**Name of Journal:** *World Journal of Nephrology*

**Manuscript NO:** 57795

**Manuscript Type:** REVIEW

**Kidney injury in COVID-19**

Ahmed AR *et al.* Kidney injury in COVID-19

Adeel Rafi Ahmed, Chaudhry Adeel Ebad, Sinead Stoneman, Muniza Manshad Satti, Peter J Conlon

**Adeel Rafi Ahmed, Chaudhry Adeel Ebad, Sinead Stoneman,** Department of Nephrology, Beaumont Hospital, Dublin D09 V2N0, Ireland

**Muniza Manshad Satti,** Department of Medicine, Connolly Hospital, Dublin D15X40D, Ireland

**Peter J Conlon,** Department of Nephrology, Beaumont Hospital and Royal College of Surgeons in Ireland, Dublin D09 V2N0, Ireland

**Author contributions:** Ahmed AR conceived and designed the study, performed literature review and analysis, drafted and critically revised and edited the manuscript and approved the final version; Ebad CA contributed to the section on management of renal transplant recipients in coronavirus disease 2019, final editing and critical analysis of the article; Stoneman S contributed to the section on direct viral invasion of renal parenchyma, final editing and critical analysis of the article; Satti MM contributed to the literature review for the pathophysiology of acute kidney injury in acute respiratory distress syndrome, final editing and critical analysis; Conlon PJ contributed and supervised with conception and design of the study, literature review and analysis, drafting and critical revision and editing and final approval of the final version.

**Corresponding author: Adeel Rafi Ahmed, MBChB, MRCP, Staff Physician,** Department of Nephrology, Beaumont Hospital, Dublin 9, Dublin D09 V2N0, Ireland. adeel.r.ahmed@gmail.com

**Received:** June 25, 2020

**Revised:** October 3, 2020

**Accepted:** October 20, 2020

**Published online:** November 29, 2020

**Abstract**

Coronavirus disease 2019 (COVID-19) continues to affect millions of people around the globe. As data emerge, it is becoming more evident that extrapulmonary organ involvement, particularly the kidneys, highly influence mortality. The incidence of acute kidney injury has been estimated to be 30% in COVID-19 non-survivors. Current evidence suggests four broad mechanisms of renal injury: Hypovolaemia, acute respiratory distress syndrome related, cytokine storm and direct viral invasion as seen on renal autopsy findings. We look to critically assess the epidemiology, pathophysiology and management of kidney injury in COVID-19.

**Key Words:** COVID-19; SARS-CoV-2; Acute kidney injury; Cytokine storm; Acute respiratory distress syndrome; Renal replacement therapy

**Citation:** Ahmed AR, Ebad CA, Stoneman S, Satti MM, Conlon PJ. Kidney injury in COVID-19. *World J Nephrol* 2020; 9(2): 18-32

**URL:** https://www.wjgnet.com/2220-6124/full/v9/i2/18.htm

**DOI:** https://dx.doi.org/10.5527/wjn.v9.i2.18

**Core Tip:** Kidney injury in coronavirus disease 2019 (COVID-19) is associated with increased mortality with hypovolaemia, acute respiratory distress syndrome, cytokine storm and direct viral invasion having a prominent pathophysiological role. Haematuria and proteinuria are present in a high proportion of cases reflecting possible glomerular involvement, and collapsing glomerulopathy has also been reported in genetically predisposed patients. This is further supported by autopsy findings showing severe acute respiratory syndrome coronavirus 2 in proximal tubules and podocytes. Evidence supports a conservative fluid management strategy in COVID-19 associated acute respiratory distress syndrome with standard indications for renal replacement therapy. Hypercoagulation is a prominent feature leading to filter clotting, thus regional citrate anticoagulation should be used. Kidney transplant recipients with COVID-19 should have immunosuppression reduced.

**INTRODUCTION**

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection leading to the coronavirus disease 2019 (COVID-19) is affecting millions of people worldwide, carrying a case fatality rate between 0.9% to 7.2% depending on the demographics, implementation of preventative measures, testing strategies and availability of health care resources[1-3]. Severe disease is seen in approximately 20% of cases, of which around 6% represents the critically ill COVID-19 patients[4,5]. Amongst the critically ill, 65% to 95% have acute respiratory distress syndrome (ARDS), followed by acute kidney injury (AKI) and acute cardiac injury/cardiomyopathy[6-8]. AKI is common among critically ill patients with COVID-19 and is an independent marker of mortality[9,10]. Prompt recognition and management of AKI in COVID-19 can limit its progression and contribute to reducing morbidity and mortality[9]. Multiple mechanisms of kidney injury have emerged as we learn more about SARS-CoV-2[11]. In this review, we look to answer the many pertinent questions regarding the epidemiology, pathophysiology and management of AKI in COVID-19 patients.

**Main Body**

***Epidemiology***

AKI, in general, has an incidence of around 3%-18% in hospitalised patients and is associated with 10%-20% mortality in the non-intensive care hospital setting, with up to 50% mortality in the intensive care setting[12-14]. There is a paucity of evidence identifying the role AKI plays in COVID-19. Majority of studies use Kidney Disease: Improving Global Outcomes (KDIGO) criteria to define AKI in COVID-19[15]. Assessment of data from major published cohorts on COVID-19, combining results from intensive care unit (ICU) admissions with non-ICU admission, reveals an overall AKI incidence of around 4.2% (Table 1)[2,4,6-8,10,16]. Amongst the non-survivors (NS), the incidence of AKI is approximately 30% and renal replacement therapy (RRT) is required in 19.5% (Table 1). Comparatively in the SARS outbreak in 2003, the incidence of AKI was around 6.7%, and multivariate analysis showed AKI as a significant independent risk factor for predicting mortality (relative risk: 4.057; 99% confidence interval: 1.461-11.27; *p* < 0.001)[17].

What is the mechanism of AKI in COVID-19? Four possible key mechanisms are becoming evident in the COVID-19 pandemic (Table 2): Hypovolaemia[9,18], ARDS related AKI[19,20], cytokine storm syndrome (CSS) associated AKI[21-23], and direct viral tropism for proximal tubular cells and podocytes *via* the angiotensin-converting enzyme 2 (ACE2) carboxypeptidase[24,25].

***Hypovolaemia***

A majority of patients have significant insensible water losses due to high-grade pyrexia and tachypnoea on presentation[26]. A subgroup of patients has substantial gastrointestinal symptoms leading to extrarenal volume loss[18]. These patients are particularly prone to developing pre-renal AKI.

***ARDS related AKI***

AKI is seen in around 35%-50% of patients who develop ARDS and substantially increases mortality by nearly two-fold in the ICU[27-30]. ARDS and its associated mechanical ventilation strategies can cause or aggravate renal injury *via* multiple pathways[31]. There are broadly five categories; haemodynamic effects, gas exchange impairment (hypoxemia/hypercapnia), acid-base dysregulation, hyper inflammation and neurohormonal effects[32]. In COVID-19, significant AKI generally develops after the onset of ARDS, suggesting lung- kidney crosstalk as the dominant mechanism of kidney injury[2,33].

The haemodynamic effects of acute pulmonary disease result in increased pulmonary artery pressures, right ventricular failure, venous congestion and increased intra-abdominal/intrathoracic pressures[34-38].

Impaired gaseous exchange with hypercapnia leads to a reduction of renal vasodilatory response and renal blood flow with altered diuresis and increased oxygen utilisation in the proximal tubule[39-41]. Severe hypoxemia also causes a reduction in renal blood flow with possible activation of the hypoxia-inducible factor system, influencing lung and kidney outcomes[42]. There is the activation of renin-angiotensin-aldosterone system, with increased aldosterone secretion with resultant activation of the sympathetic nervous system and release of non-osmotic vasopressin[31,43]. An immune-mediated/inflammatory response is noted in ARDS with the release of interleukin (IL)-6, tumour necrosis factor (TNF alpha), IL-1, transforming growth factor and substance P[44-47].

