.1164/rccm.201903-0538OC
27. Zanella A et al (2015) Respiratory electrodialysis. A novel, highly efficient extracorporeal CO2 removal technique. Am J Respir Crit Care Med 192(6):719–726
28. Terragni PP et al (2009) Tidal volume lower than 6 ml/kg enhances lung protection: role of extracorporeal carbon dioxide removal. Anesthesiology 111(4):826–833
29. Fanelli V et al (2016) Feasibility and safety of low-flow extracorporeal carbon dioxide removal to facilitate ultra-protective ventilation in patients with moderate acute respiratory distress syndrome. Crit Care 20:36
30. Schmidt M et al (2018) Feasibility and safety of low-flow extracorporeal CO2 removal managed with a renal replacement platform to enhance lung-
47. Nayak SL et al (2017) Bile cast nephropathy
46. Foshat M et al (2017) Bile cast nephropathy in patients with septic shock and elevated endotoxin level: the EUPHRATES randomized controlled trial. JAMA 320(14):1455–1463
45. Brasen JH et al (2019) Cholemic nephropathy
44. Perez-Ruiz de Garibay A et al (2019) Respiratory and metabolic acidosis correction with the ADVanced organ support system. Intensive Care Med Exp 7(1):56
43. Huber W et al (2017) First clinical experience in 14 patients treated with ADVOS: a study on feasibility, safety and efficacy of a new type of albumin dialysis. BMC Gastroenterol 17:31
42. Al-Chalabi A et al (2017) Evaluation of the hepasorb(R) treatment in pigs with acute liver failure. BMC Gastroenterol 13:83
41. Al-Chalabi A et al (2013) Evaluation of the hepasorb(R) treatment in pigs with acute liver failure. BMC Gastroenterol 13:83
40. Dhokia VD et al (2019) Novel use of cytocarb haemoadsorption to provide biochemical control in liver impairment. J Intensive Care Soc 20(2):174–181
39. Thompson J et al (2018) Extracorporeal cellular therapy (ELAD) in severe alcoholic hepatitis: a multinational, prospective, controlled, randomized trial. Liver Transpl 24(3):380–393
38. He YT et al (2019) Bioartificial liver support systems for acute liver failure: a systematic review and meta-analysis of the clinical and preclinical literature. World J Gastroenterol 25(27):3634–3648
37. Larsen FS et al (2016) High-volume plasma exchange in patients with acute liver failure: an open randomised controlled trial. J Hepatol 64(1):69–78
36. He YT et al (2019) Bioartificial liver support systems for acute liver failure: a systematic review and meta-analysis of the clinical and preclinical literature. World J Gastroenterol 25(27):3634–3648
35. Gerth HU et al (2017) Molecular adsorbent recirculating system can reduce short-term mortality among patients with acute-on-chronic liver failure—a retrospective analysis. Crit Care Med 45(10):1616–1624
34. Banares R et al (2013) Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the RELIEF trial. Hepatology 57(3):1153–1162
33. Kribben A et al (2012) Effects of fractionated plasma separation and adsorption on survival in patients with acute-on-chronic liver failure. Gastroenterology 142(4):782–789 e3
32. Schadler D et al (2017) The effect of a novel extracorporeal cytokine hemoadsorption device on IL-6 elimination in septic patients: a randomized controlled trial. PLoS ONE 12(10):e0187015
31. Brouwer WP et al (2019) Hemoadsorption with CytoSorb shows a decreased observed versus expected 28-day all-cause mortality in ICU patients with septic shock: a propensity-score-weighted retrospective study. Crit Care 23(1):317
30. Herner A et al (2019) Transpulmonary thermodilution into the extra-corporeal circuit. J Clin Monit Comput. https://doi.org/10.1007/s10877-019-00398-6
29. Lahmer T et al (2017) In-parallel connected intermittent hemodialysis through ECMO does not affect hemodynamic parameters derived from transpulmonary thermodilution. Perfusion 32(8):702–705
28. Broman ME et al (2019) Endotoxin and cytokine reducing properties of the oXiris membrane in patients with septicshock: a randomised crossover double-blind study. PLoS ONE 14(8):e220444
27. Brouwer WP et al (2019) Hemoadsorption with CytoSorb shows a decreased observed versus expected 28-day all-cause mortality in ICU patients with septic shock: a propensity-score-weighted retrospective study. Crit Care 23(1):317
26. Schadler D et al (2017) The effect of a novel extracorporeal cytokine hemoadsorption device on IL-6 elimination in septic patients: a randomized controlled trial. PLoS ONE 12(10):e0187015
