Kidney involvement in COVID-19 and rationale for extracorporeal therapies

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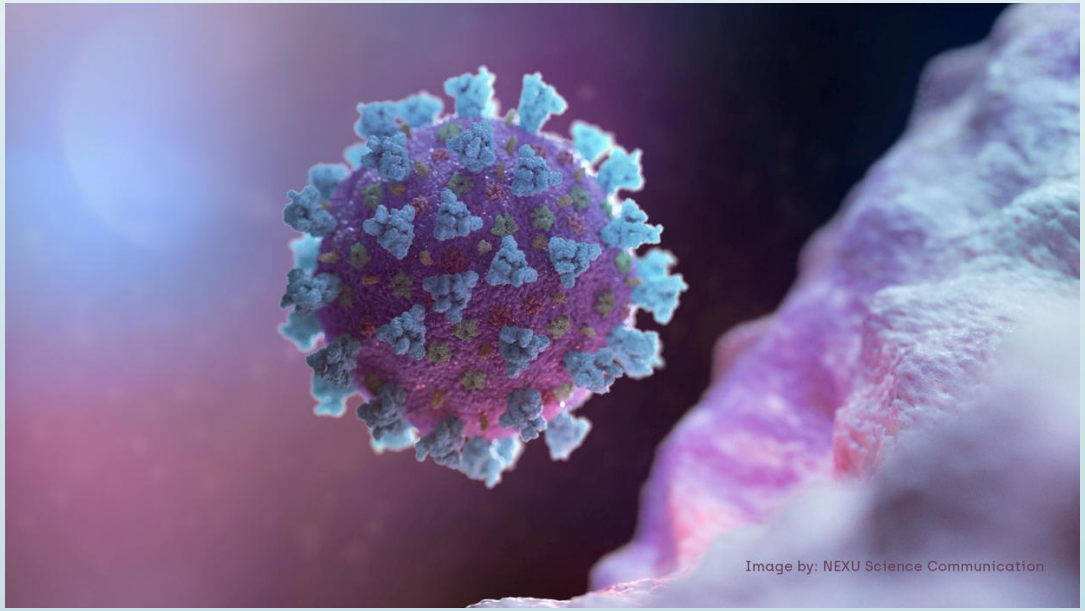
Prevalence of AKI among patients with COVID-19

- Among patients who have tested positive for COVID-19 in Italy, approximately 47% have been hospitalized and approximately 6% have required admission to ICU
- 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 ARDS and only 0.5% had AKI
- The available data suggest that the prevalence of AKI among patients with COVID-19 is low

Potential mechanisms

- Cytokine damage
- Organ crosstalk
- Systemic effects



Cytokine damage

- Cytokine release syndrome(Sepsis, Hemophagocytic syndrome, Chimeric antigen receptor T cell therapy)
  - ✓ Intrarenal inflammation
  - ✓ Increased vascular permeability
  - ✓ Volume depletion
  - ✓ Cardiomyopathy(cardiorenal syndrome type 1)
  - ✓ Systemic endothelial injury(pleural effusions, edema, intra-abdominal hypertension, third-space fluid loss, intravascular fluid depletion and hypotension)

Cytokine damage
IL-6 in COVID-19

- Plasma concentration of IL-6 is increased in those with ARDS
- Extracorporeal membrane oxygenation (ECMO), invasive mechanical ventilation and CRRT can also contribute to cytokine generation
- Anti-IL-6 monoclonal antibody tocilizumab is widely used to treat CRS in patients who have undergone CAR T cell therapy and is now also being used empirically in patients with severe COVID-19

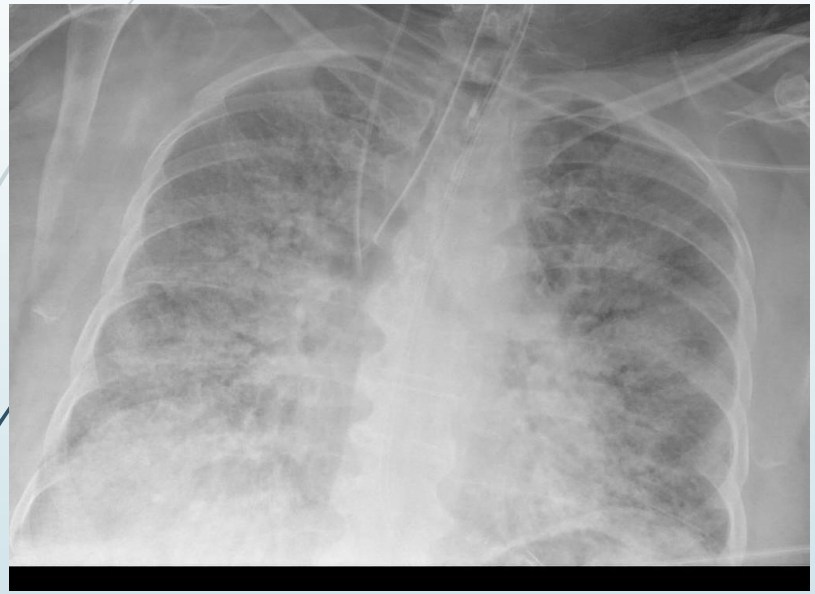
Cytokine damage
Extracorporeal therapies in COVID-19