Mechanical ventilation can worsen the haemodynamic effects and cause ventilator-induced lung injury leading to further cytokine release and multi-organ dysfunction syndrome[48]. The effects of excessive positive end-expiratory pressure (and high tidal volumes) on kidney function include a further increase in intrathoracic pressures, which causes increased right ventricular dysfunction, reduced venous return and reduced cardiac output[34-36].

AKI independently worsens ARDS. AKI leads to increased production, decreased clearance of inflammatory cytokines and down-regulation of lung aquaporin and ion channels[49,50]. The rise in circulatory cytokines, particularly IL-6, leads to increased infiltration of lungs with neutrophils and macrophages, and increased pulmonary vasculature permeability worsens ARDS[51,52]. In the later phase of inflammation, IL-6 promotes IL-10 production, which has anti-inflammatory and organ protective effects[53]. Limited data suggest AKI promotes neutrophil dysfunction, causing reduced clearance of infection and increasing lung permeability[54,55]. Haemodynamically, the inflammatory state and increased alveolar-capillary permeability combined with decreased urine output in AKI worsens pulmonary oedema[56,57]. Most immunological studies are based on animal models, however, observational data support the negative impact of AKI on pulmonary outcomes in critically ill patients, with two times more requiring invasive mechanical ventilation[58,59].

The incidence of shock is variable in COVID-19 based on the reported cohort studies; in the ICU setting it may be as high as 35%[2,8]. This vasopressor dependent state causes renal blood flow dysregulation, including ischaemia-reperfusion injury, metabolic reprogramming and inflammation resulting in AKI[60]. Preliminary reports suggest rhabdomyolysis is not a major component of COVID-19, but data vary in each centre with some case reports showing a significant rise in creatine kinase and other viral infections (H1N1 and SARS) have reported this complication[4,61-63].

Cardio-renal syndrome can play a significant role in critically ill COVID-19 patients[64,65]. In cardio-renal syndrome, excessive inflammation and rise in cytokines seem central to the pathophysiological process[64,66]. The high levels of IL-6, TNF and IL-1 have a direct cardio-depressant effect and may promote myocardial cell injury[67,68]. Acidaemia promotes pulmonary vasoconstriction, increases right ventricular afterload and exacerbates negative inotropic effect[69,70]. Myocarditis may also occur in COVID-19[71].

The overall combined effect of this entire process is an inflammatory, cardio-depressant, acidotic, volume retaining state with high intrathoracic and intraabdominal pressures resulting in high renal back pressures, decreased and dysregulated renal blood flow and severe renal tubular injury.

***Cytokine storm syndrome associated AKI***

Observational data from a subgroup of patients with COVID-19 suggest the development of features consistent with CSS triggered by SARS-CoV-2 virus characterised by high serum ferritin, D-dimer, lactate dehydrogenase, cytopenia, ARDS, acute cardiac injury, abnormal liver function test, raised IL-6 and coagulation abnormalities[72-75]. Viral infections have been reported as one of the most common triggers for cytokine storms[76]. One study demonstrated similar or lower levels of cytokines in COVID-19 pneumonia when compared to other critically ill patients, questioning the hypothesis of CSS[77]. However, the use of dexamethasone, a potent anti-inflammatory steroid, has demonstrated a significant reduction in mortality amongst critically ill COVID-19 patients, highlighting the major role of hyperinflammation[78].

Can this hyperinflammatory state cause AKI? Various case series have indicated significant renal involvement, particularly in CSS associated with secondary haemophagocytic lymphohistiocytosis (sHLH)[22,79-82]. The majority present with AKI with or without nephrotic range proteinuria[79]. Histological and observational findings indicate polymorphic renal lesions with acute tubular necrosis (ATN) being the most common, followed by tubulointerstitial nephritis (TIN), collapsing glomerulopathy (with podocytopathies) and thrombotic microangiopathy (TMA)[22,79,82]. ATN and TIN are most likely due to sepsis-related haemodynamic changes, coagulopathy (disseminated intravascular coagulopathy) and perhaps the direct toxic effect of raised cytokines (IL-6 and TNF) on renal epithelial cells[83]. Nephrotic syndrome with collapsing glomerulopathy and podocytopathies are generally seen in severe cases of sHLH with African ethnic predisposition[80]. It is hypothesised a circulating cytokine during CSS phase of sHLH may cause podocytopathy[82]. Hyperinflammation, as seen in COVID-19, also leads to a hypercoagulable state that can cause fibrin thrombi occlusions in renal capillaries (TMA pattern of renal injury)[84-86].

Renal biopsy histology of patients of black ethnicity who had AKI and were subsequently SARS-CoV-2 positive showed collapsing glomerulopathy, severe podocyte effacement with acute tubular injury (ATI)[87,88]. The APOL1 genotyping on the biopsy material was performed, and the patients were found to be homozygous for the G1 risk allele. Genetic predisposition with CSS may lead to collapsing glomerulopathy in COVID-19[89].

The hyperinflammatory state can cause renal injury *via* multiple mechanisms as highlighted, however, the discussion is incomplete without further assessing the role of direct viral tropism for renal parenchyma and renal autopsy findings.

***Direct viral invasion***

Viruses must gain entry into a cell and use the host cell machinery to replicate. The ACE2 is the coreceptor used by SARS-CoV-2 to gain entry to the cells[90]. ACE2 forms part of the renin-angiotensin-aldosterone system, a cascading peptide-pathway that regulates vascular tone and salt and water balance. The ACE2 degrades angiotensin II to angiotensin, resulting in vasodilation and countering the effects of ACE[91-94].

The ACE2 is expressed in the kidney, staining abundantly in the brush border of tubular epithelial cells, moderately in parietal epithelial cells and absent in glomerular or mesangial endothelial cells[92]. Although hypertension may be a risk factor for poor prognosis with SARS-CoV-2 infection, inferences that this is due to effects on ACE2 expression as a consequence of ACE inhibitor or angiotensin receptor blocker (ARB) use are not supported by data[91,95]. Previous studies have not shown that there is upregulation of plasma ACE2 activity in patients taking ACE inhibitors or ARBs compared to patients not on these agents[94,96,97].

There is currently no data to suggest that even if ACE inhibitors or ARBs did upregulate ACE2 expression that this would facilitate faster or greater viral entry of SARS-CoV-2 into cells[91].

SARS-CoV-2 shares 79.6% sequence identity to SARS-CoV; therefore, the mechanism of COVID-19 associated AKI may share some similarities with SARS[93].

The data on whether SARS-COV caused direct kidney injury through viral entry are conflicting. In an autopsy series of 18 patients who died of SARS infection, viral sequences were located in the epithelial cells of the renal distal tubules[98]. Similarly, using a murine monoclonal antibody specific for SARS-COV nucleoprotein in four patients who died of SARS, SARS-COV antigen and RNA was found in the epithelial cells of distal convoluted renal tubules[99]. However, in a smaller case series in which autopsy findings from kidney specimens of seven SARS patients were presented, there was no virus or viral-like particles in the tubular epithelial or glomerular cells. Similarly, SARS-COV was not detected in these seven kidney samples using *in situ* hybridization[17]. Data from the Middle East respiratory syndrome suggested the presence of the virus in the proximal tubular epithelial cells[100].

Observational and histopathological studies on COVID-19 have suggested renal parenchymal involvement[10,25,87,101-104]. A retrospective study from Tongji Hospital in Wuhan, China showed the prevalence of haematuria and proteinuria at presentation among NS was significantly more compared to recovered patients (86% and 82% *vs* 50% and 38%)[101]. This coincided with significantly higher levels of inflammatory markers on presentation. A prospective analysis of 701 patients with COVID-19 from the same hospital showed a prevalence of 43.9% with proteinuria and 26.7% with haematuria[10]. This study further demonstrated haematuria and proteinuria were independent markers of in-hospital mortality in COVID-19, suggesting more aggressive disease and early features of possible direct viral invasion and hyperinflammation.

