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CONFERENCE REPORTS AND EXPERT PANEL

Lung–kidney interactions in critically ill patients: consensus report of the Acute Disease Quality Initiative (ADQI) 21 Workgroup

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Abstract

Background: Multi-organ dysfunction in critical illness is common and frequently involves the lungs and kidneys, often requiring organ support such as invasive mechanical ventilation (IMV), renal replacement therapy (RRT) and/or extracorporeal membrane oxygenation (ECMO).

Methods: A consensus conference on the spectrum of lung–kidney interactions in critical illness was held under the auspices of the Acute Disease Quality Initiative (ADQI) in Innsbruck, Austria, in June 2018. Through review and critical appraisal of the available evidence, the current state of research, and both clinical and research recommendations were described on the following topics: epidemiology, pathophysiology and strategies to mitigate pulmonary dysfunction among patients with acute kidney injury and/or kidney dysfunction among patients with acute respiratory failure/acute respiratory distress syndrome. Furthermore, emphasis was put on patients receiving organ support (RRT, IMV and/or ECMO) and its impact on lung and kidney function.

Conclusion: The ADQI 21 conference found significant knowledge gaps about organ crosstalk between lung and kidney and its relevance for critically ill patients. Lung protective ventilation, conservative fluid management and early recognition and treatment of pulmonary infections were the only clinical recommendations with higher quality of evidence. Recommendations for research were formulated, targeting lung–kidney interactions to improve care processes and outcomes in critical illness.

Keywords: Acute kidney injury, Acute respiratory distress syndrome, Extracorporeal membrane oxygenation, Renal replacement therapy, Water-electrolyte balance

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Introduction

In critically ill patients, both lung and kidney organ injury and/or dysfunction are common and associated with significant morbidity and mortality. Patients with acute kidney injury (AKI, ESM Table 5) are twice as likely to require invasive mechanical ventilation (IMV) [1, 2]. Patients with acute respiratory failure/acute respiratory distress syndrome (ARF/ARDS, ESM Table 6) are at increased risk of AKI, especially where IMV is required, influenced by haemodynamic, neurohormonal, and inflammatory effects [3–6].

Surprisingly, lung–kidney interactions have not been extensively studied. Therefore, a consensus conference was organized under the auspices of the Acute Disease Quality Initiative (ADQI) in Innsbruck, Austria, in June 2018, involving experts in nephrology, critical care and pulmonology. Epidemiology, pathophysiology, and potential mitigating interventions/strategies relevant to lung–kidney interactions were examined, including the association between ARDS, IMV, and/or extracorporeal membrane oxygenation (ECMO) with AKI, and/or renal replacement therapy (RRT). Pulmonary-kidney diseases (e.g. anti-GBM disease) in which specific inflammatory mechanisms target both organs were not considered.

Methods

The methodology of ADQI (http://www.ADQI.org) consensus meetings is well established having undergone subsequent refinements in the past two decades [7]. ADQI methodology begins with a pre-conference comprehensive literature search and appraisal of scientific evidence to identify key themes allotted to workgroups (ESM Table 1, ESM Table 2). Consensus statements were then proposed and supported by evidence and/or consensus where evidence was limited. Consensus statements were iteratively developed and refined in response to feedback during plenary sessions involving all ADQI delegates, and final consensus statements were agreed. After the conference, the writing committee compiled the rationale for each statement based on the identified literature. Recommendations for research were formulated for all key areas. Additionally, recommendations for practice were graded using the GRADE (Gradings of Recommendations, Assessment, Development and Evaluation) criteria (Fig. 1, Table 1, ESM Table 3 and ESM Table 4) [8]. A detailed description of the methods is in the electronic supplemental material (ESM).

Results

Epidemiology

Question: What is the association between AKI and ARF/ARDS?

Consensus statements

1. The most evident association between AKI and ARF/ARDS is a common aetiology.
2. AKI is associated with increased susceptibility to respiratory failure and related pulmonary complications.
3. ARF/ARDS is associated with increased risk of developing AKI.
4. In addition to the direct effects of ARF/ARDS, receipt of IMV exhibits a strong association with risk of developing AKI, which often occurs early after institution of IMV.
5. Evidence describing this relationship is limited by the heterogeneity and retrospective design of most studies and, where reported, a lack of consensus in defining AKI and/or ARF/ARDS or kidney and respiratory dysfunction.
6. AKI may contribute to delay in weaning and liberation from IMV. The precise mechanisms contributing to these delays are poorly described.

Rationale

Epidemiological data describing the relationship between AKI and development of ARF/ARDS is limited. Among these predominantly retrospective studies, substantial heterogeneity exists in the definitions of AKI and ARF/ARDS. Furthermore, there is lack of reliable data on the time course of the failing organs. Where RRT is initiated, incidences of respiratory failure between 23 and 44% have been reported with several pathophysiological mechanisms implicated in the development of ARDS (ESM Table 7).

A study of >7 million individuals with acute ischaemic stroke showed that the need for IMV was significantly

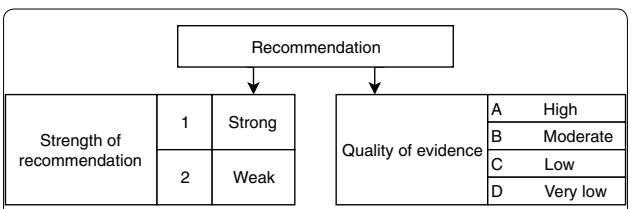


Fig. 1 GRADE system for grading recommendations according to strength of recommendation (strong vs. weak) and quality of evidence (high to very low) Modified from Guyatt et al. [8]

higher among patients with AKI than in those without (3.6% vs. 0.7%; $p < 0.0001$) [9]. Incidence of IMV was further increased among patients with AKI receiving RRT, associated with significantly higher mortality risk [10, 11], potentially suggesting that AKI contributed to greater susceptibility to respiratory failure (ESM Table 7 and Fig. 2).

There are little data describing the incidence of AKI in patients with ARF/ARDS. One study evaluating 189,561 patients with COPD found an incidence rate of hospitalization for AKI of 128/100,000 person-years with AKI rates being significantly greater among patients with acute COPD exacerbation; however, underlying COPD severity (GOLD stadium) was not an independent risk factor [12]. In community-acquired pneumonia, AKI was common and associated with increased risk of death [13]. Evidence on the association between the use of IMV and the development of AKI is stronger, although it is difficult to dissociate the effects of primary lung disease from the consequences of treatment or the associated haemodynamic failure. Overall, an incidence of AKI between 25 and 60% in mechanically ventilated patients with ARF/ARDS is observed with a consistent independent association between AKI and mortality [4, 5]. A meta-analysis across heterogeneous patient groups also demonstrated a strong association between receipt of IMV and risk of AKI with a pooled odds ratio (OR) of 3.16 (95% confidence interval (CI) 2.32–4.28) [5]. The effects of AKI on weaning from IMV have not been studied thoroughly. In a secondary analysis of 238 patients with AKI enrolled in the SAILS study, AKI for > 7 days was associated with prolonged requirement for IMV and longer ICU stay [11]. In a single-centre retrospective cohort study of patients receiving > 48 h of IMV, AKI was associated with longer duration of IMV and prolonged weaning [10].