- Proposed as approaches to remove cytokines in patients with sepsis and could potentially be beneficial in critically ill patients with COVID-19
- Cytokine removal could prevent CRS-induced organ damage

Extracorporeal therapies for cytokines

- Direct hemoperfusion using a neutro-macroporous sorbent(≥2 hours on 3 consecutive days, anticoagulation with blood flow >120 ml/min prevent clotting)
- Plasma adsorption on a resin after plasma separation from whole blood
- CRRT with hollow fiber filters with adsorptive properties
- High-dose CRRT with medium cut-off (MCO) or high cut-off (HCO) membranes

Organ crosstalk
Lung–kidney axis in ARDS



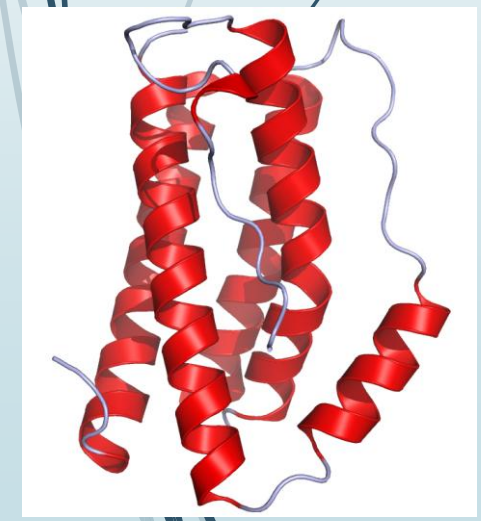
- Alveolar and tubular damage
- In 2019, a retrospective study that included 357 patients with ARDS, pneumonia was the cause of ARDS in 83% of patients and 68% of patients developed AKI(without previous CKD or AKI)

- Stage 3 AKI occurred in almost half of the patients with kidney injury

Organ crosstalk
Lung–kidney axis in ARDS

- Worse in :
  - older age
  - higher body mass index
  - diabetes mellitus
  - history of heart failure
  - higher peak airway pressure
  - higher sequential organ failure assessment
- Positive end-expiratory pressure and prone positioning, nephrotoxic agents were not associated with kidney impairment

