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What every Intensivist should know about COVID-19 associated acute kidney injury

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Abstract

Acute kidney injury (AKI) is a serious complication in critically ill patients with COVID-19 with a reported incidence ranging from <5% to >25%. Proposed aetiologies include hypovolemia, hemodynamic disturbance and inflammation but also specific factors like direct viral invasion, microvascular thrombosis, and altered regulation of the renin-angiotensin-aldosterone system. To date, there are no confirmed specific therapies, and prevention and management of AKI should follow established guidelines. Novel therapies specifically targeting COVID-19 related pathologies are under investigation. The incidence of renal replacement therapy (RRT) is variable, ranging from 0-37%. In a pandemic, RRT practice is likely to be determined by the number of patients, availability of machines, consumables and staff, clinical expertise, and acceptable alternatives. Close collaboration between critical care and renal services is essential.

In this article, we describe the epidemiology and pathophysiology of COVID-19 associated AKI, outline current management and suggest strategies to provide RRT during a pandemic when resources may be scarce.

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1. AKI epidemiology

Despite initial reports, acute kidney injury (AKI) has emerged as a serious complication in critically ill patients with COVID-19. The prevalence appears to vary with incidence rates of <5% in some initial publications from China and figures exceeding 25% in subsequent publications [1–4]. This variation may be explained by differences in pre-existing comorbidities and clinical practice (i.e. fluid management, use of nephrotoxic drugs) but socioeconomic and genetic reasons may also play a role. For instance, the SARS-CoV-2 virus uses the angiotensin-converting enzyme 2 (ACE2) receptor to enter tubular cells. Pan et al showed that the expression of the ACE2 receptor in renal podocytes and proximal tubule cells was more pronounced in Occidental subjects than in Asians, suggesting that the risk of COVID-19 associated AKI may vary between different ethnic groups [5].

2. Aetiology and pathophysiology

The aetiology of COVID-19 associated AKI is multifactorial and includes general risk factors like haemodynamic disturbance, inflammation and cytokine release, endothelial dysfunction, alteration of the microcirculation, nephrotoxic exposure, and the impact of invasive mechanical ventilation, similar to AKI in non-COVID-19 settings [6–8]. However, there is emerging evidence that additional factors specific to SARS-CoV-2 virus infection play an important role, too.

1. Viral infiltration: In the kidney, ACE2 is present in podocytes, mesangial cells, parietal epithelium of the Bowman’s capsule, proximal cells and the collecting duct [9]. It has been reported that SARS-CoV-2 can directly infect podocytes and tubular epithelial cells [9,10]. After binding to the ACE2 receptor, the spike (S) protein of SARS-CoV-2 is activated and cleaved by cellular transmembrane serine proteases. This process allows the fusion of the viral envelope with cellular membranes and entry of the virus into host cells. After entering the cytosol, the SARS-CoV-2 RNA begins the translation of its replicase exploiting the endogenous transcriptional processes of the infected cell to generate new virions [9]. The virus appears to exert direct cytopathic effects, too [9]. In addition, the tropism of SARS-CoV-2 to podocytes which form an important component of the

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glomerular filtration barrier, may explain the common finding of proteinuria in patients with COVID-19. Finally, the deposition of immune complexes of viral antigen or virus-induced specific immunological effector mechanisms (specific T-cell lymphocytes or antibodies) can induce inflammatory processes and cause additional kidney damage.

2. **Altered Renin-Angiotensin-Aldosterone (RAAS) regulation**: The role of ACE2 is to metabolize Angiotensin-II (Ang-II) to the vasodilatory and anti-inflammatory peptide angiotensin-(1–7). Imbalance of the components of the RAAS can change renal hemodynamics, alter tubular handling of electrolytes and induce pro-inflammatory changes. In the early stage of COVID-19, viral entry leads to ACE2 consumption followed by increased local Ang-II concentrations [12]. The effects of Ang-II include vasoconstriction, endothelial activation, and pro-inflammatory cytokine release [12]. Ang-II also has potent chemotactic effects that may accelerate both lymphocyte recruitment and at a later stage, pulmonary endothelial activation can lead to ACE–1 shedding where endothelial surface-bound ACE-1 is released into the interstitium [13]. This produces a decrease of Ang-II to sub-physiologic levels. Low Ang-II concentrations in this phase can lead to vasodilation, worsened capillary leak, alteration of glomerular autoregulation and reduction of glomerular filtration.