Recommendations for research

1. Description of the added risk of AKI among patients with various aetiologies of acute respiratory failure and identification of optimal intensity/frequency/type of monitoring for AKI. Currently, the KDIGO definition should be used for studies that are focused on AKI and novel kidney injury biomarkers should be considered to enrich AKI-prognostication and evaluate decision-support.
2. Quantification of the incidence of respiratory failure in patients with AKI, employing the Berlin definition for studies that are focused on ARDS.
3. Respiratory outcomes in patients with AKI should include the receipt/duration of IMV and advanced rescue measures (e.g. ECMO), the incidence of respiratory infections and long-term pulmonary outcomes.
4. Future studies evaluating strategies to treat and/or prevent AKI or ARF/ARDS should also monitor ARF/ARDS or AKI as a secondary endpoint.

Kidney–lung interactions

Question: What are the pathophysiological mechanisms of respiratory failure in patients with AKI?

Consensus statement

The pathophysiological mechanisms of respiratory failure following AKI may be broadly categorized into inflammatory (e.g. increased inflammatory mediators) and non-inflammatory (e.g. fluid overload, increased infection risk due to immune dysfunction).

Rationale

Based on ischaemia/reperfusion models in animals, the development of AKI may contribute to lung injury by reduced clearance [14] and increased production of inflammatory mediators [14, 15]. This leads to increased cytokine levels (e.g. tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-8) in the circulation and in kidney and lung tissue [16–19], as well as caspase-independent pulmonary apoptosis [18]. Correspondingly, it has been shown that ischaemia–reperfusion injury, but not bilateral nephrectomy, leads to changes in lung transcriptome, suggesting that mechanisms other than uraemia alone lead to lung injury [16]. Furthermore, bilateral nephrectomy leads to a significantly decreased expression in the pulmonary predominant water channel, aquaporin 5 (AQP-5), possibly contributing to acute lung injury [20]. Some animal data suggest that the detrimental effects of ischaemia–reperfusion induced AKI on the lung may be averted by IL-6 mediated upregulation of IL-10 production in splenic $CD4^+$ T cells [21]. Subsequent experiments showed that splenectomy exacerbates lung injury after AKI [22].

Notably, not all AKI models demonstrate consistent pulmonary involvement with some suggesting that AKI only worsens pre-existing pneumonia by reducing signalling in neutrophils (e.g. the phosphatidylinositol 3-kinase-γ pathway) leading to impaired formation and localization of F-actin (essential for neutrophil movement), reduced pulmonary neutrophil recruitment and transmigration [19, 23, 24].

In sepsis models, resistin, a uraemic toxin and inflammatory cytokine increases during AKI and may be implicated in kidney–lung interactions, as it impairs bacterial killing in neutrophils [25]. Inflammatory mediators may also activate intracellular pathways with accelerated senescence, leading to pulmonary and/or renal fibrosis

[26, 27]. Another mediator with a potential detrimental effect on the lungs in sepsis is heparin binding protein (HBP), which is released by neutrophils triggered by bacterial products and appears to increase vascular permeability leading to oedema in lungs and kidney [28–30].

Clinical data regarding the mechanistic relationship between AKI and respiratory failure is sparse. Most studies are confounded by concomitant systemic diseases which may also directly affect respiratory function.

AKI is frequently characterized by oliguria, leading to fluid retention [31]. Patients with normal or impaired cardiac function may develop low pressure pulmonary oedema due to capillary leaking associated with systemic inflammation in AKI or ARF/ARDS, which is aggravated by fluid overload [32]. As a marker of systemic inflammation, hypoalbuminaemia has been shown to be a better predictor of ARDS than C-reactive protein [33].

Recommendation for research

Experimental studies focusing on specific pathways of kidney–lung interaction and the impact of interventions that mitigate the impact of AKI on respiratory failure. These may include the effects of inhibition of HBP (albumin, heparin), IL-10 production and resistin elimination by haemoperfusion techniques for example.

Question: What are interventions or modifiable risk factors which may mitigate respiratory dysfunction among patients with AKI?

Consensus statements

1. Evidence does not support one single approach to the management of severe AKI in the setting of respiratory failure.
2. Appropriate timing of RRT initiation and the rate and volume of fluid and solute removal should be determined by patient characteristics and clinical circumstances.

Rationale

No single approach has demonstrated clear benefit for patients who have AKI and develop respiratory failure. Close monitoring and optimization of haemodynamic status and judicious use of intravascular volume expansion or careful volume removal after the initial resuscitation phase are crucial [34]. Patients with AKI are at increased risk of fluid overload and pulmonary oedema [35]. A post hoc analysis of the FACTT trial [36] demonstrated that a negative fluid balance using a higher cumulative dose of diuretics is associated with improved mortality in patients with AKI [37]. Administration of albumin together with furosemide improved oxygenation in ARDS patients with hypoalbuminaemia [38, 39] and facilitated negative fluid balance, particularly in tandem with a conservative approach to fluid replacement. However, this was not performed in patients with AKI [38, 40]. Furthermore, albumin may inactivate HBP (that increases endothelial permeability) and a HBP to albumin ratio >3 has been associated with increased risk of AKI in sepsis [30].

Initiation of RRT corrects metabolic acidosis secondary to AKI and improves oxygenation in volume overload [41]. However, the best modality, timing and intensity to optimize respiratory function are unknown [42]. The role of immune modulating interventions is poorly established [43]. Preliminary data, indicating beneficial effects of resistin elimination by sorbent-based haemoadsorption require confirmation in clinical studies [44]. Haemoadsorption has been shown to reduce levels of the uraemic toxin resistin and improving macrophage function ex vivo [44].

Recommendations for practice

1. We recommend adherence to KDIGO guidelines for AKI management, as it may translate into improved pulmonary outcomes (Grade 1D).
2. We suggest conservative fluid management and selected use of diuretics or ultrafiltration (RRT) in patients with AKI on IMV to improve respiratory function and decrease duration of IMV in patients with ARF/ARDS (Grade 2C).
3. We recommend delivery of RRT to mitigate the metabolic consequences of AKI particularly where acid–base derangement may affect ventilation (Grade 1D).

Recommendations for research

1. The role of different strategies for fluid management during episodes of AKI aiming to reduce the length of ventilatory support, facilitate weaning and optimize the respiratory function should be evaluated in a prospective trial.
2. One strategy to be investigated could be albumin administration in hypoalbuminaemic patients with AKI at risk of ARF/ARDS combined with diuretics or conservative volume management.
3. The role of inflammation modulating techniques (e.g. plasmapheresis for resistin elimination, sorbent-based haemoadsorption) in improving respiratory function among patients with AKI should be assessed.
4. Evaluation of interventions to reduce extravascular lung water in ARF/ARDS including conservative fluid management in AKI by pharmacological interventions or extracorporeal techniques.

Lung–kidney interactions

Question: What are the potential physiological and/or pathophysiological mechanisms of AKI in patients with ARF/ARDS?

Consensus statements

1. The pathophysiological mechanisms underlying the association between respiratory failure and AKI comprise inflammatory/immune-mediated effects.
2. The effects of impaired gas exchange and haemodynamic disturbance including right heart failure may contribute to the risk of AKI.

Rationale

In ARDS and acutely exacerbated COPD, AKI may be initiated or aggravated by several mechanisms [45–48] (Fig. 3) compromising both renal blood flow and compensatory mechanisms preserving renal function and may be further exacerbated by potentially nephrotoxic drugs or IMV (Table 2) [49, 50]. Endothelial injury and increased capillary permeability may predispose to respiratory and renal dysfunction precipitating AKI [51].

