Intensive Care Med (2018) 44:1447–1459
https://doi.org/10.1007/s00134-018-5329-z

REVIEW

Extracorporeal organ support (ECOS) in critical illness and acute kidney injury: from native to artificial organ crosstalk

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Abstract

The complex nature of single organ failure potentially leading to multiple organ dysfunction syndrome (MODS) in critically ill patients necessitates integrated supportive therapy. Rather than a primary disease, acute kidney injury (AKI) is considered a window to a potentially serious underlying systemic disease, which may partially explain the high morbidity and mortality rates associated with the condition. Renal replacement therapy (RRT) has been routinely used for more than a decade in various intensive care settings and there has also been an increase in the use of extracorporeal membrane oxygenation and extracorporeal carbon dioxide removal. When these renal and cardiopulmonary modalities are used together, a multidisciplinary approach is necessary to minimize negative interactions and unwanted adverse effects. In this review, we describe the patterns of organ crosstalk between the native and artificial organs, the incidence of AKI and need for RRT and associated mortality after extracorporeal organ support (ECOS) therapy, including the potential short- and long-term advantages and disadvantages of organ support in terms of renal function. We also review potential indications of RRT outside its conventional indications in patients with MODS, as well as technical considerations when RRT is used alongside other organ support therapies. Overall, available literature has not definitely established the ideal timing of these interventions, and whether early implementation impacts organ recovery and optimizes resource utilization is still a matter of open debate: it is possible that future research will be devoted to identify patient groups that may benefit from short- and long-term multiple organ support.

Keywords: Acute kidney injury, Acute respiratory distress syndrome, Cardiogenic shock, Extracorporeal membrane oxygenation, Multiple organ support therapy, Renal replacement therapy

From single to multiple organ failure and from single to multiple organ support

Evidence is growing that multiple organs are similarly and simultaneously involved in critical illness, with similar rates of organ dysfunction for the renal, cardiovascular, respiratory and central nervous systems [1]. This is because syndromes like sepsis and acute respiratory distress syndrome (ARDS) often have a significant impact on several distal organs, regardless of the site of the initial insult. Furthermore, impaired function of one organ is often related to the dysfunction of other organs. The literature on such complex clinical pictures emphasizes the need for multidisciplinary management with the engagement of the intensive care unit (ICU) physician with focus on multiple organ dysfunction syndrome (MODS) [2–7].

A typical example is acute kidney injury (AKI) which has been recognized as a heterogeneous clinical

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syndrome with multifactorial aetiology and variable clinical course [8]. Over 50% of patients develop stage 1 AKI at some point during their ICU course, while the incidences of stage 2 and 3 AKI are considerably less, and requirement for renal replacement therapy (RRT) is approximately 10% [9]. AKI can be the cause of further organ dysfunction. Conversely, AKI might be considered to be a secondary "bystander", particularly in the setting of chronic conditions and multiple pre-existing comorbidities. Regardless of whether the kidneys are the initiating cause or are secondarily involved in distal organ dysfunction, their dysfunction has been shown to be independently associated with mortality. Indeed, much of the mortality risk in patients with MODS is thought to be the consequence of complex interactions between the actual insult, the activation of inflammation and distant organ effects. The severity of organ dysfunction is independently associated with mortality: mortality may reach 50% when RRT is required [10, 11], Theoretically, preventing AKI by early identification of patients at risk or avoiding the progression of its severity may impact outcome of other organs as well [12].

A recently published viewpoint from some of the authors of the present paper proposed that all forms of therapies where blood is extracted from the body and processed with specific devices and techniques can be defined as extracorporeal organ support (ECOS) [13]. This was done to distinguish traditional mechanical ventilation and isolated cardiac support (e.g. ventricular assistance devices or total artificial hearts) from ECOS, which represent a group of increasingly applied systems in the context of MODS and critical illness [14, 15]. RRT has been routinely used for more than three decades in various ICU settings for kidney support. Veno-venous extracorporeal membrane oxygenation (VV-ECMO) and extracorporeal carbon dioxide removal ($ECCO_2R$) are currently increasingly used at the bedside for lung support, whereas veno-arterial ECMO (VA-ECMO) may be indicated in patients requiring circulatory and gas exchange support. Other artificial organ supports may include liver support [Molecular Adsorbent Recirculating System (MARS), fractionated plasma separation and adsorption (Prometheus), or a bio-artificial system that combines plasma separation with perfusion of bio-reactors filled with human or animal hepatocytes (e.g. extracorporeal liver assist device; ELAD)] or haemoperfusion (in the context of specific intoxications or endotoxaemia).

The aim of this review is to describe the different interaction patterns among failing organs and between native and artificial organs, noting that similar interactions can occur when different ECOS systems are utilized simultaneously (artificial organ interaction). We will particularly focus on the short- and long-term harms and benefits of organ support in terms of renal function, potential indications of RRT outside its conventional indications in patients with MODS and technical considerations when RRT is used alongside other organ support therapies.

Take-home message

The review is a state-of-knowledge perception of multiple organ failure and multiple organ support using the kidney and RRT as examples.

The kidney in organ crosstalk and multiple organ dysfunction syndrome

Bidirectional interactions between distant organs are commonly referred to as organ crosstalk, a term that summarizes the complex biological communication and feedback that occurs between different organs mediated via a number of mechanisms including soluble and cellular mechanisms. Organ crosstalk is thought to have a pivotal role in maintaining body homeostasis. Consequently, when pathological conditions occur in one or more organs, they may reach a level of severity that can lead to functional and structural dysfunction in other organs. Such pathological crosstalk may ultimately result in a vicious circle of continuous negative organ interactions that leads to reciprocal end-organ disease progression. The pathogenetic pathway of this process appears to be complex, involving extra- and intracellular mechanisms, biochemical pathways and systemic oxidative stress that variably contribute to worsen tissue function.