3. **Microthrombi**: COVID-19 is a pro-thrombotic state where innate immunity and coagulation pathways are closely linked [14,15]. Activation of macrophages and release of cytokines, pathogen-associated molecular patterns and damage-associated molecular proteins can result in release of tissue factor and activation of coagulation factors. Post-mortem histology of kidneys has confirmed thrombi and erythrocyte aggregates obstructing peritubular capillaries and impacting intrarenal microcirculation [11].

4. **Rhabdomyolysis**: Rhabdomyolysis is also a feature of COVID-19. Some reports of renal histology demonstrated pigmented tubular casts containing high levels of creatine phosphokinase [11].

### 3. Renal histology

In a post-mortem case series including 26 COVID-19 patients from China, the predominant kidney histology in 9 patients with AKI was acute tubular injury, erythrocyte aggregation in peritubular capillaries, segmental fibrin thrombi in glomeruli, direct viral infection of tubular epithelium and podocytes, and infiltration of inflammatory cells [11]. Features consistent with rhabdomyolysis were noted in 3 of the 9 cases. A different post-mortem report in 6 patients showed similar findings: severe acute tubular injury, lymphocyte and macrophage infiltration, detection of viral antigen in tubular epithelial cells, and complement C5b-9 deposition [10].

Collapsing glomerulopathy, an aggressive variant of focal segmental glomerulosclerosis with high rates of podocyte injury and depletion, has also been reported in renal biopsies of patients with COVID-19 associated AKI [16]. It is known to occur with a variety of conditions, including viral infections such as human immunodeficiency virus, influenza, cytomegalovirus and non-viral infections including tuberculosis, autoimmune diseases, drug exposures (such as pamidronate and interferon), hemophagocytic syndrome, and acute glomerular ischemia. Many of these exposures are thought to mediate the disease by podocyte cytotoxicity such as vaso-inflammatory cytokine expression. Given the variable renal histology findings, it is not surprising that proteinuria and haematuria have been reported in patients with COVID-19 associated AKI [17].

### 4. Medical management

During periods of scarce resources, prevention of AKI is particularly important. Where AKI develops, all efforts should be made to mitigate progression to severe AKI, particularly where renal replacement therapy (RRT) might be needed. Presently, there is no specific treatment for COVID-19 associated AKI. Until new evidence emerges, general management should follow current consensus recommendations for AKI in general [18,19]. However, potential therapies targeting specific aspects of the pathophysiology of COVID-19 associated AKI are being explored and tested [20–24]. (Table 1)

In case of progressive AKI, measures to avoid or delay the need for RRT are particularly important, including avoidance of nephrotoxic

| Conditions contributing to AKI | Pathophysiology | Recommended management and potential strategies |
|-------------------------------|----------------|-----------------------------------------------|
| Hypovolemia                   | • impairment of renal perfusion | • fluid resuscitation |
| Haemodynamic disturbance      | • disturbance of renal perfusion and microcirculation | • restoration of haemodynamics |
| Viral infection               | • direct cytotoxicity | • role of antivirals unknown |
|                               | • interstitial infiltration | • role of ACE2 receptor blockers unknown |
|                               | • alteration of glomerular filtration barrier | • role of recombinant ACE2 to neutralize SARS-CoV-2 and to rescue cellular ACE2 activity under investigation |
|                               | • role of serine inhibitors (i.e. camostat mesylate) to block transmembrane protease serine 2 activity unknown | • role of exogenous angiotensin II to decrease ACE2 expression unknown |
| Activation of pro-thrombotic processes | • formation of microthrombi and alteration of microcirculation | • role of anticoagulation unknown |
| Rhabdomyolysis                | • tubular toxicity | • fluid |
| Fluid overload                | • renal congestion | • fluid removal (diuretics, RRT) |
| Altered RAAS regulation       | • alteration of glomerular perfusion pressure and glomerular filtration | • role of exogenous angiotensin II therapy unknown |
| Invasive mechanical ventilation | • impact on cardiac output, renal perfusion and renal congestion | • optimisation of cardiac filling pressures |
| Cardiogenic shock             | • cardiorenal syndrome | • optimisation of cardiac output |

Abbreviations: ACE = angiotensin converting enzyme; ECMO = extracorporeal membrane oxygenation; RAAS = renin–angiotensin–aldosterone system; RRT = renal replacement therapy

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exposures and fluid overload, use of diuretics in case of fluid accumulation, and strategies to avoid hyperkalemia.

5. Renal replacement therapy

The incidence of RRT in critically ill COVID-19 patients with AKI appears to be highly variable with some reports suggesting that RRT is necessary in more than 30% of critically ill patients with COVID-19. (Table 2) In general, clinical practice of RRT should follow existing guidelines and be provided as optimally as possible to avoid wasting of scarce resources. However, adjustments may need to be made in case of reduced RRT capacity (environment, machines, consumables, staff) [6,25,26]. (Table 3 and Table 4) Ideally, policies and protocols for RRT during a pandemic should be in place before capacity is reached so that risks to patients, staff and the wider hospital community and the impact on quality standards are minimized [27].