Systemic release of pro-inflammatory mediators from the injured lungs has been associated with the development of AKI [13, 52]. Increased levels of plasminogen activator inhibitor-1, IL-6 and soluble TNF receptors-I and II in ARF/ARDS are associated with AKI [52]. HBP increased in sepsis may also have a detrimental effect on the kidneys by increasing endothelial permeability [53].

Concomitant hypoxaemia (SaO_2 83–87%) and hypercapnia may reduce renal blood flow in a dose-dependent manner [46, 54, 55]; correspondingly, patients with hypercapnic COPD also exhibit a loss of renal functional reserve [46, 56].

In ARDS patients, short-term hypoxaemia (SaO_2 88–90%) is associated with altered renal function [45].

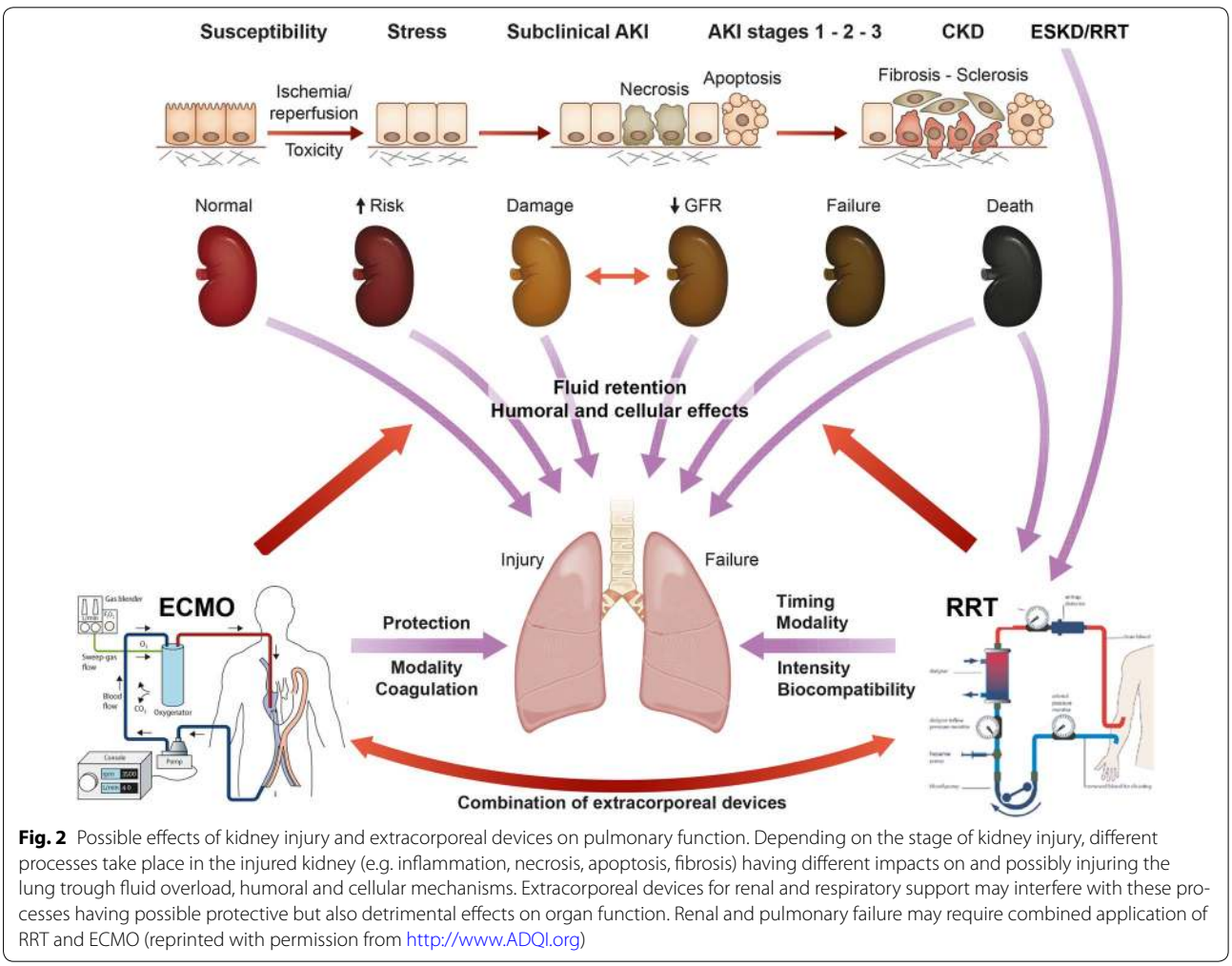


Fig. 2 Possible effects of kidney injury and extracorporeal devices on pulmonary function. Depending on the stage of kidney injury, different processes take place in the injured kidney (e.g. inflammation, necrosis, apoptosis, fibrosis) having different impacts on and possibly injuring the lung trough fluid overload, humoral and cellular mechanisms. Extracorporeal devices for renal and respiratory support may interfere with these processes having possible protective but also detrimental effects on organ function. Renal and pulmonary failure may require combined application of RRT and ECMO (reprinted with permission from http://www.ADQI.org)

Table 1 Overview of the recommendations for practice

Statement	Grade
What are interventions or modifiable risk factors which may mitigate respiratory dysfunction among patients with AKI?	
1. We recommend adherence to KDIGO guidelines for AKI management, as it may translate into improved pulmonary outcomes	1D
2. We suggest conservative fluid management and selected use of diuretics or ultrafiltration (RRT) in patients with AKI on IMV to improve respiratory function and decrease duration of IMV in patients with ARF/ARDS	2C
3. We recommend delivery of RRT to mitigate the metabolic consequences of AKI particularly where acid–base derangement may affect ventilation	1D
What are interventions or modifiable risk factors to mitigate AKI among patients with ARF/ARDS not requiring mechanical ventilation?	
1. We recommend treating patients with ARF/ARDS according to the KDIGO guidelines who are at risk of or with AKI	1C
2. We suggest at least daily measurement of serum creatinine and regular monitoring of urine output in patients with severe ARF/ARDS to detect development of AKI	1B
3. We recommend the implementation of adequate screening measures for early reorganization of pulmonary infections, followed by early initiation of appropriate antibiotic therapy, which is associated with lower risk of AKI	1C
What are the interventions or modifiable risk factors to mitigate AKI among patients with ARF/ARDS requiring mechanical ventilation?	
1. We recommend monitoring of tidal volumes and ventilation pressures and application of lung protective ventilation strategies in patients receiving IMV to reduce the risk of new or worsening AKI	1C
2. We recommend monitoring and treatment of mechanically ventilated patients for hypotension, venous congestion, right heart failure, and intraabdominal hypertension, which can contribute to renal dysfunction	1B
3. We suggest avoiding—if possible—specific ancillary interventions known to be associated with AKI, including fluid overload, nephrotoxin exposure, and high doses of iNO	2B
What is the impact of RRT on lung function?	
1. We suggest, that during RRT in patients with COPD with metabolic compensation, the correction of compensatory metabolic alkalosis should be as slow as tolerated, to avoid development of acidosis	2D
What is the impact of ECMO on kidney function?	
1. We recommend close monitoring for haemolysis and markers of coagulation and inflammation	1C
2. We recommend that in patients undergoing ECMO, kidney function should be monitored routinely with at least daily serum creatinine measurements and fluid balance assessment	1C
Are combinations of extracorporeal lung and renal support protective for organ function?	
1. We recommend initiation of CRRT should be based on absolute and relative indications for critically ill patients, given there is no evidence of benefit for combining ECMO therapy with pre-emptive use of CRRT	1D
2. We do not recommend the use of CRRT and/or haemoabsorption with the sole intention to clear pro-/anti-inflammatory mediators during ECMO	1C

Elevation of central venous pressure, due to either right heart failure [6, 57], high intrathoracic pressures (e.g. occult PEEP resulting from dynamic hyperinflation [58]) or volume overload may result in increased interstitial and tubular hydrostatic pressure within the encapsulated kidney, which decreases net glomerular filtration rate (GFR) and oxygen delivery [59].