Multiple organ interactions involving the kidney are represented in Fig. 1. Cardiorenal syndromes have been subclassified into five separate entities whose etymology reflects the primary and secondary pathology, the chronology of heart–kidney injury, as well as simultaneous cardiac and renal dysfunction due to systemic disease [3]. Renal function and congestion have been identified as important prognostic factors in the outcome of patients with acute and chronic heart failure [16, 17]. Consequently, adequate control of renal congestion and raised abdominal pressure with simultaneous improvement/preservation of renal function have been proposed as central goals of patient management in cardiorenal syndromes [18].

The term pulmonary–renal syndromes typically implies rare disease entities involving a combination of diffuse alveolar haemorrhage originating from the pulmonary microvasculature in conjunction with glomerulonephritis, such as anti-glomerular basement membrane disease (Goodpasture syndrome) and granulomatosis with polyangiitis. However, it may also refer to

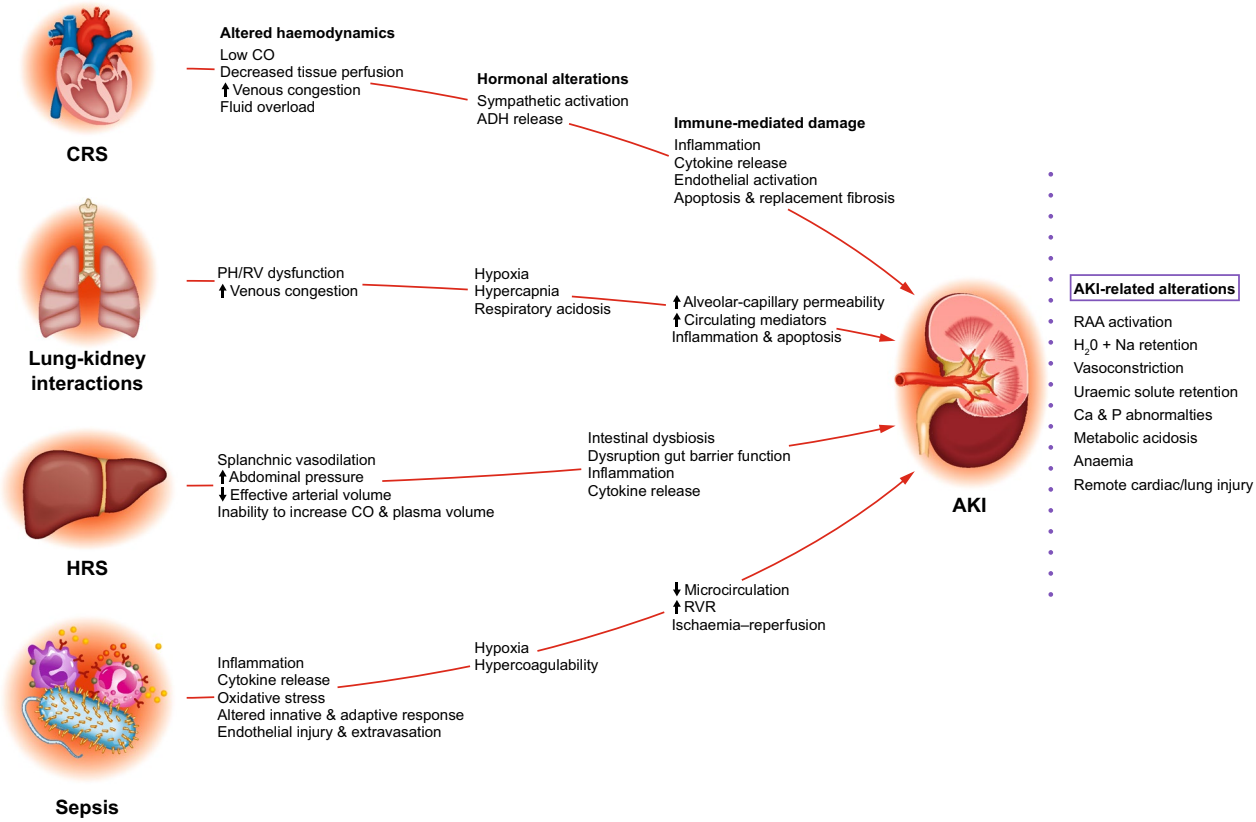


Fig. 1 The kidney during organ crosstalk. Interorgan crosstalk between the heart, lung, liver and sepsis with the kidney as the common organ. It should be noted that similar patterns of interaction can occur between other organ systems. ADH antidiuretic hormone, AKI acute kidney injury, C calcium, CRS cardiorenal syndrome, CO cardiac output, H_2O water, ↓ decreased, HRS hepatorenal syndrome, ↑ increased, Na sodium, P phosphate, PH pulmonary hypertension, RAA renin–angiotensin–aldosterone, RV right ventricular, RVR renal vascular resistance Figure illustration by Darren Lingard

more common lung–kidney interactions, such as ARDS associated with AKI and uraemic lung associated with advanced kidney disease [19, 20]. Different patterns of ARDS-associated end-organ injury have been identified and AKI may be initiated and/or aggravated via multiple mechanisms, including blood gas disturbances [21–24], pulmonary hypertension-induced renal congestion [25, 26] and neuro-hormonal dysregulation [4]. All of these conditions compromise renal blood flow and kidney compensatory mechanisms and may be amplified by mechanical ventilation-induced altered haemodynamics [4, 27].

The exacerbation of end-organ injury that occurs as a consequence of ventilator-induced lung injury is caused by the translocation of inflammatory mediators (biotrauma) from the lungs to the systemic circulation and likely activation of pro-apoptotic pathways [28, 29]. Under these circumstances, plasma concentrations of inflammatory biomarkers predict the development of AKI [30] and lack of recovered kidney function [30]. So-called lung-protective ventilation limits lung and distal organs impairment secondary to biotrauma [31, 32]. However, this approach may be associated with hypercapnia and respiratory acidosis and, in some cases, permissive hypoxia that may trigger further distal organ dysfunction and that may be eventually supported by ECOS.