Early histopathological analysis from autopsies conducted on COVID-19 patients demonstrated on light microscopy primarily proximal ATI and ATN with vacuolar degeneration, TIN, endothelial injury, diffuse red blood cell aggregation in peritubular capillaries and glomerular capillary loops, rarely with focal fibrin thrombi[25,102]. Electron microscopy showed SARS-CoV-2 viral particles in the cytoplasm of the proximal tubule, distal tubule and podocytes. The ACE2 expression was prominent in proximal tubular cells, particularly in areas with severe ATI. Furthermore, focal strong parietal epithelial cells staining was present as well as occasional weaker podocyte staining of ACE2. Six autopsy cases showed the presence of CD68+ macrophages and membrane attack complex, C5b-C9, in the tubulointerstitium[25].

Based on limited evidence, it is plausible that during severe infection and high viral loads, SARS-CoV-2 infection and replication in renal tubular cells and podocytes causes ATI and ATN with subsequent TIN, which is further exacerbated by CSS. Fibrin thrombi and a TMA pattern of renal injury may be present due to hypercoagulable state. This entire process of kidney injury with the presence of SARS-CoV-2 in the renal parenchyma can be described as COVID-19 nephropathy. Patients with dysregulation or a genetic variant of ACE2, allowing rapid SARS-CoV-2 infiltration, may show early signs of intrinsic renal injury by new-onset proteinuria and haematuria[103-105]. Larger studies looking into renal histology in COVID-19 are required to elucidate the detailed mechanism of renal injury.

***Renal management of COVID-19***

The COVID-19 can be divided into three phases with the first phase being mild symptoms, characterised by fever and cough, continuing for approximately 5 d, progressing to the second phase with new-onset or worsening of dyspnoea and or hypoxia (silent hypoxia), which lasts 2 to 5 d, and the final phase demonstrating severe viral pneumonitis and ARDS requiring ICU management[2,8,106]. Majority of the patients (81%) remain in the first phase and do not require significant hospitalisation[1]. As mentioned previously, AKI significantly increases in-hospital mortality, particularly in the ICU setting, which also holds in case of COVID-19[10,27,29,103].

***Risk factors***

A majority of the patients that present to the hospital with COVID-19 are 60 years or older with a high proportion having diabetes, hypertension and ischaemic heart disease[1,2,4]. These co-morbidities are associated with micro and macrovascular complications, all affecting renal blood flow. Any minor haemodynamic or nephrotoxic insult can lead to a substantial AKI in these patients[66,107].

All patients presenting with symptoms of COVID-19 should have urinalysis (urine dipstick, midstream urine and spot urine protein to creatinine ratio) and should be possibly repeated at each phase of the disease[108,109]. Identification of haematuria and proteinuria may allow early recognition of patients with a high risk of disease progression to ARDS, AKI and increased mortality[10,103,104,109-111]. Active urinary sediments are seen in a much larger proportion of COVID-19 patients than those with only diabetes and hypertension[10,25,102-104]. Urinalysis should be considered in conjunction with other baseline investigations such as FBC, renal profile, liver function tests, D-dimer, fibrinogen, ferritin, procalcitonin, lactate dehydrogenase, IL-6, C-reactive protein, troponins, creatine kinase and Sequential Organ Failure Assessment score[72].

Data extrapolated from research looking at risk factors for AKI in ARDS highlights age, presence of diabetes and heart failure, worsening acidosis on day 1 of ARDS, higher severity of illness score (Sequential Organ Failure Assessment and APACHE III) and obesity as strongly associated with the development of AKI[20]. Similar risk factors for AKI, with the inclusion of black race, have been identified in data specific to COVID-19[33].

Drug dosing needs to be adjusted as per creatinine clearance and potential nephrotoxic treatment options need to be assessed for risk-benefit[111]. All drugs can cause acute interstitial nephritis, and a high diagnostic suspicion is of paramount importance. Remdesivir, an antiviral drug, has shown some evidence of quicker recovery and trend towards lower mortality amongst patient with severe COVID-19[112]. However, the drug is primarily renally excreted and is currently not recommended in patients with an estimated glomerular filtration rate below 30 mL/min/1.73 m2[113]. Animal models at high doses showed it can potentially cause AKI[113].

***Volume management***

The primary management of severe COVID-19 revolves around oxygenation and achieving an appropriate volume status. From a volume perspective, patients that present early during the disease can be hypovolaemic with gastrointestinal symptoms, fever and/or have an exacerbation of heart failure; therefore, volume management should aim to achieve euvolemia and stabilisation of blood pressure, which may be achieved through diuretics or intravenous fluids[4,114,115]. The minimum required volume should be used to achieve effective arterial volume.

Choice of fluids remains a matter of literature debate, however, current data suggest large volume resuscitation should be through balanced crystalloids rather than isotonic saline due to lower incidence of AKI[116,117]. Isotonic saline can lead to the development of hyperchloremic acidosis, which harms organ perfusion[118,119]. Acidosis is also an independent risk factor for developing AKI in ARDS[20]. Isotonic bicarbonate can be considered in hypovolemic patients with significant metabolic acidosis (particularly in pH < 7.20) and AKI[120].

Once initial volume resuscitation is accomplished, the next aim should be to achieve and maintain cumulative net even balance[121-124]. The most well-established data comes from the comparison of Two Fluid-Management Strategies in the Acute Lung Injury (FACTT) trial, consisting of 1000 patients with ARDS, where the conservative fluid strategy (cumulative 7-d fluid balance -136 ± 491 mL) compared liberal fluid strategy (cumulative 7-d fluid balance 6992 ± 502 mL) had significantly more ventilator-free days and ICU-free days. A post-doc analysis showed a non-statistically significant higher incidence of AKI in the liberal fluid strategy group[124]. A large retrospective study comparing conservative fluid strategy (FACTT) with semi-conservative fluid strategy (FACTT lite: Cumulative 7-d fluid balance 1918 ± 323 mL) in ARDS showed similar ventilator-free days and incidence of AKI and lower incidence of new-onset shock[122]. Both FACTT and FACTT lite protocols contained instructions to withhold furosemide until patients achieved a mean arterial pressure of greater than 60 mmHg for 12 h. However, specific fluid management in new-onset shock was not defined in both protocols. Despite its inaccuracies, targeting a central venous pressure of around 8 mmHg and pulmonary artery occlusion pressure of around 12 mmHg with monitoring of urine output provided the best outcomes in both protocols[121,122]. Volumes assessment is based on many other factors including passive leg raise response, inferior vena cava diameter, lung ultrasound, ejection fraction, capillary refill time and blood pressure (vasopressor requirements). It is important to note volume management strategies need to be individualised and various other factors such as ethnicity may impact decision making[125].

Until more robust evidence is available in volume management of COVID-19 induced ARDS, we continue to support a relatively conservative fluid management strategy.

***Role of continuous renal replacement therapy in COVID-19***

Around 20% of NS in COVID-19 required RRT, which was primarily continuous renal replacement therapy (CRRT) (Table 1)[2,4]. Many of these patients required it due to AKI with severe electrolyte derangements and/or volume overload intending to achieve net even or negative fluid balance. The timing of initiating CRRT varies amongst centres, however, two major randomised control trials over the last decade showed a delayed strategy of either absolute indications developing or AKI KDIGO stage 3 for more than 48 h compared to an early strategy of RRT within 6-12 h of AKI KDIGO stage 3 that had no difference in mortality, ICU-free days, ventilator-free days and vasopressor-free days[126-129]. Many patients did not require CRRT in the delayed group due to recovery of native renal function. However, a large proportion of COVID-19 patients are in ARDS at the time of AKI and some small randomised control trials have suggested early initiation of CRRT in ARDS improved oxygenation and mechanical ventilation-free days[130-132]. A post-hoc analysis of Artificial Kidney Initiation in Kidney Injury trial assessing subgroup of patients with ARDS (*n* = 207) showed no difference in ventilator-free days between the two RRT strategies and quicker renal function recovery with delayed strategy once AKI KDIGO 3 had occurred[126]. Some observational data are suggesting a higher incidence of circuit clotting in COVID-19, thus regional citrate anticoagulation should be first-line based on the availability of trained staff and centre experience[9,133].