Recommendations for research

1. Identify risk factors for AKI that are specifically related to ARF/ARDS and its treatment. This may allow the recognition of preventive and therapeutic measures to limit AKI.
2. Candidate molecules characterizing lung–kidney crosstalk should be identified and their potential as targets for interventions investigated.

Question: What additional mechanisms attributable to invasive mechanical ventilation may contribute to AKI?

Consensus statement

The mechanisms by which IMV contributes to AKI are multi-factorial and related to incremental effects of haemodynamic, neurohormonal and immune-mediated processes.

Rationale

In addition to well-described haemodynamic alterations [60, 61] (Table 2), animal data suggest that IMV is associated with proinflammatory mediator release (e.g. IL-6) if higher tidal volumes are applied [62]. Whether ventilation-induced cytokine release leads directly to AKI is unclear. However, injurious IMV induces apoptosis in tubular kidney cells, reduced by blocking soluble

Fas-ligand with Fas:Ig, indicating that Fas-ligand may play a role in mediating distant organ injury [63].

In patients receiving IMV, application of PEEP shows several beneficial effects like recruitment of lung-volume (potentially decreasing pulmonary artery pressure and right ventricular afterload) and decrease of left ventricular pre- and afterload (which may improve cardiac output in left ventricular dysfunction). However, when increasing PEEP and/or tidal volumes excessively, elevated intrathoracic pressure will decrease cardiac output and increase right ventricular afterload, impairing right ventricular function. This may lead to elevated systemic venous pressure, reduced renal perfusion and venous congestion (Fig. 3; Table 2) [57, 64].

Furthermore, fluid retention may occur because of neuro-hormonal alterations, including activation of the sympathetic nervous system (SNS) and renin–angiotensin–aldosterone system and suppression of atrial natriuretic peptide release [65–67]. The effects of PEEP on renal function are believed to be partly mitigated by the SNS, but after renal denervation, a PEEP effect is still observed, presumably in a perfusion pressure-dependent manner [68].

In comparing lung protective ventilation with conventional strategies, lower levels of TNF-α, IL-1b, IL-6 and IL-8 were detected in bronchoalveolar lavage fluid and plasma under protective ventilation strategies [69] with lower rates of AKI at 72 h [50].

Recommendation for research

Identify risk factors for AKI that are specifically related to mechanical ventilation.

Question: What are interventions or modifiable risk factors to mitigate AKI among patients with AFR/ARDS not requiring mechanical ventilation?

Consensus statement

In addition to the recommendations by KDIGO, no proven specific interventions exist to prevent or treat AKI complicating critical illness in the context of ARF/ARDS.

Rationale

Current recommendations for the care of patients with, or at risk of, AKI are based on the recommendations by the KDIGO expert committee in 2012 [41], suggesting several interventions based around mitigating risk of further renal injury, including regular monitoring of urinary output [70], careful evaluation of fluid balance, optimization of haemodynamic status and review of potentially nephrotoxic medications [41, 71]. There is no strong evidence for any specific intervention affecting the course of AKI arising in the context of respiratory disease, although the early recognition of systemic or pulmonary infection followed by timely treatment with antibiotics is key [72], as is attention to adequate fluid status [35].

Recommendations for practice

1. We recommend treating patients with ARF/ARDS according to the KDIGO guidelines who are at risk of or with AKI (Grade 1C).
2. We recommend at least daily measurement of serum creatinine and regular monitoring of urine output in patients with severe ARF/ARDS to detect development of AKI (Grade 1B).
3. We recommend the implementation of adequate screening measures for early recognition of pulmonary infections, followed by early initiation of appropriate antibiotic therapy, which is associated with lower risk of AKI (Grade 1C).

Recommendations for research

1. As a sentinel organ failure associated with worsening prognosis, renal outcomes should be reported in studies of interventions for ARF/ARDS in the ICU.
2. Further research should aim at refining fluid management strategies and haemodynamic management that might favourably affect both kidney and lung function.

Question: What are the interventions or modifiable risk factors to mitigate AKI among patients with ARF/ARDS requiring mechanical ventilation?

Consensus statements

1. There is limited evidence that lung protective ventilation is associated with reduced risk of AKI in patients with ARF/ARDS.
2. There is evidence that certain adjunctive measures used for ARF/ARDS treatment may be detrimental to kidney function and that some ICU care processes may modify the risk of AKI.
3. There is insufficient evidence that non-invasive respiratory support is associated with lower risk of AKI compared with IMV.
4. There is insufficient evidence that specific weaning strategies from IMV impact the risk of AKI.

5. Fluid overload should be avoided in ARF/ARDS patients.

Rationale

Volutrauma and barotrauma are associated with a release of proinflammatory mediators and protective ventilation strategies may result in lower cytokine burden with reduced organ dysfunction (Table 3) [50]. In the ARDSNet study, patients allocated to low tidal volume ventilation had fewer days of AKI, defined as sCr > 177 μmol/L (20 vs. 18 days; $p < 0.005$) [73]. However, analysis of a large, multinational database of patients with > 24 h of IMV and normal renal function failed to identify any ventilation-associated parameters as risk factors for AKI [74]. There are limited data related to the effects of lung protective ventilation on renal function in patients without ARDS. Secondary analysis of an RCT comparing higher tidal volume (10 mL/kg) to low tidal volume

Table 2 Pathophysiological processes involved in lung–kidney interactions

	Haemodynamic effects	Inflammatory/ immune- mediated effects	Effects of altered acid–base status	Effects of impaired gas exchange	Neuro-hormonal effects
Potential pathophysiological mechanisms	*Effects of acute pulmonary disease on kidney function*				
	Increased pulmonary arterial pressure leading to right ventricular failure with venous congestion [6, 57] Increased intra-abdominal pressure [77, 83] Increased intra-thoracic pressure [57, 64]	Increased release of pro-inflammatory mediators (IL-6, TNF-α, IL-1 beta, TGF-β, substance P) [16–19] Decreased release of anti-inflammatory mediators (IL-10)	Increased oxygen consumption in the proximal renal tubular system in respiratory acidosis [119]	*Hypercapnia* ($pCO_2 > 50$ *mmHg*): Loss of renal vasodilatory response, reduction of RBF and change in diuresis [46, 56] *Severe hypoxaemia* ($pO_2 < 40$ *mm Hg*): Reduction of RBF [45]	Activation of RAAS [65] Increased aldosterone secretion [65] Reduction of ANP/BNP levels [65] Activation of the sympathetic nervous system [65] Release of non-osmotic vasopressin [48]
	Additional effects of positive pressure ventilation on kidney function				
	Excessive increase in intrathoracic pressure leading to: reduced venous return [64] reduced left ventricular preload [64] reduced cardiac output [64] increased right ventricular afterload [57, 64] resulting in right ventricular dysfunction and venous congestion with increased renal back pressure [6, 57]	*Effect of injurious ventilation*: increased release of IL-6, PAI-1, TNFR-1 and TNFR-2 into systemic circulation [62] induction of renal epithelial cell apoptosis and dysregulation of extracellular ligands [63]	As above	*Permissive Hypercapnia:* as above *Hyperoxaemia:* lack of data	As above
Parameters to monitor lung–kidney interaction	CVP [47] MAP Cardiac output [57, 64] Renal perfusion pressure [77] Cumulative fluid balance [37, 40] PEEP [68] Ventilatory tidal volume [73–75] Inspiratory pressure [62] Intra-abdominal pressure [47]	Inflammatory markers [50, 69]	Arterial pH [95]	pO_2 [46, 54, 55] pCO_2 [46, 54, 55] O_2 saturation [46, 54, 55]	BNP [67]