Hepatorenal syndrome describes the development of AKI in patients with advanced liver failure (acute or chronic). It is characterized by marked splanchnic vasodilation, raised abdominal pressure in the presence of ascites and overactivity of the sympathetic nervous and renin–angiotensin system, with subsequent renal vasoconstriction, structural kidney damage and alterations in cardiovascular function [33]. The kidneys are involved in about 50% of all patients with liver failure and AKI is an independent risk factor for mortality [6].

Finally, the gut and kidney may also undergo reciprocal negative interactions due to primary alterations in the host microbiome profile and disruption of the barrier

function of the gut, leading to systemic inflammation, AKI, progression of chronic kidney disease (CKD) with effects on uraemic toxicity and a potential increase in cardiovascular risk [34]. In turn, once kidney function deteriorates in heart, lung, liver or gut disease, a progressive worsening of the syndrome is typically observed, with unfavourable outcomes.

The sepsis syndrome is another clear example of multiple organ failure, where the contribution of the host response to the initially infected organ may ultimately involve several other "innocent" tissues. Sepsis is the most common clinical scenario where with AKI and MODS are associated [11], and early improvements in renal, cardiovascular or respiratory function are significantly related to improved survival [35], indicating that outcome is strongly related to resolution of AKI. Multiple mechanisms by which sepsis causes AKI have been proposed. These include microcirculatory dysfunction and intrarenal shunting rather than systemic alteration of renal perfusion and renal tubular injury in response to the ultrafiltration of circulating microbial toxins or the release of inflammatory mediators following peritubular microvascular dysfunction, coagulative disturbances with in situ thrombosis or adaptive cell responses to injury [36, 37].

The kidney during extracorporeal organ support

Critically ill patients with AKI in the context of MODS require a complex and articulated therapeutic approach that includes pharmacological and organ-specific preventive and supportive strategies. Currently, various organ support therapies are used in the ICU, although very little is known about their interactions with native organs and other organ support systems. In the following sections, we review the most common types of organ support and their potential effects on renal function.

Extracorporeal lung and mechanical circulatory support

Extracorporeal lung support (VV-ECMO and $ECCO_2R$) and mechanical circulatory support (MCS, such as VA-ECMO) continue to evolve, and are used more often. More than 70% of patients receiving ECMO develop AKI [38] and similar figures are expected for $ECCO_2R$ [39]. It is likely that the high prevalence of AKI during extracorporeal lung support and MCS is the result of multiple variables, including underlying disease and severity, comorbid conditions, pre-existing kidney injury and possible adverse effects of lung support and MCS on renal function (Fig. 2).

The beneficial effects of ECMO and $ECCO_2R$ may be related to the early correction of blood gas disturbances

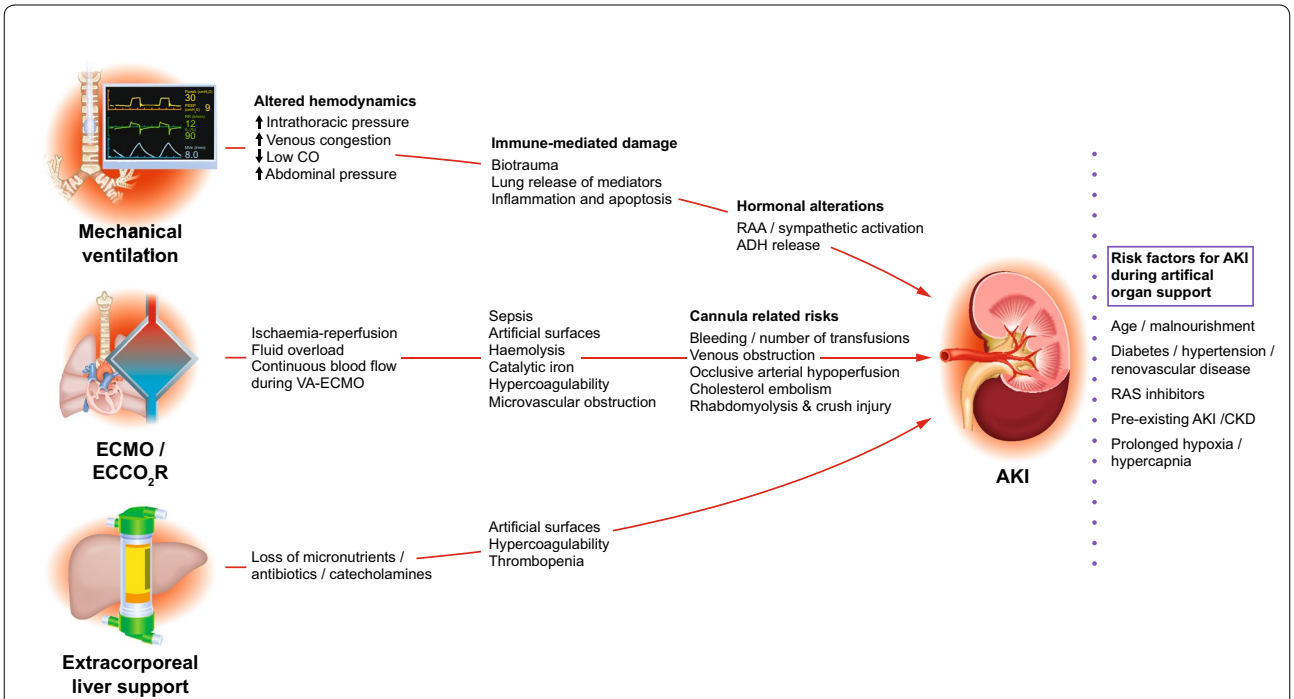


Fig. 2 The kidney during artificial organ support. The figure illustrates the potential risks associated with multiple organ support, which may increase the risk of AKI. ADH antidiuretic hormone, AKI acute kidney injury, CKD chronic kidney disease, CO cardiac output, ECMO extracorporeal membrane oxygenation, $ECCO_2R$ extracorporeal carbon dioxide removal, ↑ increased, RAA renin–angiotensin–aldosterone, RAS renin angiotensin system, VA veno-arterial