5.1. Modality

Continuous renal replacement therapy (CRRT), prolonged intermittent RRT (PIRRT) and intermittent haemodialysis (IHD) are the most common modalities of RRT for AKI in most ICUs. Acute peritoneal dialysis (PD) is used less often. There is no consistent evidence that CRRT is superior to IHD with regards to mortality and renal recovery. However, CRRT provides superior removal of fluid and resolution of fluid overload, and is associated with more consistent metabolic control and less hypotension, in particular in patients with haemodynamic instability [18].

In the absence of data clearly demonstrating superiority of one modality over another, during a pandemic, the choice of RRT modality should be informed foremost by clinical expertise and resources readily available [25]. In surge situations where CRRT machines may be limited, alternative strategies, including acute PD and the use of IHD and PIRRT with standard CRRT machines (i.e. 40–50 ml/kg for 6–8 hours) should be considered to provide renal support for a higher number of patients.

If IHD is employed, extra trained staff may be needed. In addition, IHD requires access to permanent or mobile reverse osmosis units and sufficient water and drain resources with adequate water pressures to generate a dialysate.

5.2. Timing

The optimal timing for initiation of RRT in COVID-19 patients is unknown [28-32]. In patients not suffering from COVID-19, there is no convincing evidence that earlier initiation is beneficial [32]. Therefore, in a pandemic with scarce resources, initiation of acute RRT should only be considered to control or prevent complications of AKI which cannot be managed medically. Ideally, this decision should be made collaboratively with all relevant specialties involved (critical care, nephrology, nursing, patient, surrogate decision maker).

5.3. Vascular access

During a pandemic, appropriate vascular access is important in order to maintain circuit patency and avoid wasting of scarce resources. In patients who need regular proning, internal jugular access is preferred over femoral lines and the catheter length should be chosen based on insertion site [33]. (Table 5)

5.4. Anticoagulation

COVID-19 is a prothrombotic illness, and premature filter clotting is frequently reported. Appropriate vascular access is essential and systemic
anticoagulation is recommended to prolong filter life [34]. In case of ongoing problems with premature filter clotting, other forms of thrombophilia should be excluded (i.e., heparin induced thrombocytopenia).

5.5 Blood purification

The role of blood purification using specific membranes, adsorption, hemoperfusion or other extracorporeal techniques in COVID-19 has not been studied formally and remains unknown to-date [21].

6. Staff wellbeing

During a pandemic, all members of the multidisciplinary team will be experiencing emotional, physical, psychological and moral stress. The need for RRT will add to this and additional support and resources may be necessary. Access to appropriate personal protective equipment is essential.

7. Operational aspects

Close collaboration with other ICUs, critical care networks, local renal units and local health care systems in general is essential to share equipment, consumables, expertise and support. Clear criteria for transfer of patients to renal units need to be agreed between all stakeholders.

8. Outcome

Evidence is clearly emerging that AKI is associated with an increased risk of mortality in patients with COVID-19, especially if RRT is required [35,36]. The long-term impact of COVID-19 associated AKI on kidney function, risk of chronic dialysis, cardiovascular morbidity and mortality remain unknown at this stage.

9. Conclusions

The COVID-19 pandemic provides unique challenges for patients, healthcare providers, administrators and the community in general. Preparedness for rapid changes, flexibility, resilience and team work are the key essentials to enable everyone to overcome the challenges. In addition to the high physical and emotional demand, the situation also offers opportunities for fascinating clinical and basic science research, and new ways of working.

Declaration of Competing Interest

The authors have no conflict of interest.

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References

[1] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382(18):1708–20.

[2] Arentz M, Yim E, Klaff L, Lokhandwala S, Riede FX, Chen H, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. JAMA 2020;Mar 19;323(16):1612–4.

[3] Pei G, Zhang Z, Peng J, Liu L, Zhang C, Yu C, et al. Renal involvement and early prognosis in patients with COVID-19 pneumonia. JASN 2020; (Apr 28).

[4] Wang L, Li X, Chen H, Yan S, Li D, Li Y, et al. Coronavirus Disease 19 Infection does not result in acute kidney injury: an analysis of 116 hospitalized patients from Wuhan, China. Am J Nephrol 2020;51(3):343–58.