AKI acute kidney injury, *ANP* atrial natriuretic peptide, *BNP* brain natriuretic peptide, *IL* interleukin, *CVP* central venous pressure, *MAP* mean arterial pressure, *PAI* plasminogen activator inhibitor, *PEEP* positive end-expiratory pressure, *RAAS* renin–angiotensin–aldosterone system, *RBF* renal blood flow, *TNF* tumor necrosis factor, *TGF* transforming growth factor, *PAI-1* plasminogen activator inhibitor-1, *TNFR* tumor necrosis factor receptor

ventilation (6 mL/kg) in patients without ARF/ARDS showed no differences in risk of development or worsening of AKI [75]. Spontaneous breathing during IMV appears to be favourable in terms of renal perfusion and function as demonstrated in a small prospective randomized study in 12 ICU patients with mild ARDS [76]. In 16 mechanically ventilated patients with ARDS, prone positioning was associated with a small increase in intra-abdominal pressure but did not adversely affect renal blood flow, glomerular filtration, filtration fraction, urine volume, sodium excretion and free water clearance [77]. Additionally, another trial including 466 patients found a (non-significant) decrease of RRT requirement for prone positioning (11.4% vs. 17.1%) [78].

Neuromuscular blockade applied to facilitate lung protective ventilation was associated with more ventilator-free days and more days without renal failure (20.5 ± 10.1 vs. 18.1 ± 11.6 days; $p = 0.05$) in the ACURASYS trial [79], however, this finding could not be reproduced in the more recent large multicentre ROSE trial which was terminated early for futility [80]. Of note, in the ROSE trial, a higher number of patients was excluded as compared to the ACURASYS trial due to previous use of neuromuscular blocking agents (17.1% vs. 4.3%). It is conceivable that patients, already requiring neuromuscular blockade at enrolment, would have benefited the most from it [81].

The "Dose–Response Multicentre Investigation on Fluid Assessment in Critically Ill Patients" study prospectively enrolled patients admitted to 21 ICUs in nine countries and concluded that fluid accumulation preceded and followed the diagnosis of AKI [82]. In the FACTT-trial patients with ARF/ARDS receiving IMV who received a conservative fluid strategy showed improved lung function and a trend toward reduced use of RRT [36]. The FACTT Lite trial confirmed that fluid restriction increased ventilator-free days and reduced AKI rates [40].

Corticosteroids are frequently used in patients with severe ARDS receiving prolonged IMV [83–85]. An RCT studying low-dose methylprednisolone infusion on lung function in 91 patients with early severe ARDS showed that steroids were associated with decreased IMV duration and improvement in extrapulmonary organ function, including less AKI by day 7 (18% vs. 37%; $p = 0.06$) [85]. However, this finding was inconsistent [84]. Inhaled nitric oxide (iNO), used in ARDS and pulmonary hypertension, may be associated with AKI [49]. A systematic review concluded that treatment with a high cumulative-dose of iNO significantly increased the risk of AKI compared with controls (relative risk 1.52; 95% CI 1.14–2.02; $p = 0.004$), whereas medium and low cumulative-doses did not [86]. No trials specifically designed to mitigate the risk of AKI during IMV have been conducted. Indirect evidence from general ventilation and ARDS studies implies that some management strategies carry a greater risk to kidney function (Table 3). For instance, patients treated with propofol and dexmedetomidine have a lower risk of AKI than patients receiving longer acting sedatives [36].

The specific contributory effects of non-invasive respiratory support to AKI are unknown. An RCT in 64 patients with acute hypoxaemic respiratory failure reported a 9% incidence of AKI in the non-invasive arm compared with 16% in the IMV group [87].

There are limited data on the impact of weaning strategies on kidney function and no prospective trials investigating effects on recovery of AKI. A recent single-centre retrospective analysis showed that early tracheostomy (< 14 days post-surgery) was associated with a shorter ventilation time and hospital stay compared with late tracheostomy, but did not influence the requirement for RRT [88].

Recommendations for practice

1. We recommend monitoring of tidal volumes and ventilation pressures and application of lung protective ventilation strategies in patients receiving IMV to reduce the risk of new or worsening AKI (Grade 1C).
2. We recommend monitoring and treatment of mechanically ventilated patients for hypotension, venous congestion, right heart failure and intraabdominal hypertension, which can contribute to renal dysfunction (Grade 1B).
3. We suggest avoiding—if possible—specific ancillary interventions known to be associated with AKI, including liberal fluid administration, nephrotoxin exposure and high doses of iNO (Grade 2B).

Recommendations for research

1. Future trials investigating ancillary therapies in patients receiving IMV should include the development of new or worsening AKI as a core outcome of interest.
2. Determine the impact of improved modes of mechanical ventilation (e.g. neurally adjusted ventilatory assist (NAVA), proportional assist ventilation (PAV) or transpulmonary pressure guided ventilation) on kidney function.
3. Future studies investigating the role of non-invasive respiratory support should include the effects on kidney function as a core outcome of interest.
4. Studies on weaning from ventilator support studies should include the effects on kidney function as a core outcome of interest.

Table 3 Potential interventions to modify kidney–lung interactions

Therapeutic category	Intervention type	Patient population/number of patients/trial type	Results	Level of evidence
Ventilation strategies	Spontaneous breathing during APRV	Acute lung injury 12 patients [OT]	Improved renal blood flow and GFR with spontaneous breathing vs. controlled ventilation [76]	C
	Lung protective ventilation	ARDS 861 patients [RCT]	Less days with renal failure (defined as sCr ≥ 2 mg/dL) in the lung protective ventilation group [73]	B
	Neuromuscular blockade and lung-protective ventilation	Early ARDS 340 patients [RCT]	Significantly more ventilator-free days ($p = 0.04$) and more days without renal failure (20.5 ± 10.1 vs. 18.1 ± 11.6 days; $p = 0.05$) [79]	B
		1006 patients [RCT]	No effect on mortality and kidney failure free days by day 28 in another trial [80]	B
	Prone ventilation	ARDS 16 patients [OT]	No effect on renal blood flow index, glomerular filtration rate index, filtration fraction, urine volume, fractional sodium excretion, and osmolar and free water clearances [77]	C
Anti-inflammatories	Glucocorticoids ± mineralocorticoid	ARDS 91 patients [RCT]	Improvement in extra-pulmonary organ function, including a trend towards less AKI by day 7 (18% vs. 37%; $p = 0.06$) No effect on RRT [85]	C
Fluids	Albumin and diuretics	ARDS 40 [RCT]/37 [RCT] patients	Administration of Albumin together with diuretics improved oxygenation and facilitated negative fluid balance in hypoproteinaemic ARDS patients [38, 39]	C
	Conservative fluid management	ARDS 1000 patients [RCT]	Trend towards reduced need for RRT with fluid restrictive strategy [36]	C
		2124 patients [RCT]	Less AKI with fluid restrictive strategy after correction for fluid balance [40]	C
	Furosemide and conservative fluid management	ARDS 1000 [RCT]	Trend towards reduced need for RRT (10% vs. 14%; $p = 0.06$) [36]	C
		ARDS + AKI 306 [SG] patients	Reduced mortality in patients with AKI and ARDS [37]	C

APRV airway pressure release ventilation, *ARDS* acute respiratory distress syndrome, *AKI* acute kidney injury, *RRT* renal replacement therapy, *OT* observational trial, *RCT* randomised controlled trial, *SG* subgroup analysis, *GFR* glomerular filtration rate, *sCR* serum creatinine

Effects of extracorporeal devices

Question: What is the impact of RRT on lung function?