and decrease in ventilator-induced lung injury, whereas VA-ECMO restores adequate end-organ perfusion during low cardiac output in cardiogenic shock, which is a common trigger for AKI (a type-1 cardiorenal syndrome) [3]. Harmful renal effects may include prolonged pre-hypoxaemia and hypercapnia, hypoperfusion, ischaemia–reperfusion injury, increased risk of bleeding, blood contact with an artificial membrane, haemodynamic instability, malposition of the cannula leading to venous obstruction/arterial hypoperfusion and iatrogenic plaque rupture during arterial cannulation. In particular, patients with underlying CKD, diabetes, hypertension, renovascular disease or ongoing fluid overload with congestion may not reverse their AKI despite the potential beneficial effects of organ support on renal function. Other risk factors include malnourishment, advanced age and use of renin–angiotensin system inhibitors immediately before implantation of extracorporeal lung support and MCS [40].

Even when kidney function improves, there can be a subsequent late decline during prolonged organ support therapy. The risk of sepsis increases with the length of ICU stay as a result of multiple factors, such as the number of cannulation sites, which raises the risk of catheter-related nosocomial bacteraemia, and progressive host defence dysfunction [41]. Other risk factors include bleeding, haemolysis, diminished pulsatility during continuous flow devices and progressive right ventricular failure. Furthermore, once liver failure develops, death usually follows shortly [42, 43].

Haemolysis is thought to result from the combination of shear stress as blood travels through the pump, exposure to the air–fluid interface, excessive negative pressure and the properties of non-endothelialised surfaces [44]. Resultant catalytic iron, formation of obstructive casts and reduced nitric oxide bioavailability may impact vascular responses and multi-organ system function [45]. In addition, the non-pulsatile nature of VA-ECMO may also contribute to a decline in renal function. Continuous blood flow may alter endothelial integrity and result in accelerated oedema formation; it may also activate the renin–angiotensin–aldosterone system and cause systemic vasoconstriction and reduced renal perfusion, extending end-organ recovery [46]. However, whether these effects seen in animal models occur identically in humans remains controversial [47].

Finally, pulmonary hypertension and increased right atrial filling pressures have been identified as risk factors for progressive AKI in patients with heart failure [48] and overall outcome in patients undergoing ECMO [49]. Most commonly, VA-ECMO is instituted in the setting of severe cardiac failure (e.g. cardiogenic shock due to cardiac arrest, myocardial infarction) or as bridge to recovery or to transplant in patients with end-stage heart failure [50]. In this scenario, normalising left-ventricular cardiac output and decompressing the right heart by implementing VA-ECMO can improve the arteriovenous pressure gradient across the kidney. On the other hand, the detrimental effect of increased left ventricular afterload and the presence of a low ejection fraction can lead to left ventricular overdistension which can worsen right-sided heart failure and lead to AKI as a result of congestion. Adding a left-ventricular assist device in addition to VA-ECMO in patients with low left ventricular ejection fraction and concomitant right heart dysfunction may actively unload the left ventricle and improve outcomes [51]. However, renal outcome in these patients is unknown. In contrast, patients with acute decompensated pulmonary hypertension without pre-existing left heart disease are less likely to develop left ventricular overdistension and congestion.

Renal replacement therapy and the support of multiple organ dysfunction

RRT, the most commonly used form of organ support therapy worldwide, is required in 10–15% of ICU patients and represents the only effective support for severe AKI [52]. There is a perceived lack of standardization of acute RRT practice, with significant variation among centres worldwide. In various ICU settings, early RRT (outside its conventional indications [53], e.g. significant uraemia, refractory acidosis, hyperkalaemia) has been proposed for conditions such as fluid overload, mediator removal and hypercapnic acidosis in conjunction with $ECCO_2R$. We discuss these applications in the following sections.

Fluid balance

Optimization of fluid balance is a central component of the management of critically ill patients, for example to reduce the need for mechanical ventilation [54] or reduce right ventricular filling pressure in the context of heart failure [17]. Patients requiring ECMO with high blood flows are particularly prone to develop fluid overload as fluids may be generally continued in large amounts to prevent suction of the cannulae. However, fluid overload is associated with prolonged use of ECMO [55, 56] and extracellular fluid volume is recommended to be normalised [57]. Procedures have been proposed to achieve negative fluid balance during ECMO, particularly in patients with severe ARDS [58]. Early renal support in the form of extracorporeal ultrafiltration rather than RRT by dialysis may resolve fluid overload by achieving better sodium removal per unit volume than diuretic therapy. This may improve cardiopulmonary function and long-term outcomes; it may also facilitate nutritional support

and drug delivery. However, there are no studies examining the effect of early implementation of ultrafiltration in ECMO/ECCO$_2$R; thus, this subject remains an area of active study.

Mediator removal

Various mediators and cytokines have been implicated in the development and progression of single to multiple organ dysfunction [59]. The kidneys play a causal and modulatory role in MODS via the production, and also decreased clearance, of mediators [20, 60]. Plasma interleukin-6 is the best described mediator of lung injury following AKI [19]. The role of mechanical ventilation-induced biotrauma in the progression of ARDS and development of end-organ dysfunction was discussed above. In patients with ARDS undergoing VV-ECMO [61] and in patients with cardiogenic shock receiving VA-ECMO support [62], high interleukin-10 level is a strong predictor of adverse outcomes. Post-cardiac arrest patients exhibit particularly high levels of cytokines, which may partially explain the high rates of respiratory failure and AKI seen in these patients [63]. Furthermore, levels of cytokines increase significantly during membrane oxygenator exposure, probably as a result of the mobilization of cellular stores [64].

