



# Kidney involvement in COVID-19 and rationale for extracorporeal therapies

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The prevalence of direct kidney involvement in novel coronavirus disease (COVID-19) is low, but such involvement is a marker of multiple organ dysfunction and severe disease. Here, we explore potential pathways of kidney damage and discuss the rationale for extracorporeal support with various blood purification strategies in patients who are critically ill with COVID-19.

“ cytokine removal could prevent CRS-induced organ damage ”

On 11 March 2020, the World Health Organization declared novel coronavirus disease (COVID-19) to be a global pandemic. Among patients who have tested positive for COVID-19 in Italy, approximately 47% have been hospitalized and approximately 6% have required admission to intensive care units (ICUs)<sup>1</sup>. Here, we focus on the mechanisms and management of COVID-19-associated acute kidney injury (AKI).

The available data suggest that the prevalence of AKI among patients with COVID-19 is low. For example, in a Chinese cohort of 1,099 patients with COVID-19, 93.6% were hospitalized, 91.1% had pneumonia, 5.3% were admitted to the ICU, 3.4% had acute respiratory distress syndrome (ARDS) and only 0.5% had AKI<sup>2</sup>. The potential mechanisms of kidney involvement in these patients can be didactically divided into three aspects: cytokine damage, organ crosstalk and systemic effects. These mechanisms are profoundly interconnected and have important implications for extracorporeal therapy (TABLE 1).

## Cytokine damage

Cytokine release syndrome (CRS), also termed ‘cytokine storm’, can occur in various conditions including sepsis, haemophagocytic syndrome and chimeric antigen receptor (CAR) T cell therapy<sup>3</sup>. The occurrence of CRS in COVID-19 has been documented since the first reports of this disease<sup>4,5</sup>. In patients with CRS, AKI might occur as a result of intrarenal inflammation, increased vascular permeability, volume depletion and cardiomyopathy, which can lead to cardiorenal syndrome type 1. The syndrome includes systemic endothelial injury, which manifests clinically as pleural effusions, oedema, intra-abdominal hypertension, third-space fluid loss, intravascular fluid depletion and hypotension.

Pro-inflammatory IL-6 is considered to be the most important causative cytokine in CRS. Among patients with COVID-19, the plasma concentration of IL-6 is increased in those with ARDS<sup>6</sup>. Extracorporeal membrane oxygenation (ECMO), invasive mechanical ventilation and continuous kidney replacement therapy (CKRT) can also contribute to cytokine generation. The

anti-IL-6 monoclonal antibody tocilizumab is widely used to treat CRS in patients who have undergone CAR T cell therapy<sup>3</sup> and is now also being used empirically in patients with severe COVID-19.

Extracorporeal therapies have also been proposed as approaches to remove cytokines in patients with sepsis<sup>6</sup> and could potentially be beneficial in critically ill patients with COVID-19 (REF<sup>7</sup>). The rationale for use of these therapies is that cytokine removal could prevent CRS-induced organ damage. Four different approaches can be used for cytokine removal: direct haemoperfusion using a neutro-macroporous sorbent; plasma adsorption on a resin after plasma separation from whole blood; CKRT with hollow fibre filters with adsorptive properties; and high-dose CKRT with medium cut-off (MCO) or high cut-off (HCO) membranes.

Cytokine removal is mainly carried out using a neutro-macroporous sorbent. Haemoperfusion should be used for  $\geq 2$  hours on 3 consecutive days. Anticoagulation with heparin or citrate should be used during the procedure along with blood flow  $>120$  ml/min to prevent premature clotting of the circuit. The adsorptive capacity of the cartridge is usually exhausted after 4 hours and the therapy is concluded. CKRT filters with special membranes (acrylonitrile and sodium methallyl sulfonate plus polyethyleneimine or polymethylmethacrylate) also adsorb cytokines. These filters should be changed every 24 hours owing to the saturation of the adsorptive sites.