Organ crosstalk
Lung–kidney axis in ARDS

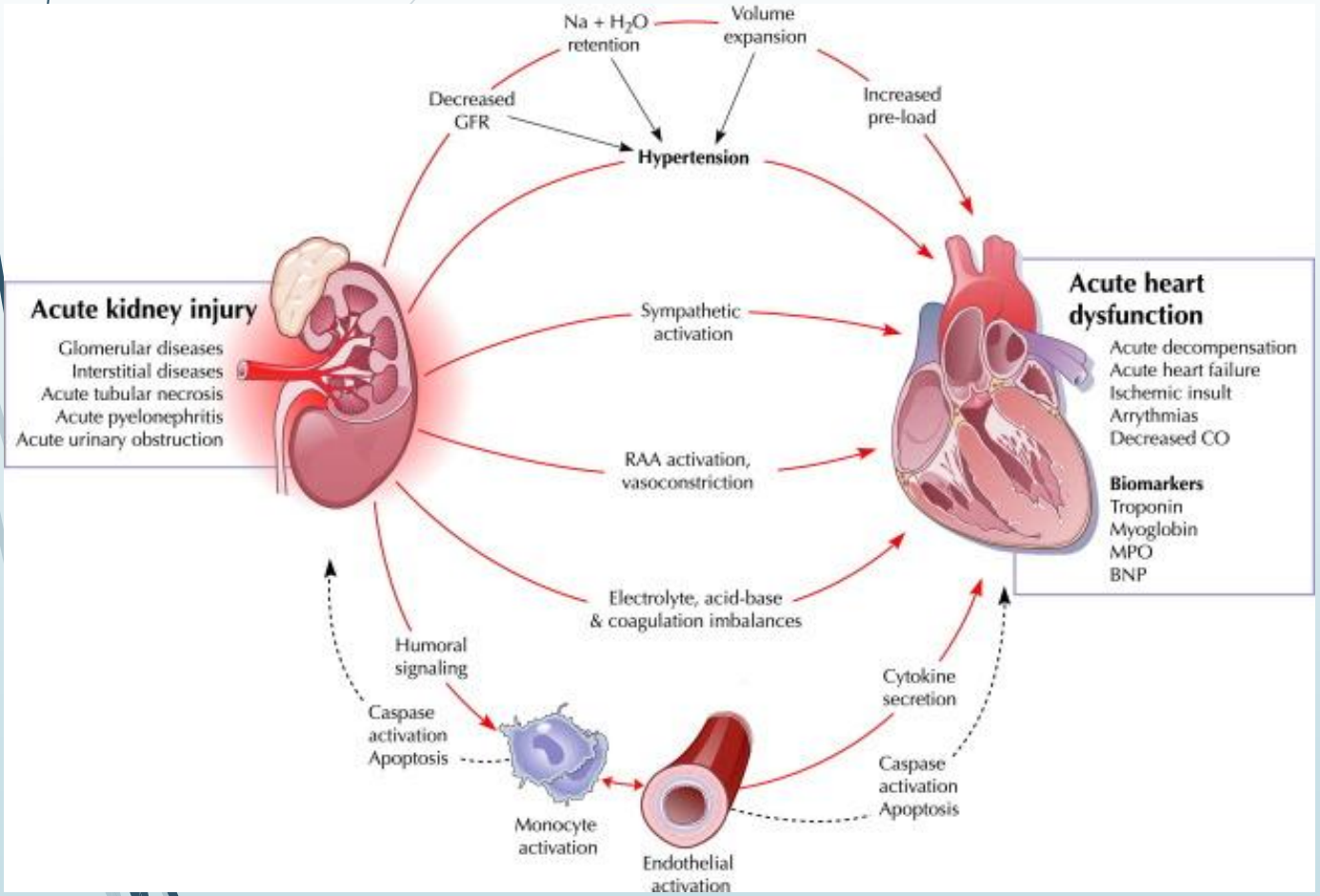


- Cytokine overproduction is involved in lung–kidney bidirectional damage
- Injured renal tubular epithelium promotes the upregulation of IL-6, and in human and animal studies increased IL-6 serum concentration in AKI
- Higher alveolar-capillary permeability and pulmonary hemorrhage
- The direct mechanism 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

Organ crosstalk
Lung–kidney axis in ARDS with COVID-19

- An excessively high concentration of anti-inflammatory mediators might be harmful as it could predispose the patient to a state of relative immunosuppression
- A huge difference exists in the prevalence of AKI in patients with ARDS secondary to COVID-19 pneumonia (4.5%) compared with ARDS due to pneumonia with other causes (68%), reason unknown

Organ crosstalk
Heart–kidney crosstalk

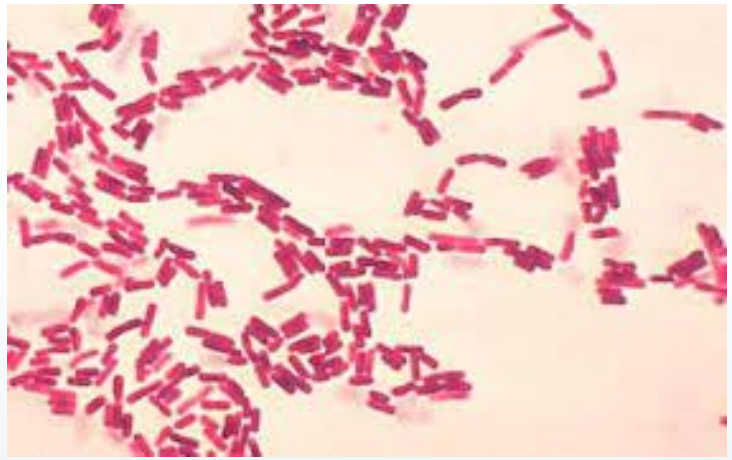


- CRS cardiomyopathy and acute viral myocarditis can both contribute to renal vein congestion, hypotension and renal hypoperfusion, leading to a reduction in glomerular filtration rate
- ECMO provides support to both the heart and the lungs and can be used in conjunction with CRRT
- It is advisable to connect the CKRT circuit directly to the ECMO apparatus

Systemic effects

- Fluid expansion may lead to positive fluid balance in patients with shock
  - Increases alveolar-capillary leakage
  - Worsens renal vein congestion(renal compartment syndrome)
  - Rhabdomyolysis, metabolic acidosis and hyperkalemia can also occur in patients with COVID-19 and are almost always associated with hemodynamic instability
- Encourages the use of CRRT in these patients, preferentially with MCO or HCO membranes

Systemic effects



- Superimposed infections
  - Lipopolysaccharide in the membrane of Gram-negative bacteria becomes endotoxin when metabolized by enzymes in the blood, causing septic shock
  - Chinese cohort of 1,099 patients mentioned, septic shock was present in 11 of 173 (6.4%) patients with severe COVID-19

Systemic effects

- 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 hemoperfusion with a cartridge containing polystyrene fibers functionalized with polymyxin-B provides effective endotoxin adsorption

Systemic effects

- The functionalized surface has sites that bind to the endotoxin, reducing its plasma concentration
- Hemoperfusion 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.
- CRRT filters with acrylonitrile and sodium methallyl sulfonate plus polyethyleneimine also have adsorptive capacity for endotoxins
- Daily changes of all CRRT filters are recommended irrespective of their composition

Pathway[a]	Mechanism of kidney damage	Suggested treatment strategy
Cytokine damage		
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		
Organ crosstalk		
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_2 removal, CKRT
Rhabdomyolysis	Tubular toxicity	CKRT using a HCO or MCO membrane
Systemic effects		
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 polysterene fibres functionalized with polymyxin-B

Conclusion

- These approaches might help patients who are critically ill with COVID-19 who currently have limited treatment options.
- 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