CRRT timing should be based on an individual patient’s physiological reserve. This depends on age, cardiovascular risk factors, pulmonary comorbidities, baseline renal function and the trend of inflammatory and renal injury markers[129]. A delayed strategy of waiting for 48–72 h after progressing to AKI KDIGO 3 or until an absolute indication that arises may apply to most COVID-19 patients with septic shock[129]. CRRT can be applied earlier in ARDS patients, who despite optimum volume management with diuretics are not able to attain an early cumulative net even or negative fluid balance.

Some authors have suggested using extracorporeal blood purification technologies particularly in the context of CSS seen in COVID-19 patients[134,135]. These technologies are primarily direct haemoperfusion, plasma adsorption on a resin, CRRT with hollow fibre filters with adsorptive properties and high-dose CRRT with medium cut-off or high cut-off membranes[134]. Extracorporeal cytokine adsorption and removal can be potentially beneficial in patients with CSS[136-138]. Yet, no conclusive data exist regarding its benefits, particularly when managing COVID-19. Previous studies involving these technologies have been either too small to reach a conclusion or showed no benefit[139-143]. Some data are emerging from Italy and Germany where cytokine adsorption technology was applied in managing COVID-19. We cannot currently recommend the use of extracorporeal blood purification outside the standard use of CRRT in COVID-19 due to inconclusive evidence but look forward to future studies.

***Management of COVID-19 in renal transplant recipients***

Renal transplant recipients with COVID-19 have a higher incidence of AKI and mortality compared to the general population[144-150]. Data from case series show AKI in 30%-57% of presentations with a mortality of up to 28%[144-146]. A relatively high percentage present with gastrointestinal symptoms, particularly diarrhoea, causing hypoperfusion of renal parenchyma and loss of bicarbonate ion[144,145,149]. Appropriate volume resuscitation in the early phase, stabilisation of blood pressure and withholding nephrotoxic medication including ACE-inhibitors and ARBs remain the principles of treatment. Diarrhoea can also cause supra-therapeutic calcineurin inhibitor (CNI) levels causing AKI.

Viral infection can be severe in patients on immunosuppression as immune system response, particularly T cell-mediated, is diminished. Transplant recipients with suspected or confirmed COVID-19 should have immunosuppression adjusted immediately based on case to case and severity of disease[151].

In general, antimetabolites (mycophenolate mofetil, azathioprine) should be stopped completely. CNI (tacrolimus, cyclosporin) dose should be reduced by up to 50% or stopped completely in severe cases[148,150]. The aim is target trough tacrolimus 3-5 ng/mL and cyclosporine 25-50 ng/mL. The mammalian target of rapamycin (mTOR) inhibitors (sirolimus, everolimus) should be stopped or switched to CNI. The mTOR inhibitors have a well-known side effect of pneumonitis, which may worsen pneumonia associated with COVID-19 disease. Steroids dose should be increased to stress dose strengths during this initial phase[151].

The time frame to restart immunosuppression is not clear and can be considered based on improvement in clinical parameters and negative results of SARS-CoV-2 swab polymerase chain reaction. Each case needs to be evaluated in-depth merited on risks and benefit to recommence immunosuppressive therapy with a multi-disciplinary team approach, especially infectious disease and transplant physicians.

A suggested approach is to restart CNI at a half dose of usual maintenance dose with aim of trough level at a lower threshold in cases where CNI was stopped, with aim of up-titration of dose in further 2 wk. Steroids dose should be continued at a stress dose level during this titration period. Anti-metabolites and mTOR inhibitor recommencement can be considered after 2-4 wk based on case outcome[151].

Drug interactions need to be considered in transplant recipients with new potential therapies in the management of the disease. Risk of rejection will persist when off immunosuppression, which may need to be balanced on an individual case severity basis.

**CONCLUSION**

AKI leads to worse outcomes in COVID-19. Multiple mechanisms of renal injury are involved but can broadly be categorised into hypovolaemic, ARDS related, CSS associated and direct viral invasion of the renal parenchyma. Haematuria and proteinuria are associated with higher mortality and may signify aggressive disease early, thus all patients should have a baseline urinalysis. SARS-CoV-2 has an affinity towards the renal parenchyma and is seen in renal autopsies with associated intrinsic renal damage, collectively termed as COVID-19 nephropathy. Volume assessment is key in managing COVID-19; patients can present hypovolaemic during the early phase, particularly transplant recipients due to a high incidence of gastrointestinal symptoms, and aim should be to achieve euvolemia. Current evidence supports a conservative fluid management strategy during ARDS. Standard indications for CRRT apply, however, early initiation can be considered in ARDS if diuretics fail to support a conservative fluid management strategy. Renal transplant recipients have a higher case fatality rate, and immunosuppression needs to be reduced in COVID-19.

**REFERENCES**

1 **Wu Z**, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020; **323**: 1239-1242 [PMID: 32091533 DOI: 10.1001/jama.2020.2648]

2 **Zhou F**, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395**: 1054-1062 [PMID: 32171076 DOI: 10.1016/S0140-6736(20)30566-3]

3 **Onder G**, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. *JAMA* 2020; **323**: 1775-1776 [PMID: 32203977 DOI: 10.1001/jama.2020.4683]

4 **Guan WJ**, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382**: 1708-1720 [PMID: 32109013 DOI: 10.1056/NEJMoa2002032]

5 **Grasselli G**, Pesenti A, Cecconi M. Critical Care Utilization for the COVID-19 Outbreak in Lombardy, Italy: Early Experience and Forecast During an Emergency Response. *JAMA* 2020; **323**: 1545-1546 [PMID: 32167538 DOI: 10.1001/jama.2020.4031]

6 **Arentz M**, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, Lee M. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. *JAMA* 2020; **323**: 1612-1614 [PMID: 32191259 DOI: 10.1001/jama.2020.4326]

7 **Luigi Palmieri XA,** Antonino Bella, Stefania Bellino, Stefano Boros, Marco Canevelli, Maria. Characteristics of COVID-19 patients dying in Italy Report based on available data on March 20th, 2020 Epidemiology for public health. Higher Institute of Health 2020. Available from: https://www.epicentro.iss.it/coronavirus/bollettino/Report-COVID-2019\_20\_marzo\_eng.pdf

8 **Yang X**, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; **8**: 475-481 [PMID: 32105632 DOI: 10.1016/S2213-2600(20)30079-5]

9 **Ronco C**, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. *Lancet Respir Med* 2020; **8**: 738-742 [PMID: 32416769 DOI: 10.1016/S2213-2600(20)30229-0]

10 **Cheng Y**, Luo R, Wang K, Zhang M, Wang Z, Dong L, Li J, Yao Y, Ge S, Xu G. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int* 2020; **97**: 829-838 [PMID: 32247631 DOI: 10.1016/j.kint.2020.03.005]

11 **Gupta A**, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, Bikdeli B, Ahluwalia N, Ausiello JC, Wan EY, Freedberg DE, Kirtane AJ, Parikh SA, Maurer MS, Nordvig AS, Accili D, Bathon JM, Mohan S, Bauer KA, Leon MB, Krumholz HM, Uriel N, Mehra MR, Elkind MSV, Stone GW, Schwartz A, Ho DD, Bilezikian JP, Landry DW. Extrapulmonary manifestations of COVID-19. *Nat Med* 2020; **26**: 1017-1032 [PMID: 32651579 DOI: 10.1038/s41591-020-0968-3]