## Organ crosstalk

Recent findings confirmed the close relationship between alveolar and tubular damage — the lung–kidney axis — in ARDS<sup>8</sup>. In 2019, a retrospective study that included 357 patients with ARDS who did not have chronic kidney disease or AKI before ARDS presentation reported that pneumonia was the cause of ARDS in 83% of patients, and 68% of patients developed AKI<sup>8</sup>. Stage 3 AKI occurred in almost half of the patients with kidney injury. Older age, greater severity of illness, diabetes mellitus and positive fluid balance were independently associated with AKI development. In addition, the severity of AKI was

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Table 1 | Potential mechanisms of kidney damage and treatment strategies in COVID-19

Pathway <sup>a</sup>	Mechanism of kidney damage	Suggested treatment strategy
<b>Cytokine damage</b>		
Cytokine release syndrome	Direct cytokine lesion	Cytokine removal using various approaches: direct haemoperfusion using a neutro-macroporous sorbent; plasma adsorption on resin after separation from whole blood; CKRT with hollow fibre filters with adsorptive properties; high-dose CKRT with MCO or HCO membranes
Increased cytokine generation owing to ECMO, invasive mechanical ventilation and/or CKRT		
Haemophagocytic syndrome		
<b>Organ crosstalk</b>		
Cardiomyopathy and/or viral myocarditis	Cardiorenal syndrome type 1	LVAD, arteriovenous ECMO
Alveolar damage	Renal medullary hypoxia	Venovenous ECMO
High peak airway pressure and intra-abdominal hypertension	Renal compartment syndrome	Venovenous ECMO, extracorporeal CO <sub>2</sub> removal, CKRT
Rhabdomyolysis	Tubular toxicity	CKRT using a HCO or MCO membrane
<b>Systemic effects</b>		
Positive fluid balance	Renal compartment syndrome	Continuous ultrafiltration and diuretics
Endothelial damage, third-space fluid loss and hypotension	Renal hypoperfusion	Vasopressors and fluid expansion
Rhabdomyolysis	Tubular toxicity	CKRT using a HCO or MCO membrane
Endotoxins	Septic AKI	Endotoxin removal using polystyrene fibres functionalized with polymyxin-B

AKI, acute kidney injury; CKRT, continuous kidney replacement therapy; ECMO, extracorporeal membrane oxygenation; HCO, high cut-off; LVAD, left ventricular assist device; MCO, medium cut-off. <sup>a</sup>The pathways and mechanisms are interconnected and treatment strategies will influence different aspects simultaneously.

positively associated with older age, higher body mass index, diabetes mellitus, history of heart failure, higher peak airway pressure and higher sequential organ failure assessment. Positive end-expiratory pressure and prone positioning were not associated with kidney impairment, and nephrotoxic agents were not associated with clinical AKI<sup>8</sup>.

Cytokine overproduction is involved in lung–kidney bidirectional damage. Injured renal tubular epithelium promotes the upregulation of IL-6, and in human and animal studies increased IL-6 serum concentration in AKI was associated with higher alveolar-capillary permeability and pulmonary haemorrhage<sup>9</sup>. The direct mechanism of IL-6 injury to lung epithelial and endothelial cells remains to be further explored. ARDS also may cause renal medullary hypoxia, which is an additional insult to tubular cells<sup>9</sup>.

A retrospective study of 201 patients with confirmed COVID-19 pneumonia in China showed that 41.8% developed ARDS and 4.5% developed AKI<sup>4</sup>. Older age, hypertension and diabetes were associated with ARDS development. Although higher serum concentration of IL-6 was not a risk factor for the development of ARDS, it was a risk factor for death in patients who developed ARDS. In another Chinese cohort<sup>5</sup> of 41 patients with confirmed COVID-19 pneumonia, the prevalence of ARDS was 27% and that of AKI was 7%. IL-6 concentration was similar between patients who were admitted to the ICU (39%) and those who did not receive ICU care, whereas the plasma concentration of the anti-inflammatory cytokine IL-10 was higher in patients

who were admitted to the ICU. An excessively high concentration of anti-inflammatory mediators might be harmful as it could predispose the patient to a state of relative immunosuppression. Clearly, a huge difference exists in the prevalence of AKI in patients with ARDS secondary to COVID-19 pneumonia (4.5%)<sup>4</sup> compared with ARDS due to pneumonia with other causes (68%)<sup>8</sup>. The reasons for this difference are yet to be elucidated.