[5] Pan XW, Xu D, Zhang H, Zhou W, Wang LH, Cui XC. Identification of a potential mechanism of acute kidney injury during the COVID-19 outbreak: a study based on single-cell RNA sequencing analysis. Intensive Care Med 2020;46(4):654–72.

[6] Ostermann M, Liu K. Pathophysiology of AKI. Best Pract Res Clin Anaesthesiol 2017;31(3):305–14.

[7] Martinez-Rojas MA, Vega-Vega O, Bobadilla NA. Is the kidney a target of SARS-CoV-2? Am J Physiol Ren Physiol 2020 May 15;F1454–62.

[8] Diao B, Wang C, Wang R, Feng Z, Tan Y, Wang H, et al. Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. medRxiv 2020. https://doi.org/10.1101/2020.03.04.20031120.

[9] Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int 2020;98(1):1–21.

[10] Hall A, Busse LW, Ostermann M. Angiotensin in Critical Care. Crit Care 2018;22(1):69.

[11] Joannidis M, Forni LG, Klein SJ, Honore PM, Kashani K, Ostermann M, et al. Long-key interactions in critically ill patients: consensus report of the Acute Disease Quality Initiative (ADQI) 21 Workgroup. Intensive Care Med 2020;46(4):654–72.

[12] Ostermann M, Liu K. Pathophysiology of AKI. Best Pract Res Clin Anaesthesiol 2017;31(3):305–14.

[13] Martinez-Rojas MA, Vega-Vega O, Bobadilla NA. Is the kidney a target of SARS-CoV-2? Med. 2020 May 15;11(5):F1454–62.

[14] Diao B, Wang C, Wang R, Feng Z, Tan Y, Wang H, et al. Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. medRxiv 2020. https://doi.org/10.1101/2020.03.04.20031120.

[15] Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int 2020;98(1):1–21.

[16] Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. Lancet Respir Med 2020;8(7):738–42.

[17] Zhang H, Penninger JM, Li Y, Zhong N, Slutsky A. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med 2020;46:585–90.

[18] Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. Lancet Respir Med 2020;8(7):738–42.

[19] Diao B, Wang C, Wang R, Feng Z, Tan Y, Wang H, et al. Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. medRxiv 2020. https://doi.org/10.1101/2020.03.04.20031120.

[20] Donoghue DJ, Wilson FP, et al. COVID-19. medRxiv 2020.https://doi.org/10.1101/2020.03.04.20031120.

[21] Vege S, D’Agati V, Siddall E, Ahmad S, Kisselev S, et al. Acute kidney injury due to collapsing glomerulopathy following COVID-19 infection. Kidney Int. Rep. 2020;5(4):224–33.

[22] Zheng D, Zeng Z, Li Y, Li J, Li F, Zhou J, et al. Clinical and epidemiological characteristics of novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in China: the clinical and epidemiological characteristics of 72,314 cases. medRxiv 2020. https://doi.org/10.1101/2020.03.04.20031120.

[23] Donoghue DJ, Wilson FP, et al. COVID-19. medRxiv 2020.https://doi.org/10.1101/2020.03.04.20031120.

[24] Vege S, D’Agati V, Siddall E, Ahmad S, Kisselev S, et al. Acute kidney injury due to collapsing glomerulopathy following COVID-19 infection. Kidney Int. Rep. 2020;5(4):224–33.

[25] Donoghue DJ, Wilson FP, et al. COVID-19. medRxiv 2020.https://doi.org/10.1101/2020.03.04.20031120.

[26] Donoghue DJ, Wilson FP, et al. COVID-19. medRxiv 2020.https://doi.org/10.1101/2020.03.04.20031120.

[27] Donoghue DJ, Wilson FP, et al. COVID-19. medRxiv 2020.https://doi.org/10.1101/2020.03.04.20031120.
[33] Huriaux L, Costille P, Quintard H, Journois D, Kellum JA, Rimmele T. Haemodialysis catheters in the intensive care unit. Anaesth Crit Care Pain Med 2017;36:313–9.

[34] NHS England. Clinical Guide for Renal Replacement Therapy Options in Critical Care During the Coronavirus Pandemic. https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/04/C0298-speciality-guide-clinical-guide-for-renal-replacement-therapy-options-in-critical-care-v1.1.pdf.

[35] Ali H, Daoud A, Mohamed MM, Salim SA, Yessayan L, Baharani J, et al. Survival rate in acute kidney injury superimposed COVID-19 patients: a systematic review and meta-analysis. Ren Fail 2020;42:393–7.

[36] Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney impairment is associated with in-hospital death of COVID-19 patients. medRxiv 2020.18. https://doi.org/10.1101/2020.02.18.20023242.