Blood-purification techniques such as high-volume haemofiltration, plasma adsorption, plasma filtration, high cut-off haemofiltration and haemoperfusion have a hypothesized therapeutic benefit in patients with ARDS, with or without ECMO, cardiogenic shock and/or AKI. This is thought to be due to their ability to remove inflammatory mediators and cytokines, decrease macrophage and monocyte activity and inactivate circulating pro-apoptotic factors involved in sepsis [65]. However, insufficient evidence exists of a therapeutic benefit for their routine use, possibly because of differences in the timing of implementation and patient selection criteria [66–68]. Inflammatory mediator levels vary widely [69] and extracorporeal blood purification may fail to significantly modulate their plasma levels [70]. Still, up to 11–22% of patients with sepsis receive high-volume haemofiltration [71, 72].

Furthermore, unlike the native kidney, which can regulate the loss of electrolytes and micronutrients, RRT (particularly with high effluent doses) demands close monitoring to avoid hypophosphataemia and hypokalaemia (Fig. 3). Increased solute clearance is accompanied by losses of antibiotics and other medications, which may counter the beneficial effects of blood-purification techniques [66]. This is less likely to occur with extracorporeal ultrafiltration. In contrast, RRT may lead

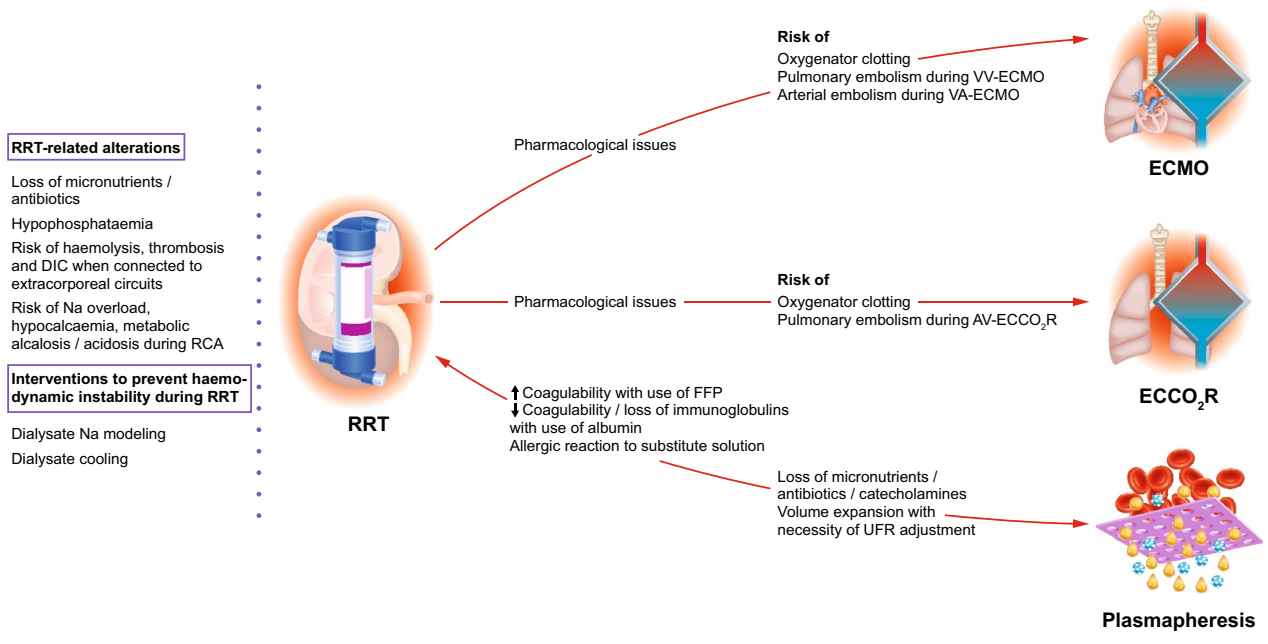


Fig. 3 Interactions between renal replacement therapy and other extracorporeal organ supports. The different patterns of interaction between renal replacement therapy and other extracorporeal organ support therapies, including possible interventions to prevent haemodynamic instability during joint therapy. AKI acute kidney injury, AV arteriovenous, DIC disseminated intravascular coagulation, ECMO extracorporeal membrane oxygenation, ECCO$_2$R extracorporeal carbon dioxide removal, FFP fresh frozen plasma, Na sodium, RCA regional citrate anticoagulation, RRT renal replacement therapy, UFR ultrafiltration rate, VA veno-arterial, VV veno-venous

to non-significant loss of catecholamines [73]. Only case reports are available on the use of extracorporeal blood-purification techniques with ECMO [74, 75]. Given the absence of clear evidence for improved survival, blood purification techniques cannot be routinely recommended as an adjuvant therapy for septic shock and MODS. Future investigations will need to evaluate whether a personalized approach that links the use of extracorporeal blood-purification techniques to mediator levels [76] and matches antibiotic and electrolyte loss to RRT intensity improves outcomes in these patients. The results of a multicentre randomized clinical trial, the Evaluating Use of Polymyxin B Haemoperfusion in a Randomized Controlled Trial of Adults Treated for Endotoxaemia and Septic Shock (EUPHRATES) (NCT01046669), should help to define the clinical efficacy of extracorporeal endotoxin removal in patients with septic shock.

Hypercapnic acidosis

Protective ventilation is the current standard of care for patients with ARDS [31]. However, further reductions in tidal volume to 4 ml/kg and plateau pressure to 25 cmH_2O have been suggested to further attenuate the pulmonary, renal and systemic inflammatory response due to ventilator-induced lung injury [77, 78], which may improve clinical outcome [79]. $ECCO_2R$ may be required to manage the respiratory acidosis secondary to low minute ventilation [80]; RRT and $ECCO_2R$ may be combined in a single treatment to allow 'super-protective' settings [78] and the reduction of vasopressor demands in patients with ARDS experiencing AKI [81, 82]. Patients with severe respiratory acidosis require more invasive $ECCO_2R$ devices with higher blood flow rates (>750 ml/min) to stabilize pH and RRT in combination with $ECCO_2R$ [83]. However, $ECCO_2R$, particularly in combination with RRT, remains experimental, especially in patients with ARDS in whom the evidence of the benefits has only been suggested on the basis of case series, studies involving surrogate markers and post hoc analyses [77, 79, 84]. Prospective studies are required to confirm that the combination of $ECCO_2R$ and RRT can improve survival in this cohort.