Heart–kidney crosstalk could also contribute to AKI in patients with COVID-19. For example, CRS cardiomyopathy and acute viral myocarditis can both contribute to renal vein congestion, hypotension and renal hypoperfusion, leading to a reduction in glomerular filtration rate. ECMO provides support to both the heart and the lungs and can be used in conjunction with CKRT. It is advisable to connect the CKRT circuit directly to the ECMO apparatus.

### Systemic effects

Fluid expansion may lead to positive fluid balance in patients with shock. Such expansion has a detrimental effect in ARDS, as it increases alveolar-capillary leakage, and in AKI, as it worsens renal vein congestion, leading to renal compartment syndrome. We speculate that a similar clinical picture occurs in patients with COVID-19; however, fluid balance status was not reported in the recent publications. Rhabdomyolysis, metabolic acidosis and hyperkalaemia can also occur in patients with COVID-19 and are almost always associated with haemodynamic instability. Our team encourages the use of CKRT in these patients, preferentially with MCO or

“ECMO provides support to both the heart and the lungs and can be used in conjunction with CKRT”

HCO membranes. Of note, compared with HCO membranes, MCO membranes have higher pore density and more uniformity in pore size distribution in the range that enables effective and selective removal of middle molecules such as myoglobin (17 kDa), IL-6 (21 kDa) and IL-10 (18 kDa). Importantly, intrinsic characteristics such as tridimensional configuration, hydrophilicity, protein binding and electrical charge are equally as important as pore size in determining the clearance of solutes while minimizing albumin loss.

Superimposed infections can occur in patients during a long ICU stay. When metabolized by enzymes in the blood, lipopolysaccharide expressed in the membrane of Gram-negative bacteria becomes endotoxin, which can cause septic shock. In the Chinese cohort of 1,099 patients mentioned above, septic shock was present in 11 of 173 (6.4%) patients with severe COVID-19 (REF.<sup>2</sup>). We assume that septic AKI may occur in such patients and act synergistically with other mechanisms of kidney damage. In patients with suspected or confirmed Gram-negative bacterial infections and an endotoxin activity assay result of 0.6–0.9, the use of haemoperfusion with a cartridge containing polystyrene fibres functionalized with polymyxin-B provides effective endotoxin adsorption<sup>10</sup>. The functionalized surface has sites that bind to the endotoxin, reducing its plasma concentration. Haemoperfusion should be used for 2 hours a day for 2 subsequent days. The recommendation for use of anticoagulation during cytokine adsorption also applies to endotoxin adsorption and we suggest a blood flow of around 100–120 ml/min. CKRT filters with acrylonitrile and sodium methallyl sulfonate plus polyethyleneimine also have adsorptive capacity for endotoxins. Daily changes of all CKRT filters are recommended irrespective of their composition. Multi-organ support along the course of the ICU stay is referred to as sequential extracorporeal therapy.

### Future directions

In the absence of established drugs or vaccines for COVID-19, pathophysiological rationale may support the application of the above-mentioned therapies. These approaches might help patients who are critically ill with COVID-19 who currently have limited treatment options. In these circumstances, specific conditions (such as shock-like syndrome, the need for vasopressors and capillary leak syndrome) and laboratory criteria (such as the levels of IL-6 and other cytokines as well as cell cycle arrest biomarkers with high predictive value for AKI such as [TIMP2]\*[IGFBP7]) could represent objective and standardized criteria to guide therapy.

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### Competing interests

In the past 3 years, C.R. has been a consultant or advisory board member for ASAHI, Astute, Baxter, Biomerieux, B. Braun, Cytosorbents, ESTOR, Fresenius Medical Care, General Electric, Medtronic and Toray. In the past 3 years T.R. has been a consultant or advisory board member for Baxter, B. Braun and Eurofarma.