25. Huang Z et al (2013) Effect on extrapulmonary sepsis-induced acute lung injury by hemoperfusion with neutral microporous resin column. Ther Apher Dial 14(4):596–602
24. Huang Z et al (2013) Effect on extrapulmonary sepsis-induced acute lung injury by hemoperfusion with neutral microporous resin column. Ther Apher Dial 17(4):454–461
23. He YT et al (2019) Bioartificial liver support systems for acute liver failure: a systematic review and meta-analysis of the clinical and preclinical literature. World J Gastroenterol 25(27):3634–3648
22. Thompson J et al (2018) Extracorporeal cellular therapy (ELAD) in severe alcoholic hepatitis: a multinational, prospective, controlled, randomized trial. Liver Transpl 24(3):380–393
21. Dohokia VD et al (2019) Novel use of cytocarb haemadsorption to provide biochemical control in liver impairment. J Intensive Care Soc 20(2):174–181
20. Al-Chalabi A et al (2013) Evaluation of the hepasorb(R) treatment in pigs with acute liver failure. BMC Gastroenterol 13:83
19. Al-Chalabi A et al (2017) Evaluation of an ADVanced organ support (ADVOS) system in a two-hit porcine model of liver failure plus endotoxemia. Intensive Care Med Exp 5(1):31
18. Huber W et al (2017) First clinical experience in 14 patients treated with ADVOS: a study on feasibility, safety and efficacy of a new type of albumin dialysis. BMC Gastroenterol 17(1):32
17. Perez-Ruiz de Garibay A et al (2019) Respiratory and metabolic acidosis correction with the ADVanced organ support system. Intensive Care Med Exp 7(1):56
16. Brasen JH et al (2019) Cholemic nephropathy causes acute kidney injury and is accompanied by loss of aquaporin 2 in collecting ducts. Hepatology 69(5):2107–2119
15. Brasen JH et al (2019) Cholemic nephropathy causes acute kidney injury and is accompanied by loss of aquaporin 2 in collecting ducts. Hepatology 69(5):2107–2119
14. Foshat M et al (2017) Bile cast nephropathy in cirrhotic patients: effects of chronic hyperbilirubinemia. Am J Clin Pathol 147(5):525–535
13. Nayak SL et al (2017) Bile cast nephropathy in patients with acute kidney injury due to hepatorenal syndrome: a postmortem kidney biopsy study. J Clin Transl Hepatol 5(1):92–100
12. Keymann B et al (1999) Albumin dialysis: effective removal of copper in a patient with fulminant Wilson disease and successful bridging to liver transplantation: a new possibility for the elimination of protein-bound toxins. J Hepatol 31(6):1080–1085
11. Dilleinger RP et al (2018) Effect of targeted polymyxin B hemoperfusion on 28-day mortality in patients with septic shock and elevated endotoxin level: the EUPHRATES randomized controlled trial. JAMA 320(14):1455–1463
10. Al-Chalabi A et al (2013) Evaluation of the hepa- renal syndrome: a postmortem kidney study. J Clin Transl Hepatol 5(2):92–100
9. Rimola J et al (2011) Albumin dialysis in acute renal failure due to hyperbilirubinemia. Am J Med 120(5):525–535
8. Jager B et al (2012) Jaundice increases the rate of complications and one-year mortality in patients with hypoxic hepatitis. Hepatology 56(6):2297–2304
7. Fuji T et al (2018) Polymyxin B-immobilized hemoperfusion and mortality in critically ill adult patients with sepsis/septic shock: a systematic review with meta-analysis and trial sequential analysis. Intensive Care Med 44(2):167–178
6. Broman ME et al (2019) Endotoxin and cytokine reducing properties of the oXiris membrane in patients with septic shock: a randomized crossover double-blind study. PLoS ONE 14(8):e220444
5. Umgeelter A et al (2008) Treatment of septic patients with an arginine-based endotoxin adsorber column improves hemodynamics and reduces oxidative stress: results of a feasibility study. Blood Purif 26(4):333–339
4. Schadler D et al (2017) The effect of a novel extracorporeal cytokine hemoadsorption device on IL-6 elimination in septic patients: a randomized controlled trial. PLoS ONE 12(10):e0187015
3. Gerth HU et al (2017) Molecular adsorbent recirculating system can reduce short-term mortality among patients with acute-on-chronic liver failure—a retrospective analysis. Crit Care Med 45(10):1616–1624
2. Schadler D et al (2017) The effect of a novel extracorporeal cytokine hemoadsorption device on IL-6 elimination in septic patients: a randomized controlled trial. PLoS ONE 12(10):e0187015
1. Dilleinger RP et al (2018) Effect of targeted polymyxin B hemoperfusion on 28-day mortality in patients with septic shock and elevated endotoxin level: the EUPHRATES randomized controlled trial. JAMA 320(14):1455–1463