Consensus statements

1. RRT applied for diuretic-resistant fluid overload may improve pulmonary function.
2. There is little evidence that RRT, using current methods, directly leads to lung injury.
3. The pathophysiological mechanisms of the potential association between RRT and lung function comprise haemodynamic, inflammatory, electrolyte-mediated, and acid–base effects.

Rationale

RRT is usually initiated to compensate for complications of AKI. This includes fluid overload in patients with diuretic resistance, repeatedly described as a major risk factor for adverse outcome [89]. Early correction of fluid

accumulation may be important to reduce further damage to the injured lung [82, 90]. However, earlier initiation of RRT in patients with severe AKI and ARDS has not been shown to improve outcome [42, 91].

Data on the direct effects of RRT on the lung are sparse and mostly from patients with ESRD receiving IHD. Alternating episodes of volume depletion and overload, and leukocyte activation resulting from IHD, have been identified as triggers for deterioration of lung function [92]. Few studies have compared the impact of different RRT modalities on respiratory function in AKI patients, having found no significant difference between modalities (peritoneal dialysis vs. IHD [93] and IHD and SLED [94]).

Rapid correction of acid–base balance during intermittent haemodialysis may also impact the lungs and should be avoided when commencing RRT [95]. When RRT is delivered to COPD patients with metabolic compensation, it may cause eventual "iatrogenic" acidosis, which increases the respiratory drive and may overstretch the lungs through air trapping. This effect has been poorly studied and the intravenous administration of sodium bicarbonate is a possible solution. Alternatively, CO_2 removal through the haemofilter could be an option, but has shown to be successful only in in vitro models [96].

Recommendation for practice

We suggest, that during RRT in patients with COPD with metabolic compensation, the correction of compensatory metabolic alkalosis should be as slow as tolerated, to avoid development of acidosis (Grade 2D).

Recommendations for research

1. Future work should aim to determine if there is any impact of current RRT practices [continuous renal replacement therapy (CRRT), slow extended dialysis (SLED) and intermittent haemodialysis (IHD)] on lung function and determine which approach to acute RRT is most beneficial for the lung.
2. The application of different reinfusion/dialysate solutions should be evaluated in patients with hypercapnia (COPD or permissive hypercapnia).
3. Further research on CO_2 removal techniques should be undertaken as an ancillary measure in hypercapnic patients receiving RRT.

Question: What is the impact of ECMO on kidney function?

Consensus statements

1. Patients with ARF/ARDS treated with ECMO are at increased risk of severe AKI. It remains unclear whether ECMO itself contributes to AKI or if early initiation prevents AKI.
2. Development of AKI, as well as positive fluid balance in AKI patients receiving ECMO, is associated with increased mortality.
3. The pathophysiological interactions between ECMO and AKI include haemodynamic (pulsatile flow vs. laminar flow), inflammatory and immune-mediated effects and haemolysis.

Rationale

As many as 60–80% of patients receiving ECMO may receive RRT [97–100]. A meta-analysis evaluating venoarterial (VA)-ECMO for treating cardiogenic shock and cardiac arrest found a pooled rate of RRT after VA-ECMO of 46% (95% CI 36.7–55.5%) [101], and this was associated with reduced odds for survival to hospital discharge (OR 0.77 [0.61–0.89]) and a higher 90-day mortality rate (31% vs. 15%) [97, 98, 100]. RCTs suggest that acuity of illness and burden of multi-organ failure, rather than ECMO per se, drive the risk of severe AKI. Volume balance during ECMO and RRT is key given that a negative fluid balance from day 3 is associated with improved survival [100]. ESM Table 8 summarizes studies evaluating AKI/RRT in patients treated with ECMO.

With increasing severity of ARDS, extracorporeal methods of CO_2-removal and/or oxygenation may become necessary [102] and, depending on technique in animal studies, a significant benefit on renal cortical blood flow can be observed [103].

The EOLIA trial [104] showed that patients treated with venovenous (VV)-ECMO had lower incidence of AKI and use of RRT compared with controls receiving standard treatment. A similar trend, albeit not significant, was also shown in the CESAR trial [99]. However, autoregulation of renal microcirculation may deteriorate during non-pulsatile ECMO as shown in an acute cardiac failure model in pigs [105]. Other factors negatively influencing renal function during ECMO treatment may be fluid overload [106] ischaemia/reperfusion injury [107], and circuit-related factors [108, 109]. Haemolysis and increased load of filtered pigment (e.g. myoglobin, CK) may result from muscle damage due to local ischaemia during ECMO [31, 110]. Also, raised levels of pro-inflammatory cytokines (e.g. TNF-α, IL-6, IL-8) [111], activation of the complement system [112], and leucocyte activation may lead to endothelial injury, altered microcirculation and end-organ dysfunction [108].

There are no data evaluating the early use of ECMO to prevent AKI in patients with ARF/ARDS.

Recommendations for practice

1. We recommend close monitoring for haemolysis and markers of coagulation and inflammation (Grade 1C).
2. We recommend that in patients undergoing ECMO, kidney function should be monitored routinely with at least daily serum creatinine measurements and fluid balance assessment (Grade 1C).

Recommendations for research

1. Future trials should determine the incidence of AKI (as defined by the KDIGO criteria), risk factors, as well as the time course of AKI developing after initiation of ECMO.
2. The different impacts of VV- and VA-ECMO on renal function and risk of AKI need to be evaluated in future studies.
3. The effects and pathophysiological pathways of systemic inflammation originating from the ECMO on the kidney need to be studied.