12 **Bedford M**, Stevens PE, Wheeler TW, Farmer CK. What is the real impact of acute kidney injury? *BMC Nephrol* 2014; **15**: 95 [PMID: 24952580 DOI: 10.1186/1471-2369-15-95]

13 **Hoste EAJ**, Kellum JA, Selby NM, Zarbock A, Palevsky PM, Bagshaw SM, Goldstein SL, Cerdá J, Chawla LS. Global epidemiology and outcomes of acute kidney injury. *Nat Rev Nephrol* 2018; **14**: 607-625 [PMID: 30135570 DOI: 10.1038/s41581-018-0052-0]

14 **Sawhney S**, Marks A, Fluck N, Levin A, Prescott G, Black C. Intermediate and Long-term Outcomes of Survivors of Acute Kidney Injury Episodes: A Large Population-Based Cohort Study. *Am J Kidney Dis* 2017; **69**: 18-28 [PMID: 27555107 DOI: 10.1053/j.ajkd.2016.05.018]

15 **Robbins-Juarez SY**, Qian L, King KL, Stevens JS, Husain SA, Radhakrishnan J, Mohan S. Outcomes for Patients with COVID-19 and Acute Kidney Injury: A Systematic Review and Meta-Analysis. *Kidney Int Rep* 2020; **5**: 1149-1160 [PMID: 32775814 DOI: 10.1016/j.ekir.2020.06.013]

16 **Wan S**, Xiang Y, Fang W, Zheng Y, Li B, Hu Y, Lang C, Huang D, Sun Q, Xiong Y, Huang X, Lv J, Luo Y, Shen L, Yang H, Huang G, Yang R. Clinical features and treatment of COVID-19 patients in northeast Chongqing. *J Med Virol* 2020; **92**: 797-806 [PMID: 32198776 DOI: 10.1002/jmv.25783]

17 **Chu KH**, Tsang WK, Tang CS, Lam MF, Lai FM, To KF, Fung KS, Tang HL, Yan WW, Chan HW, Lai TS, Tong KL, Lai KN. Acute renal impairment in coronavirus-associated severe acute respiratory syndrome. *Kidney Int* 2005; **67**: 698-705 [PMID: 15673319 DOI: 10.1111/j.1523-1755.2005.67130.x]

18 **Mao R**, Qiu Y, He JS, Tan JY, Li XH, Liang J, Shen J, Zhu LR, Chen Y, Iacucci M, Ng SC, Ghosh S, Chen MH. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2020; **5**: 667-678 [PMID: 32405603 DOI: 10.1016/S2468-1253(20)30126-6]

19 **Bautista E**, Arcos M, Jimenez-Alvarez L, García-Sancho MC, Vázquez ME, Peña E, Higuera A, Ramírez G, Fernández-Plata R, Cruz-Lagunas A, García-Moreno SA, Urrea F, Ramírez R, Correa-Rotter R, Pérez-Padilla JR, Zúñiga J. Angiogenic and inflammatory markers in acute respiratory distress syndrome and renal injury associated to A/H1N1 virus infection. *Exp Mol Pathol* 2013; **94**: 486-492 [PMID: 23542734 DOI: 10.1016/j.yexmp.2013.03.007]

20 **Panitchote A**, Mehkri O, Hastings A, Hanane T, Demirjian S, Torbic H, Mireles-Cabodevila E, Krishnan S, Duggal A. Factors associated with acute kidney injury in acute respiratory distress syndrome. *Ann Intensive Care* 2019; **9**: 74 [PMID: 31264042 DOI: 10.1186/s13613-019-0552-5]

21 **Tisoncik JR**, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the eye of the cytokine storm. *Microbiol Mol Biol Rev* 2012; **76**: 16-32 [PMID: 22390970 DOI: 10.1128/MMBR.05015-11]

22 **Ramos-Casals M**, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. *Lancet* 2014; **383**: 1503-1516 [PMID: 24290661 DOI: 10.1016/S0140-6736(13)61048-X]

23 **Mehta P**, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; **395**: 1033-1034 [PMID: 32192578 DOI: 10.1016/S0140-6736(20)30628-0]

24 **Ye M**, Wysocki J, William J, Soler MJ, Cokic I, Batlle D. Glomerular localization and expression of Angiotensin-converting enzyme 2 and Angiotensin-converting enzyme: implications for albuminuria in diabetes. *J Am Soc Nephrol* 2006; **17**: 3067-3075 [PMID: 17021266 DOI: 10.1681/ASN.2006050423]

25 **Diao B,** Wang C, Wang R, Feng Z, Tan Y, Wang H, Wang C, Liu L, Liu Y, Liu Y, Wang G, Yuan Z, Ren L, Wu Y, Chen Y. Human Kidney is a Target for Novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection. medRxiv. 2020: 2020.03.04.20031120. [DOI: 10.1101/2020.03.04.20031120]

26 **Selby NM**, Forni LG, Laing CM, Horne KL, Evans RD, Lucas BJ, Fluck RJ. Covid-19 and acute kidney injury in hospital: summary of NICE guidelines. *BMJ* 2020; **369**: m1963 [PMID: 32457068 DOI: 10.1136/bmj.m1963]

27 **Cooke CR**, Kahn JM, Caldwell E, Okamoto VN, Heckbert SR, Hudson LD, Rubenfeld GD. Predictors of hospital mortality in a population-based cohort of patients with acute lung injury. *Crit Care Med* 2008; **36**: 1412-1420 [PMID: 18434894 DOI: 10.1097/CCM.0b013e318170a375]

28 **Liu KD**, Matthay MA. Advances in critical care for the nephrologist: acute lung injury/ARDS. *Clin J Am Soc Nephrol* 2008; **3**: 578-586 [PMID: 18199848 DOI: 10.2215/CJN.01630407]

29 **McNicholas BA**, Rezoagli E, Pham T, Madotto F, Guiard E, Fanelli V, Bellani G, Griffin MD, Ranieri M, Laffey JG; ESICM Trials Group and the Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE (LUNG SAFE) Investigators. Impact of Early Acute Kidney Injury on Management and Outcome in Patients with Acute Respiratory Distress Syndrome: A Secondary Analysis of a Multicenter Observational Study. *Crit Care Med* 2019; **47**: 1216-1225 [PMID: 31162201 DOI: 10.1097/CCM.0000000000003832]

30 **Darmon M**, Clec'h C, Adrie C, Argaud L, Allaouchiche B, Azoulay E, Bouadma L, Garrouste-Orgeas M, Haouache H, Schwebel C, Goldgran-Toledano D, Khallel H, Dumenil AS, Jamali S, Souweine B, Zeni F, Cohen Y, Timsit JF. Acute respiratory distress syndrome and risk of AKI among critically ill patients. *Clin J Am Soc Nephrol* 2014; **9**: 1347-1353 [PMID: 24875195 DOI: 10.2215/CJN.08300813]

31 **Husain-Syed F**, Slutsky AS, Ronco C. Lung-Kidney Cross-Talk in the Critically Ill Patient. *Am J Respir Crit Care Med* 2016; **194**: 402-414 [PMID: 27337068 DOI: 10.1164/rccm.201602-0420CP]

32 **Joannidis M**, Forni LG, Klein SJ, Honore PM, Kashani K, Ostermann M, Prowle J, Bagshaw SM, Cantaluppi V, Darmon M, Ding X, Fuhrmann V, Hoste E, Husain-Syed F, Lubnow M, Maggiorini M, Meersch M, Murray PT, Ricci Z, Singbartl K, Staudinger T, Welte T, Ronco C, Kellum JA. Lung-kidney interactions in critically ill patients: consensus report of the Acute Disease Quality Initiative (ADQI) 21 Workgroup. *Intensive Care Med* 2020; **46**: 654-672 [PMID: 31820034 DOI: 10.1007/s00134-019-05869-7]