Special aspects

Haemodynamic instability during organ support therapy

Haemodynamic instability during RRT is a frequent complication in critically ill patients. Even during continuous RRT, the rate of haemodynamic instability ranges from 13% to 43% [85] and this rate can increase when RRT is used alongside other organ support therapies. Hypotensive episodes during organ support may exacerbate organ hypoperfusion and negatively affect organ recovery [86]. Continuous RRT with variable ultrafiltration rates is by far the preferred option internationally to prevent haemodynamic instability in patients on vasopressors, receiving other forms of organ support. However, there is a lack of evidence on the efficacy of any particular intervention in mitigating haemodynamic instability when RRT is used with other organ support therapies. Most studies were performed in end-stage renal disease patients on maintenance dialysis, which may not be transferrable to the critically ill patient. Automated biofeedback systems have been advocated to maintain a balance between ultrafiltration and plasma refilling rate while preventing haemodynamic instability during RRT. Such systems would continuously adjust dialysate conductivity and ultrafiltration rate in response to changes in blood volume (e.g. by dialysate sodium modelling) and vital signs (Fig. 3) [87]. Cooler dialysate promotes vasoconstriction by reducing heat transfer from the dialysate and may mitigate myocardial stunning [88], a phenomenon that has recently been shown to occur in patients with AKI treated with RRT [89]. However, patients requiring vasopressors may not benefit from cooler dialysate to prevent haemodynamic instability; thus, this subject remains an area of active study.

Extracorporeal membrane oxygenation and renal replacement therapy: artificial organ crosstalk

The use of ECMO is increasing worldwide [13]. However, more than 50–65% of patients who develop AKI undergo RRT during ECMO treatment [38]. RRT is associated with high mortality rates in patients receiving ECMO [38]; yet these results are controversial [90]. Currently, common indications for RRT during ECMO include fluid overload (43%), AKI (35%), prevention of fluid overload (16%) and electrolyte disturbances (4%) [91]. The figures are similar for $ECCO_2R$ [39]. Recently, a favourable trend towards lower mortality has been observed in patients with severe ARDS when these were randomized to early VV-ECMO [92]; however, it remains unknown when and how to apply a hybrid therapy for multiple organ dysfunction.

The relationship between ECMO and RRT is important in a number of ways and is related to catheters, coagulation, technical aspects and the management of haemodynamics, acid–base balance, fluids and drugs. During ECMO, the most commonly used RRT modality is continuous veno-venous haemofiltration (43%); extracorporeal ultrafiltration is performed in only 18% of patients [91]. Approximately 21% of centres use a haemodiafilter in the ECMO circuit (in-line) primarily for extracorporeal ultrafiltration; in most cases (51%), RRT is connected to the circuit [91]. The risks associated with use of additional catheters for RRT delivery must be weighed against the risks of haemolysis, thrombosis and disseminated

intravascular coagulation as a result of manipulation of the ECMO circuit (Fig. 3). Many centres prefer to perform RRT through venous access independent of the ECMO circuit, despite an increased risk of bleeding, as continuous anticoagulation may be required to minimize clot formation in the ECMO circuit. Connection of RRT to ECMO, however, is particularly important in paediatric patients because of the paucity of sites available for direct vessel cannulation. If a patient requires only carbon dioxide removal, ECMO can be continued with lower blood flow rates (ca. 1000 ml/min). However, if a patient receiving $ECCO_2R$ requires ECMO support, larger cannulae must be used to ensure sufficient flow rates.