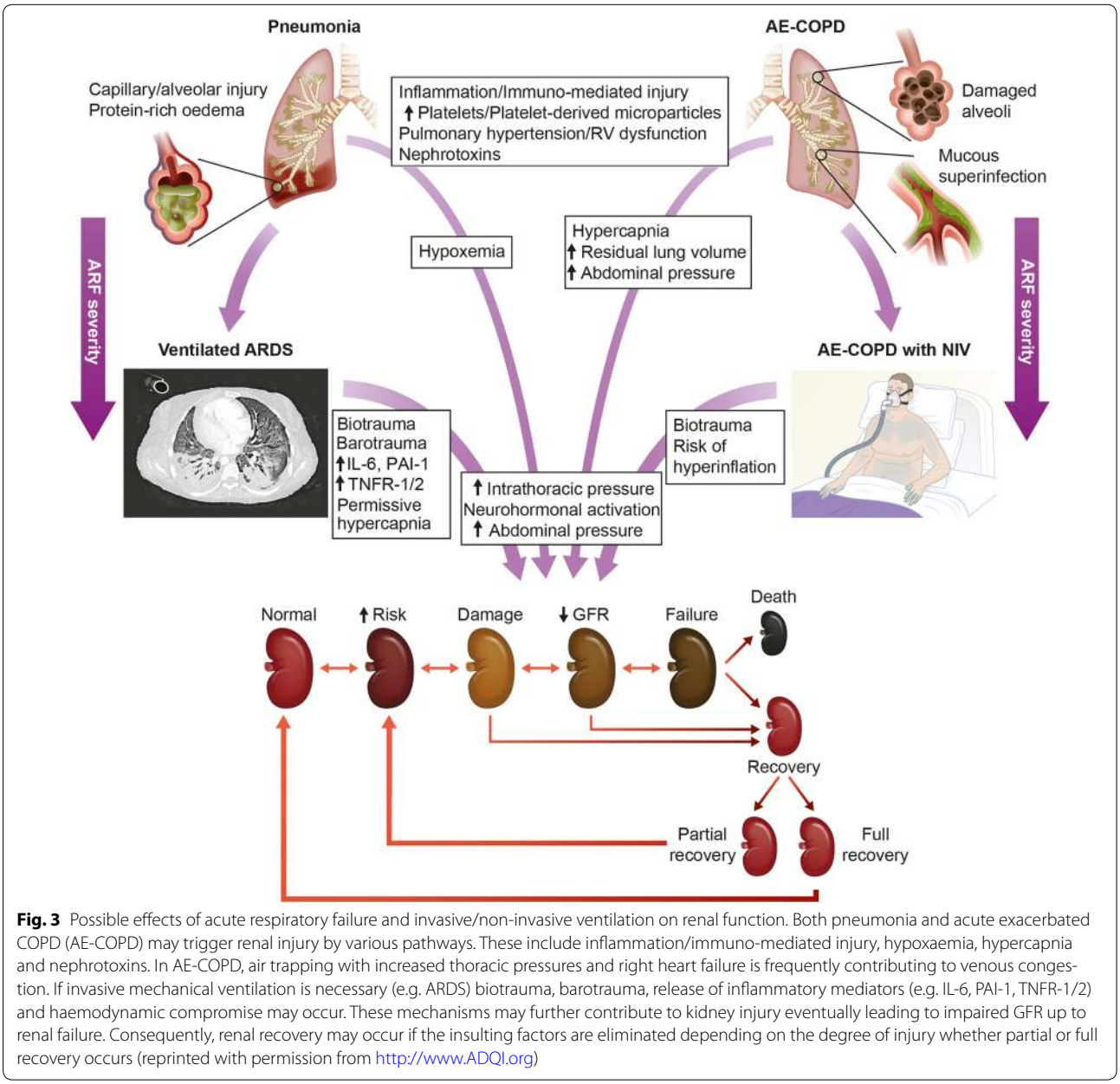


Fig. 3 Possible effects of acute respiratory failure and invasive/non-invasive ventilation on renal function. Both pneumonia and acute exacerbated COPD (AE-COPD) may trigger renal injury by various pathways. These include inflammation/immuno-mediated injury, hypoxaemia, hypercapnia and nephrotoxins. In AE-COPD, air trapping with increased thoracic pressures and right heart failure is frequently contributing to venous congestion. If invasive mechanical ventilation is necessary (e.g. ARDS) biotrauma, barotrauma, release of inflammatory mediators (e.g. IL-6, PAI-1, TNFR-1/2) and haemodynamic compromise may occur. These mechanisms may further contribute to kidney injury eventually leading to impaired GFR up to renal failure. Consequently, renal recovery may occur if the insulting factors are eliminated depending on the degree of injury whether partial or full recovery occurs (reprinted with permission from http://www.ADQI.org)

4. Novel circuits to reduce shear stress and to reduce hyperinflammation and the effects on AKI should be evaluated.

Question: Are combinations of extracorporeal lung and renal support protective for organ function?

Consensus statements

1. There is no clear evidence that immediate combination of organ support is of benefit.
2. There is no evidence that supports the role of mediator removal during combination of ECMO and CRRT.

Rationale

While many studies [97–100, 104] have evaluated the use of combinations of extracorporeal organ support, it is unclear whether and when to combine ECMO and RRT, and the optimal methods for combination are unknown.

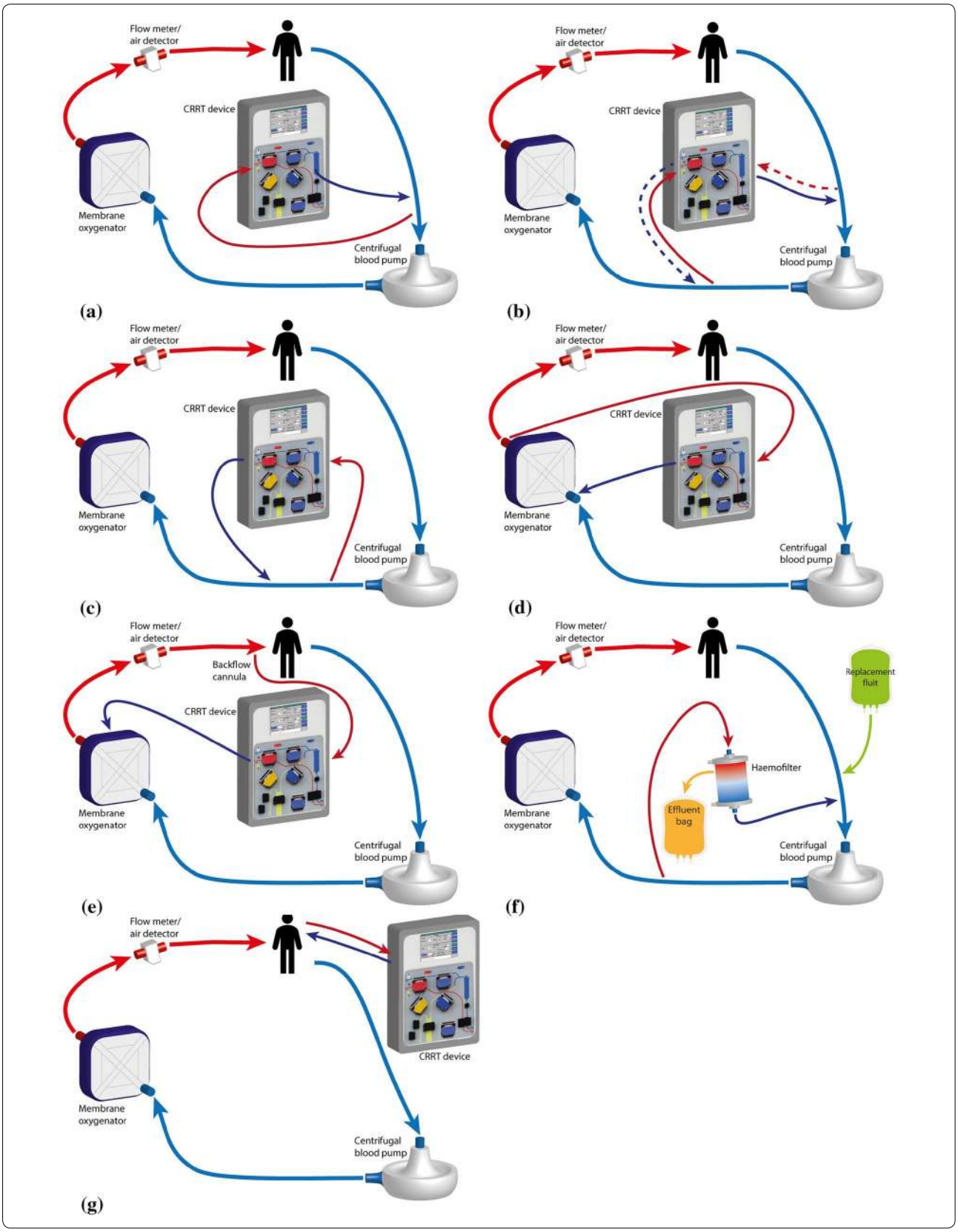
Early combinations of ECMO and RRT may be beneficial for some patients, although the indications for RRT after initiation of ECMO may deviate from traditional ones. Fluid overload appears to be the commonest indication for RRT in patients with ARDS on VV-ECMO [113, 114]. Mediator removal during extracorporeal circuit treatment to reduce biotrauma has been proposed, although evidence is lacking [115, 116].