33 **Hirsch JS**, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, Hazzan AD, Fishbane S, Jhaveri KD; Northwell COVID-19 Research Consortium; Northwell Nephrology COVID-19 Research Consortium. Acute kidney injury in patients hospitalized with COVID-19. *Kidney Int* 2020; **98**: 209-218 [PMID: 32416116 DOI: 10.1016/j.kint.2020.05.006]

34 **Mitaka C**, Nagura T, Sakanishi N, Tsunoda Y, Amaha K. Two-dimensional echocardiographic evaluation of inferior vena cava, right ventricle, and left ventricle during positive-pressure ventilation with varying levels of positive end-expiratory pressure. *Crit Care Med* 1989; **17**: 205-210 [PMID: 2646069 DOI: 10.1097/00003246-198903000-00001]

35 **Pinsky MR**, Desmet JM, Vincent JL. Effect of positive end-expiratory pressure on right ventricular function in humans. *Am Rev Respir Dis* 1992; **146**: 681-687 [PMID: 1519848 DOI: 10.1164/ajrccm/146.3.681]

36 **Husain-Syed F**, McCullough PA, Birk HW, Renker M, Brocca A, Seeger W, Ronco C. Cardio-Pulmonary-Renal Interactions: A Multidisciplinary Approach. *J Am Coll Cardiol* 2015; **65**: 2433-2448 [PMID: 26046738 DOI: 10.1016/j.jacc.2015.04.024]

37 **Hering R**, Wrigge H, Vorwerk R, Brensing KA, Schröder S, Zinserling J, Hoeft A, Spiegel TV, Putensen C. The effects of prone positioning on intraabdominal pressure and cardiovascular and renal function in patients with acute lung injury. *Anesth Analg* 2001; **92**: 1226-1231 [PMID: 11323351 DOI: 10.1097/00000539-200105000-00027]

38 **Narendra DK**, Hess DR, Sessler CN, Belete HM, Guntupalli KK, Khusid F, Carpati CM, Astiz ME, Raoof S. Update in Management of Severe Hypoxemic Respiratory Failure. *Chest* 2017; **152**: 867-879 [PMID: 28716645 DOI: 10.1016/j.chest.2017.06.039]

39 **Sharkey RA**, Mulloy EM, Kilgallen IA, O'Neill SJ. Renal functional reserve in patients with severe chronic obstructive pulmonary disease. *Thorax* 1997; **52**: 411-415 [PMID: 9176530 DOI: 10.1136/thx.52.5.411]

40 **Howes TQ**, Deane CR, Levin GE, Baudouin SV, Moxham J. The effects of oxygen and dopamine on renal and aortic blood flow in chronic obstructive pulmonary disease with hypoxemia and hypercapnia. *Am J Respir Crit Care Med* 1995; **151**: 378-383 [PMID: 7842195 DOI: 10.1164/ajrccm.151.2.7842195]

41 **Barnes T**, Zochios V, Parhar K. Re-examining Permissive Hypercapnia in ARDS: A Narrative Review. *Chest* 2018; **154**: 185-195 [PMID: 29175086 DOI: 10.1016/j.chest.2017.11.010]

42 **Del Vecchio L**, Locatelli F. Hypoxia response and acute lung and kidney injury: possible implications for therapy of COVID-19. *Clin Kidney J* 2020; **13**: 494-499 [PMID: 32905208 DOI: 10.1093/ckj/sfaa149]

43 **Pannu N**, Mehta RL. Effect of mechanical ventilation on the kidney. *Best Pract Res Clin Anaesthesiol* 2004; **18**: 189-203 [PMID: 14760882 DOI: 10.1016/j.bpa.2003.08.002]

44 **Hassoun HT**, Grigoryev DN, Lie ML, Liu M, Cheadle C, Tuder RM, Rabb H. Ischemic acute kidney injury induces a distant organ functional and genomic response distinguishable from bilateral nephrectomy. *Am J Physiol Renal Physiol* 2007; **293**: F30-F40 [PMID: 17327501 DOI: 10.1152/ajprenal.00023.2007]

45 **Rabb H**, Wang Z, Nemoto T, Hotchkiss J, Yokota N, Soleimani M. Acute renal failure leads to dysregulation of lung salt and water channels. *Kidney Int* 2003; **63**: 600-606 [PMID: 12631124 DOI: 10.1046/j.1523-1755.2003.00753.x]

46 **Hassoun HT**, Lie ML, Grigoryev DN, Liu M, Tuder RM, Rabb H. Kidney ischemia-reperfusion injury induces caspase-dependent pulmonary apoptosis. *Am J Physiol Renal Physiol* 2009; **297**: F125-F137 [PMID: 19403643 DOI: 10.1152/ajprenal.90666.2008]

47 **Singbartl K**, Bishop JV, Wen X, Murugan R, Chandra S, Filippi MD, Kellum JA. Differential effects of kidney-lung cross-talk during acute kidney injury and bacterial pneumonia. *Kidney Int* 2011; **80**: 633-644 [PMID: 21734638 DOI: 10.1038/ki.2011.201]

48 **Hepokoski M**, Englert JA, Baron RM, Crotty-Alexander LE, Fuster MM, Beitler JR, Malhotra A, Singh P. Ventilator-induced lung injury increases expression of endothelial inflammatory mediators in the kidney. *Am J Physiol Renal Physiol* 2017; **312**: F654-F660 [PMID: 28365585 DOI: 10.1152/ajprenal.00523.2016]

49 **Yap SC**, Lee HT. Acute kidney injury and extrarenal organ dysfunction: new concepts and experimental evidence. *Anesthesiology* 2012; **116**: 1139-1148 [PMID: 22415388 DOI: 10.1097/ALN.0b013e31824f951b]

50 **Andres-Hernando A**, Dursun B, Altmann C, Ahuja N, He Z, Bhargava R, Edelstein CE, Jani A, Hoke TS, Klein C, Faubel S. Cytokine production increases and cytokine clearance decreases in mice with bilateral nephrectomy. *Nephrol Dial Transplant* 2012; **27**: 4339-4347 [PMID: 22778179 DOI: 10.1093/ndt/gfs256]

51 **Klein CL**, Hoke TS, Fang WF, Altmann CJ, Douglas IS, Faubel S. Interleukin-6 mediates lung injury following ischemic acute kidney injury or bilateral nephrectomy. *Kidney Int* 2008; **74**: 901-909 [PMID: 18596724 DOI: 10.1038/ki.2008.314]

52 **Hoke TS**, Douglas IS, Klein CL, He Z, Fang W, Thurman JM, Tao Y, Dursun B, Voelkel NF, Edelstein CL, Faubel S. Acute renal failure after bilateral nephrectomy is associated with cytokine-mediated pulmonary injury. *J Am Soc Nephrol* 2007; **18**: 155-164 [PMID: 17167117 DOI: 10.1681/ASN.2006050494]

53 **Andres-Hernando A**, Okamura K, Bhargava R, Kiekhaefer CM, Soranno D, Kirkbride-Romeo LA, Gil HW, Altmann C, Faubel S. Circulating IL-6 upregulates IL-10 production in splenic CD4+ T cells and limits acute kidney injury-induced lung inflammation. *Kidney Int* 2017; **91**: 1057-1069 [PMID: 28214022 DOI: 10.1016/j.kint.2016.12.014]

54 **Bentzer P**, Fisher J, Kong HJ, Mörgelin M, Boyd JH, Walley KR, Russell JA, Linder A. Heparin-binding protein is important for vascular leak in sepsis. *Intensive Care Med Exp* 2016; **4**: 33 [PMID: 27704481 DOI: 10.1186/s40635-016-0104-3]

55 **Miller L**, Singbartl K, Chroneos ZC, Ruiz-Velasco V, Lang CH, Bonavia A. Resistin directly inhibits bacterial killing in neutrophils. *Intensive Care Med Exp* 2019; **7**: 30 [PMID: 31147868 DOI: 10.1186/s40635-019-0257-y]