Anticoagulation

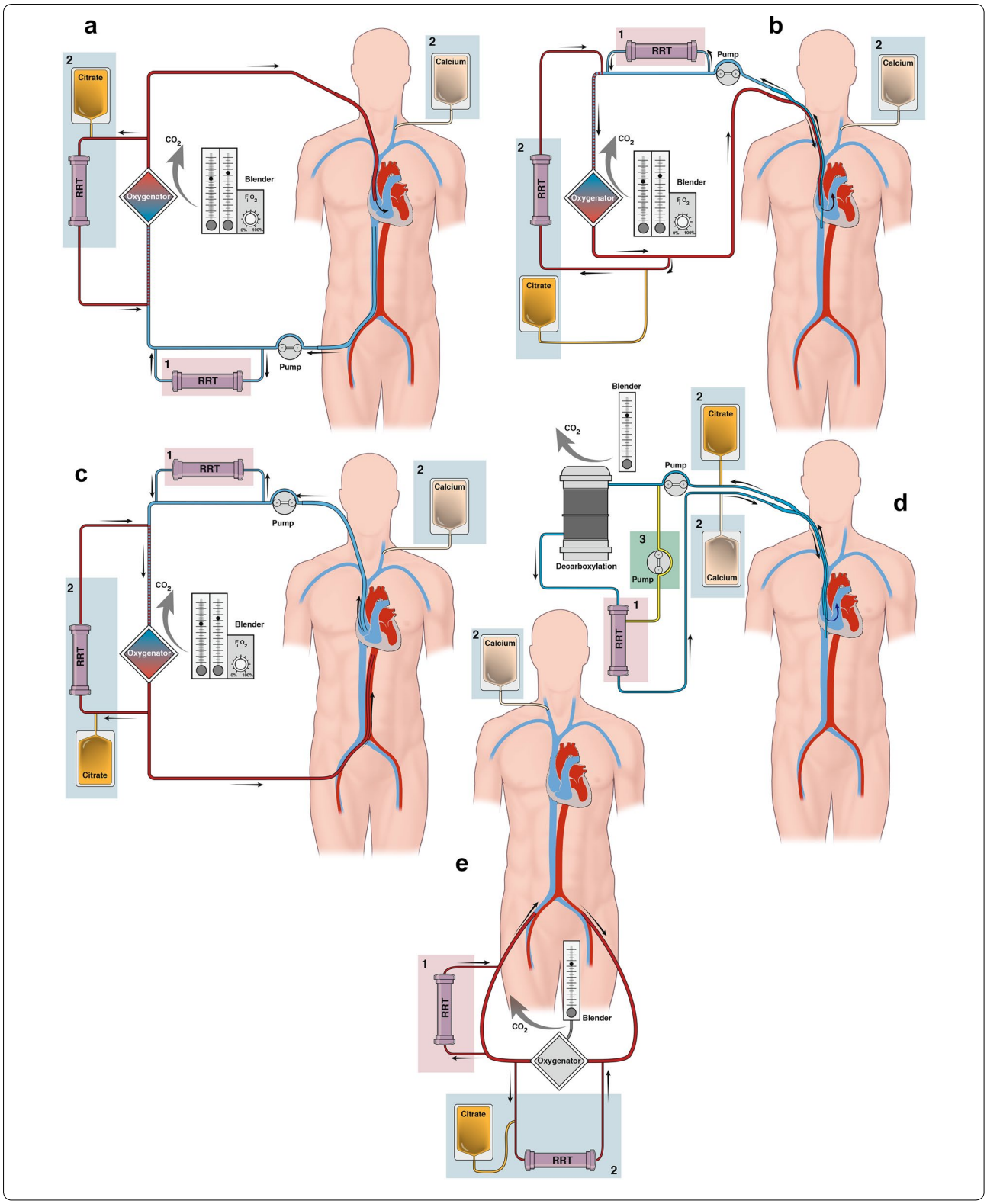
In the presence of systemic anticoagulation, additional anticoagulation for the RRT circuit during ECMO/$ECCO_2R$ is usually unnecessary. Depending on the site of connection of RRT to the ECMO/$ECCO_2R$ circuit, clotting in the haemofilter may have important implications. It may contribute to clotting of the oxygenator (when post-RRT blood is returned pre oxygenator), to pulmonary embolism (when post-RRT blood is returned post oxygenator in VV-ECMO/$ECCO_2R$ and AV-$ECCO_2R$) or to arterial embolism (when post-RRT blood is returned post oxygenator in VA-ECMO) (Fig. 3). Greater systemic anticoagulation could alleviate this problem but would also increase the risk of haemorrhage [93]. Figure 4 illustrates possible RRT set-ups in conjunction with ECMO/$ECCO_2R$. Regional citrate anticoagulation is the method of choice for RRT: its advantages include longer filter survival time and fewer bleeding events [53, 93]. Because of their stiffness and large size, ECMO cannulae are associated with systemic thrombogenic risk and therefore regional citrate anticoagulation alone is insufficient. RRT with regional citrate anticoagulation in combination with ECMO/$ECCO_2R$ may ensure effective RRT delivery and allow the use of low-dose heparin for ECMO/$ECCO_2R$ despite significant citrate dilution through the ECMO/$ECCO_2R$ blood flow [93, 94]. With the inflow of the RRT circuit connected to the post-oxygenator port and the outflow connected to the pre-oxygenator port (Fig. 4, position 2), regional citrate anticoagulation is mixed with pre-oxygenator blood, passes through the oxygenator, and partially recirculates in the RRT circuit; this may further reduce clotting events in the oxygenator. Calcium infused through a separate central venous catheter helps avoid coagulation in the distal limb of the ECMO/$ECCO_2R$ circuit. In patients with VV-$ECCO_2R$, citrate can be infused in the proximal limb of the extracorporeal circuit, while calcium can be infused in the distal limb (Fig. 4, position 2). In particular, patients with a high bleeding risk and recurrent clot formation in the membrane ventilator may benefit from this hybrid technique. However, it should be noted that use of regional citrate anticoagulation remains experimental in the context of artificial lung support, and patients with co-existing liver failure require close attention to avoid the risk of citrate accumulation and toxicity [95]. In general, high ECMO blood flow without catheter dysfunction is associated with less clotting of RRT filters, and since ECMO circuits are heparin-coated systemic anticoagulation may be suspended in case of serious bleedings.

Antibiotics and other medications

Selection of antibiotic and sedation/opioid doses in critically ill patients is challenging because their pharmacokinetic profile is markedly altered by the increased volume of distribution and impaired liver and renal function. RRT with ECMO/$ECCO_2R$ support further complicates the issue because the concentration and half-life of

(See figure on next page.)

Fig. 4 Set-ups of RRT connection to other extracorporeal organ support systems. **a** Dual-cannulation veno-venous ECMO. Schematic representation of RRT circuit in parallel (position 1) and countercurrent with regional citrate coagulation (position 2) to the veno-venous ECMO circuit using a dual cannulation technique. An outflow connection to the post-oxygenator limb should be avoided as there is high risk of systemic gas embolism and the oxygenator can serve as a protective barrier. **b** Dual-lumen veno-venous ECMO. The dual-lumen ECMO circuit drains blood from the intrahepatic portion of the inferior vena cava via the internal jugular vein and returns the blood to the right atrium to avoid recirculation. The RRT circuit can be connected in parallel (position 1) and countercurrent with regional citrate coagulation (position 2) to the ECMO circuit. **c** Veno-arterial ECMO. Using a dual cannulation technique, the veno-arterial ECMO circuit drains blood either from the right atrium or inferior vena cava, and returns the blood to the patient through a cannula inserted in the proximal descending aorta. The RRT circuit can be connected in parallel (position 1) and countercurrent with regional citrate coagulation (position 2) to the ECMO circuit. An outflow connection to the post-oxygenator limb should be avoided as there is high risk of arterial embolism and the oxygenator can serve as a protective barrier. **d** Veno-venous $ECCO_2R$. RRT can be connected to veno-venous $ECCO_2R$ circuit for combined pulmonary and renal support (position 1). Ultrafiltrate from the RRT filter may be used as an optional choice to create a greater flow rate through the lung membrane to achieve additional CO_2 removal (position 3). **e** Arteriovenous $ECCO_2R$. The illustration demonstrates essential components of a pumpless arteriovenous $ECCO_2R$, including a representation of the RRT circuit in parallel (position 1) and countercurrent with regional citrate coagulation (position 2) to the $ECCO_2R$ circuit. CO_2 carbon dioxide, $ECCO_2R$ extracorporeal carbon dioxide removal, ECMO extracorporeal membrane oxygenation, F_IO_2 fraction of inspired oxygen, RRT renal replacement therapy Figure illustration by Hans Jörg Schütze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medications are affected by RRT variables such as blood/dialysate flow and the sieving coefficient of the haemodialyser. This is particularly the case for plasma separation and haemoperfusion. They may also be affected by inflammatory activation induced by the extracorporeal circulation, exposure of blood to foreign material and drug sequestration in the circuit [96, 97]. Conversely, the ECMO circuit may serve as a reservoir and redistribute the sequestered drug back into the patient even after administration of the drug has been discontinued, potentially leading to prolonged undesirable pharmacological effects. In general, lipophilic medications with a large volume of distribution are markedly sequestered in the circuit (e.g. voriconazole, propofol, fentanyl, midazolam [98–100]), whereas hydrophilic medications with a small volume of distribution are dialysed and adsorbed less by the membrane (e.g. piperacillin–tazobactam, vancomycin, aminoglycosides [100–104]). Evidence-based guidelines for antibiotic therapy and other drugs with therapeutic narrow window during RRT and ECMO/$ECCO_2R$ are awaited.