There is insufficient evidence and lack of consensus regarding the best way to combine ECMO and CRRT. Approaches depend on local practice, training and the patient population (adult vs. paediatric). Combining CRRT into the ECMO circuit may have several benefits, as no additional vascular access is needed [117]. However, problems may arise in the combined-circuit approach. First, it is unclear what section of the ECMO circuit is best to connect the CRRT device to, or if an in-line haemofilter should be used (Fig. 4a–g). When using a centrifugal ECMO pump, the CRRT device must be placed post-pump to prevent air entrapment (Fig. 4c–e). However, high circuit pressure post-pump may limit the ability of the CRRT device to return blood, frequently leading to pressure alarms. An alternative approach may be to withdraw blood from the ECMO circuit post-oxygenator and return it from the CRRT device post-pump (Fig. 4d). However, risk of air embolism is increased whenever a line is connected to the circuit post-oxygenator. Furthermore, recirculation into the CRRT circuit may occur with this approach and must be considered, when prescribing CRRT dosing. Furthermore, one must consider whether CRRT circuit interruption poses any risk to the ECMO circuit. In this regard, it is unclear if and how anticoagulation should be performed during combined ECMO and CRRT treatment. The feasibility of VV-ECMO with prophylactic anticoagulation only has been proven and may lead to fewer bleeding complications [118].

Lung-protective ventilation with lower tidal volumes (6 mL/kg) is desirable but may lead to hypercapnia and acidaemia [73]. However, permissive hypercapnia may have a negative effect on the kidney through reduced renal plasma flow and increased renal vascular resistance [119]. In theory, RRT helps compensate respiratory acidosis and may remove CO_2 through additional filters included in the CRRT circuit [extracorporeal CO_2 removal ($ECCO_2R$)] [96, 120, 121]. While $ECCO_2R$ showed some benefit in a trial including 33 patients and may have aided application of ultraprotective ventilation among ARDS patients [122], another one was terminated due to insufficient CO_2 removal (PROVAP, clincialtrials.gov: NCT03004885). When CRRT is coupled to $ECCO_2R$, clinicians should maintain a blood flow > 400 mL/min to ensure adequate CO_2 removal [123] (Fig. 4).

(See figure on next page.)

Fig. 4 Different possible methods to combine ECMO and CRRT circuits. **a** The inlet and the outlet of the CRRT device are connected before the centrifugal blood pump in the negative/low-pressure part of the ECMO circuit. High risk of air aspiration. **b** The inlet of the CRRT device is connected after the centrifugal blood pump in the high-pressure part of the ECMO circuit, while the CRRT outlet is connected before the centrifugal blood pump in the low-pressure part. Another possibility would be the connection of the inlet in the low-pressure part and the outlet in the high-pressure part. Every connection at the low-pressure part has a high risk of air aspiration. **c** Both the inlet and the outlet of the CRRT device are connected in the high-pressure part after the centrifugal blood pump. **d** The inlet of the CRRT device is connected directly after the membrane oxygenator, while the outlet is connected directly before the oxygenator. The minimal re-circulation is outweighed by increased safety as the gas exchange membrane is used as a clot and air trap. **e** The inlet of the CRRT device is connected to the additional port of the backflow cannula, while the outlet is connected directly to the membrane oxygenator. This approach keeps the connectors pre and post oxygenator available for pressure and gas exchange monitoring of the oxygenator. **f** A haemofilter is integrated into the ECMO circuit in-line, therefore relying on blood flow and pressure provided by the ECMO device alone. Replacement fluid is directly supplied into the ECMO circuit. The inlet of the haemofilter is connected after the centrifugal blood pump into the high-pressure part, while the outlet is connected before the centrifugal blood pump to create a sufficient pressure gradient. **g** The CRRT device is connected to the patient through a separate catheter and, therefore, being independent of the ECMO circuit (reprinted with permission from http://www.ADQI.org)


Flow meter/
air detector
CRRT device
Membrane
oxygenator
Centrifugal
blood pump
(a)
(b)
(c)
(d)
Backflow
cannula
(e)
Replacement
fluit
Haemofilter
Effluent
bag
(f)
(g)

Recommendations for practice

1. We recommend initiation of CRRT should be based on absolute and relative indications for critically ill patients, given there is no evidence of benefit for combining ECMO therapy with pre-emptive use of CRRT (Grade 1D).
2. We do not recommend the use of CRRT and/or haemoabsorption with the sole intention to clear pro-/anti-inflammatory mediators during ECMO (Grade 1C).

Recommendations for research

1. The ideal mode of combination of ECMO and CRRT (stand-alone vs. integrated approach) needs to be further examined.
2. The best access point to integrate CRRT into the ECMO circuit, when using an integrated approach, needs to be determined.
3. Future trials should determine if regional citrate anticoagulation may have clinical benefits when integrating CRRT into the ECMO circuit.
4. Randomized trials are necessary to evaluate the integration of CO_2 removal into the CRRT circuit ($ECCO_2R$). They should focus on the mode of combination, possibilities for anticoagulation and the optimization of conditions and settings (e.g. blood flow).

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-019-05869-7) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest
MJ has received honoraria and research support from Baxter Healthcare Corp, AM-Pharma, CLS Behring, Fresenius, and Astute Medical. LGF has received honoraria and research support from Astute Medical, La Jolla Pharmaceuticals, Medibeacon, Baxter, and Fresenius. PMH has received honoraria and research support from Baxter and CytoSorbent. MO has received honoraria from Fresenius Medical and Baxter and has an advisory role to Biomerieux and Nxstage. JP has received speaker's honoraria from Fresenius Medical, Baxter and Nikkiso, research support from Biomerieux and Abbott, and has consulted for Nikkiso, Baxter, Medibeacon and Quark Pharma. SMB has consulted and received research support from Baxter Health Care. MD has received research support from MSD and from ASTUTE medical, speaker fees from MSD, Astellas and Bristol-Myers-Squibb, support to organize educational meetings from MSD, Astellas, and Jazz Pharma and has participated in an advisory board from SANOFI-AVENTIS. VF has received honoraria from HepaWash. EH has received speaker's fee and travel fee from Alexion, AM Pharma, Sopachem, and Bellco. M. Maggiorini has a MAB membership from Baxter and has received an unrestricted research grant from Baxter. M. Meersch has received lecture fees from Astute Medical, Fresenius Medical and Baxter. PTM has advisory board memberships with FAST Biomedical, AM-Pharma, Sphingotec. TS has an advisory board membership with Xenios and has received speaker fees from Getinge, Xenios, Zoll, Orion Pharma, and Fresenius. JAK has received consulting fees and research support from Astute Medical, Baxter and Fresenius. None of the other authors have any conflicts of interest to declare with regard to this manuscript.

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