56 **Siddall E**, Khatri M, Radhakrishnan J. Capillary leak syndrome: etiologies, pathophysiology, and management. *Kidney Int* 2017; **92**: 37-46 [PMID: 28318633 DOI: 10.1016/j.kint.2016.11.029]

57 **Klein SJ**, Lehner GF, Forni LG, Joannidis M. Oliguria in critically ill patients: a narrative review. *J Nephrol* 2018; **31**: 855-862 [PMID: 30298272 DOI: 10.1007/s40620-018-0539-6]

58 **Hoste EA**, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, Edipidis K, Forni LG, Gomersall CD, Govil D, Honoré PM, Joannes-Boyau O, Joannidis M, Korhonen AM, Lavrentieva A, Mehta RL, Palevsky P, Roessler E, Ronco C, Uchino S, Vazquez JA, Vidal Andrade E, Webb S, Kellum JA. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. *Intensive Care Med* 2015; **41**: 1411-1423 [PMID: 26162677 DOI: 10.1007/s00134-015-3934-7]

59 **Ostermann M**, Chang RW. Impact of different types of organ failure on outcome in intensive care unit patients with acute kidney injury. *J Crit Care* 2011; **26**: 635.e1-635.e10 [PMID: 21798703 DOI: 10.1016/j.jcrc.2011.05.014]

60 **Peerapornratana S**, Manrique-Caballero CL, Gómez H, Kellum JA. Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment. *Kidney Int* 2019; **96**: 1083-1099 [PMID: 31443997 DOI: 10.1016/j.kint.2019.05.026]

61 **Wu VC**, Hsueh PR, Lin WC, Huang JW, Tsai HB, Chen YM, Wu KD; SARS Research Group of the National Taiwan University College of Medicine and National University Hospital. Acute renal failure in SARS patients: more than rhabdomyolysis. *Nephrol Dial Transplant* 2004; **19**: 3180-3182 [PMID: 15575009 DOI: 10.1093/ndt/gfh436]

62 **Chen LL**, Hsu CW, Tian YC, Fang JT. Rhabdomyolysis associated with acute renal failure in patients with severe acute respiratory syndrome. *Int J Clin Pract* 2005; **59**: 1162-1166 [PMID: 16178983 DOI: 10.1111/j.1368-5031.2005.00540.x]

63 **Meegada S**, Muppidi V, Wilkinson DC 3rd, Siddamreddy S, Katta SK. Coronavirus Disease 2019-Induced Rhabdomyolysis. *Cureus* 2020; **12**: e10123 [PMID: 32879836 DOI: 10.7759/cureus.10123]

64 **Yang C**, Jin Z. An Acute Respiratory Infection Runs Into the Most Common Noncommunicable Epidemic-COVID-19 and Cardiovascular Diseases. *JAMA Cardiol* 2020; **5**: 743-744 [PMID: 32211809 DOI: 10.1001/jamacardio.2020.0934]

65 **Apetrii M**, Enache S, Siriopol D, Burlacu A, Kanbay A, Kanbay M, Scripcariu D, Covic A. A brand-new cardiorenal syndrome in the COVID-19 setting. *Clin Kidney J* 2020; **13**: 291-296 [PMID: 32695320 DOI: 10.1093/ckj/sfaa082]

66 **Ronco C**, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol* 2008; **52**: 1527-1539 [PMID: 19007588 DOI: 10.1016/j.jacc.2008.07.051]

67 **Krishnagopalan S**, Kumar A, Parrillo JE, Kumar A. Myocardial dysfunction in the patient with sepsis. *Curr Opin Crit Care* 2002; **8**: 376-388 [PMID: 12357104 DOI: 10.1097/00075198-200210000-00003]

68 **Chen D**, Assad-Kottner C, Orrego C, Torre-Amione G. Cytokines and acute heart failure. *Crit Care Med* 2008; **36**: S9-16 [PMID: 18158483 DOI: 10.1097/01.CCM.0000297160.48694.90]

69 **Figueras J**, Stein L, Diez V, Weil MH, Shubin H. Relationship between pulmonary hemodynamics and arterial pH and carbon dioxide tension in critically ill patients. *Chest* 1976; **70**: 466-472 [PMID: 10136 DOI: 10.1378/chest.70.4.466]

70 **Brady JP**, Hasbargen JA. A review of the effects of correction of acidosis on nutrition in dialysis patients. *Semin Dial* 2000; **13**: 252-255 [PMID: 10923354 DOI: 10.1046/j.1525-139x.2000.00068.x]

71 **Madjid M**, Safavi-Naeini P, Solomon SD, Vardeny O. Potential Effects of Coronaviruses on the Cardiovascular System: A Review. *JAMA Cardiol* 2020; **5**: 831-840 [PMID: 32219363 DOI: 10.1001/jamacardio.2020.1286]

72 **Ruan Q**, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020; **46**: 846-848 [PMID: 32125452 DOI: 10.1007/s00134-020-05991-x]

73 **Mo P**, Xing Y, Xiao Y, Deng L, Zhao Q, Wang H, Xiong Y, Cheng Z, Gao S, Liang K, Luo M, Chen T, Song S, Ma Z, Chen X, Zheng R, Cao Q, Wang F, Zhang Y. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. *Clin Infect Dis* 2020 [PMID: 32173725 DOI: 10.1093/cid/ciaa270]

74 **Zhang W**, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, Wang J, Qin Y, Zhang X, Yan X, Zeng X, Zhang S. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives of clinical immunologists from China. *Clin Immunol* 2020; **214**: 108393 [PMID: 32222466 DOI: 10.1016/j.clim.2020.108393]

75 **Cao X**. COVID-19: immunopathology and its implications for therapy. *Nat Rev Immunol* 2020; **20**: 269-270 [PMID: 32273594 DOI: 10.1038/s41577-020-0308-3]

76 **Rouphael NG**, Talati NJ, Vaughan C, Cunningham K, Moreira R, Gould C. Infections associated with haemophagocytic syndrome. *Lancet Infect Dis* 2007; **7**: 814-822 [PMID: 18045564 DOI: 10.1016/S1473-3099(07)70290-6]

77 **Kox M**, Waalders NJB, Kooistra EJ, Gerretsen J, Pickkers P. Cytokine Levels in Critically Ill Patients With COVID-19 and Other Conditions. *JAMA* 2020 [PMID: 32880615 DOI: 10.1001/jama.2020.17052]

78 **RECOVERY Collaborative Group**, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *N Engl J Med* 2020 [PMID: 32678530 DOI: 10.1056/NEJMoa2021436]

79 **Aulagnon F**, Lapidus N, Canet E, Galicier L, Boutboul D, Peraldi MN, Reuter D, Bernard R, Schlemmer B, Azoulay E, Zafrani L. Acute kidney injury in adults with hemophagocytic lymphohistiocytosis. *Am J Kidney Dis* 2015; **65**: 851-859 [PMID: 25480521 DOI: 10.1053/j.ajkd.2014.10.012]

80 **Thaunat O**, Delahousse M, Fakhouri F, Martinez F, Stephan JL, Noël LH, Karras A. Nephrotic syndrome associated with hemophagocytic syndrome. *Kidney Int* 2006; **69**: 1892-1898 [PMID: 16557222 DOI: 10.1038/sj.ki.5000352]

81 **Kapoor S**, Morgan CK, Siddique MA, Guntupalli KK. Intensive care unit complications and outcomes of adult patients with hemophagocytic lymphohistiocytosis: A retrospective study of 16 cases. *World J Crit Care Med* 2018; **7**: 73-83 [PMID: 30596029 DOI: 10.5492/wjccm.v7.i6.73]

82 **Karras A**. What nephrologists need to know about hemophagocytic syndrome. *Nat Rev Nephrol* 2009; **5**: 329-336 [PMID: 19424103 DOI: 10.1038/nrneph.2009.73]