Technical considerations

When RRT is used in conjunction with the ECMO circuit, inflow and outflow can be connected in some devices to the post-pump and pre-oxygenator limbs using two high-flow Luer lock three-way taps. Of note, probably the safest placement of RRT in the ECMO circuit is an outflow connection to the pre-oxygenator limb as the oxygenator can serve as a bubble trap and minimize the risk of gas embolism in the lungs (during VV-ECMO/AV-$ECCO_2R$) and systemic circulation (during VA-ECMO) (Fig. 3). The ECMO circuit between the pump and the oxygenator has the highest positive pressure (ranging from +150 mmHg to +350 mmHg), and this may interfere with the functioning of the RRT circuit. However, most modern RRT machines can tolerate positive pressure on the outflow limb (from +350 mmHg to +500 mmHg) [93]. If the pressure within the ECMO circuit causes the access pressure in the RRT circuit to exceed the alarm limit for inflow pressure, a long monitoring extension line attached to the RRT access can help lower the pressure and allow the RRT to function appropriately. In case of high return pressures, a pinch clamping of the dialysate outflow line could be used to achieve pressure equalization between the blood and dialysate, or the outflow limb could be connected to an alternative venous access.

Conclusions

Multiple organ support therapy (MOST) appears as a viable ECOS option in the critically ill patient with MODS. The rationale is both to provide a rescue life-saving therapy with the hope of bridging patients to recovery (i.e. up to source control achievement or lung-renal function recovery in the context of complicated viral ARDS) and to interrupt negative native organ interactions. Multiple organ support should take into account the technical effort and dedicated skills of the multidisciplinary staff in order to be safely and effectively delivered. Furthermore, native to artificial organ interaction in (i.e. RRT with the lungs) and artificial to artificial organ crosstalk (i.e. in case of RRT connection to ECMO) must be carefully considered when these complex cases are treated.

Drug delivery, anticoagulation modalities and staff organization are all deeply challenged when MOST is delivered. Careful assessment of risk factors and effective engagement of a multidisciplinary team (such as intensivists, nephrologists, cardiologists; cardiac, thoracic and vascular surgeons; perfusionists, dedicated nurses, pharmacists, respiratory therapists and others) in the artificial organ support planning may help improve outcomes. Further studies are needed to establish the ideal timing of interventions, to assess whether early implementation affects organ recovery and optimizes resource utilization. Finally, it is our belief that future research will be able to conceive a MOST integrated platform, facilitating application and timing of any form of ECOS.

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Acknowledgements

This paper was produced in conjunction with the participants of the Round Table Conference on extracorporeal membrane oxygenation (ECMO) at the ISICEM, Brussels, Belgium, on March 18–20, 2017. The authors wish to acknowledge the contributions of the Round Table participants. Chairpersons: BRODIE Daniel, RANIERI V. Marco. Participants: BAKKER Jan, BROCHARD Laurent, BROOME Michael, COMBES Alain, CRETEUR Jacques, DE BACKER Daniel, FERGUSON Niall, LAFFEY John, LORUSSO Roberto, MERCAT Alain, NAVA Stefano, PAPAZIAN Laurent, PESENTI Antonio, QUINTEL Michael, RIMENSBERGER Peter, SLADEN Robert, STAUDINGER Thomas.

Author contributions
FHS is an internist, nephrologist, pulmonologist and intensivist, and prepared all drafts of the manuscript. ZR's expertise is in the field of extracorporeal lung support and renal replacement therapy; he was involved in the writing and editing of the manuscript, including the figures. DB provided expertise in the field of extracorporeal lung support and was involved in writing and editing the manuscript, including the figures. JLV provided expertise in the field of critical care and was involved in writing and editing the manuscript, including the figures. MR provided expertise in the field of extracorporeal lung support and was involved in writing and editing the manuscript, including the figures. ASS provided expertise in the field of lung disorders and was involved in writing and editing the manuscript, including the figures. FST provided expertise in the field of extracorporeal lung support and was involved in writing and editing the manuscript. LG provided expertise in the field of extracorporeal lung support and was involved in writing and editing the manuscript. CR was involved in the writing and editing of the manuscript, including the figures. Claudio Ronco conceived the concept underlying the manuscript and is the senior author of the paper.

Funding
There was no funding source for this review.

Compliance with ethical standards

Conflicts of interest
None of the other authors declare any competing interests. The authors shared manuscript design, literature collection, literature analysis and literature interpretation; preparation, review and approval of the manuscript. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit for publication. All authors declare that the results presented in this paper have not been published previously in whole or part, except in abstract format.

Received: 13 May 2018 Accepted: 18 July 2018
Published online: 24 July 2018

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