83 **Nahum E**, Ben-Ari J, Stain J, Schonfeld T. Hemophagocytic lymphohistiocytic syndrome: Unrecognized cause of multiple organ failure. *Pediatr Crit Care Med* 2000; **1**: 51-54 [PMID: 12813287 DOI: 10.1097/00130478-200007000-00010]

84 **Panigada M**, Bottino N, Tagliabue P, Grasselli G, Novembrino C, Chantarangkul V, Pesenti A, Peyvandi F, Tripodi A. Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelastography findings and other parameters of hemostasis. *J Thromb Haemost* 2020; **18**: 1738-1742 [PMID: 32302438 DOI: 10.1111/jth.14850]

85 **Spiezia L**, Boscolo A, Poletto F, Cerruti L, Tiberio I, Campello E, Navalesi P, Simioni P. COVID-19-Related Severe Hypercoagulability in Patients Admitted to Intensive Care Unit for Acute Respiratory Failure. *Thromb Haemost* 2020; **120**: 998-1000 [PMID: 32316063 DOI: 10.1055/s-0040-1710018]

86 **Zhang Y**, Xiao M, Zhang S, Xia P, Cao W, Jiang W, Chen H, Ding X, Zhao H, Zhang H, Wang C, Zhao J, Sun X, Tian R, Wu W, Wu D, Ma J, Chen Y, Zhang D, Xie J, Yan X, Zhou X, Liu Z, Wang J, Du B, Qin Y, Gao P, Qin X, Xu Y, Zhang W, Li T, Zhang F, Zhao Y, Li Y, Zhang S. Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19. *N Engl J Med* 2020; **382**: e38 [PMID: 32268022 DOI: 10.1056/NEJMc2007575]

87 **Larsen CP**, Bourne TD, Wilson JD, Saqqa O, Sharshir MA. Collapsing Glomerulopathy in a Patient with COVID-19. *Kidney Int Rep* 2020; **5**: 935-939 [PMID: 32292867 DOI: 10.1016/j.ekir.2020.04.002]

88 **Kissling S**, Rotman S, Gerber C, Halfon M, Lamoth F, Comte D, Lhopitallier L, Sadallah S, Fakhouri F. Collapsing glomerulopathy in a COVID-19 patient. *Kidney Int* 2020; **98**: 228-231 [PMID: 32471639 DOI: 10.1016/j.kint.2020.04.006]

89 **Wu H**, Larsen CP, Hernandez-Arroyo CF, Mohamed MMB, Caza T, Sharshir M, Chughtai A, Xie L, Gimenez JM, Sandow TA, Lusco MA, Yang H, Acheampong E, Rosales IA, Colvin RB, Fogo AB, Velez JCQ. AKI and Collapsing Glomerulopathy Associated with COVID-19 and *APOL* *1* High-Risk Genotype. *J Am Soc Nephrol* 2020; **31**: 1688-1695 [PMID: 32561682 DOI: 10.1681/ASN.2020050558]

90 **Wan Y**, Shang J, Graham R, Baric RS, Li F. Receptor Recognition by the Novel Coronavirus from Wuhan: an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. *J Virol* 2020; **94**: [PMID: 31996437 DOI: 10.1128/JVI.00127-20]

91 **Vaduganathan M**, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19. *N Engl J Med* 2020; **382**: 1653-1659 [PMID: 32227760 DOI: 10.1056/NEJMsr2005760]

92 **Hamming I**, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004; **203**: 631-637 [PMID: 15141377 DOI: 10.1002/path.1570]

93 **Zhou P**, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020; **579**: 270-273 [PMID: 32015507 DOI: 10.1038/s41586-020-2012-7]

94 **Ramchand J**, Patel SK, Kearney LG, Matalanis G, Farouque O, Srivastava PM, Burrell LM. Plasma ACE2 Activity Predicts Mortality in Aortic Stenosis and Is Associated With Severe Myocardial Fibrosis. *JACC Cardiovasc Imaging* 2020; **13**: 655-664 [PMID: 31607667 DOI: 10.1016/j.jcmg.2019.09.005]

95 **Shibata S**, Arima H, Asayama K, Hoshide S, Ichihara A, Ishimitsu T, Kario K, Kishi T, Mogi M, Nishiyama A, Ohishi M, Ohkubo T, Tamura K, Tanaka M, Yamamoto E, Yamamoto K, Itoh H. Hypertension and related diseases in the era of COVID-19: a report from the Japanese Society of Hypertension Task Force on COVID-19. *Hypertens Res* 2020; **43**: 1028-1046 [PMID: 32737423 DOI: 10.1038/s41440-020-0515-0]

96 **Epelman S**, Shrestha K, Troughton RW, Francis GS, Sen S, Klein AL, Tang WH. Soluble angiotensin-converting enzyme 2 in human heart failure: relation with myocardial function and clinical outcomes. *J Card Fail* 2009; **15**: 565-571 [PMID: 19700132 DOI: 10.1016/j.cardfail.2009.01.014]

97 **Ramchand J**, Patel SK, Srivastava PM, Farouque O, Burrell LM. Elevated plasma angiotensin converting enzyme 2 activity is an independent predictor of major adverse cardiac events in patients with obstructive coronary artery disease. *PLoS One* 2018; **13**: e0198144 [PMID: 29897923 DOI: 10.1371/journal.pone.0198144]

98 **Gu J**, Gong E, Zhang B, Zheng J, Gao Z, Zhong Y, Zou W, Zhan J, Wang S, Xie Z, Zhuang H, Wu B, Zhong H, Shao H, Fang W, Gao D, Pei F, Li X, He Z, Xu D, Shi X, Anderson VM, Leong AS. Multiple organ infection and the pathogenesis of SARS. *J Exp Med* 2005; **202**: 415-424 [PMID: 16043521 DOI: 10.1084/jem.20050828]

99 **Ding Y**, He L, Zhang Q, Huang Z, Che X, Hou J, Wang H, Shen H, Qiu L, Li Z, Geng J, Cai J, Han H, Li X, Kang W, Weng D, Liang P, Jiang S. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. *J Pathol* 2004; **203**: 622-630 [PMID: 15141376 DOI: 10.1002/path.1560]

100 **Alsaad KO**, Hajeer AH, Al Balwi M, Al Moaiqel M, Al Oudah N, Al Ajlan A, AlJohani S, Alsolamy S, Gmati GE, Balkhy H, Al-Jahdali HH, Baharoon SA, Arabi YM. Histopathology of Middle East respiratory syndrome coronovirus (MERS-CoV) infection - clinicopathological and ultrastructural study. *Histopathology* 2018; **72**: 516-524 [PMID: 28858401 DOI: 10.1111/his.13379]

101 **Chen T**, Wu D, Chen H, Yan W, Yang D, Chen G, Ma K, Xu D, Yu H, Wang H, Wang T, Guo W, Chen J, Ding C, Zhang X, Huang J, Han M, Li S, Luo X, Zhao J, Ning Q. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ* 2020; **368**: m1091 [PMID: 32217556 DOI: 10.1136/bmj.m1091]

102 **Su H**, Yang M, Wan C, Yi LX, Tang F, Zhu HY, Yi F, Yang HC, Fogo AB, Nie X, Zhang C. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int* 2020; **98**: 219-227 [PMID: 32327202 DOI: 10.1016/j.kint.2020.04.003]

103 **Li Z,** Wu M, Yao J, Guo J, Liao X, Song S, Li J, Duan G, Zhou Y, Wu X, Zhou Z, Wang T, Hu M, Chen X, Fu Y, Lei C, Dong H, Xu C, Hu Y, Han M, Zhou Y, Jia H, Chen X, Yan J. Caution on Kidney Dysfunctions of COVID-19 Patients. medRxiv. 2020: 2020.02.08.20021212.[doi:10.2139/ssrn.3559601]

104 **Zhou H,** Zhang Z, Fan H, Li J, Li M, Dong Y, Guo W, Lin L, Kang Z, Yu T, Tian C, Gui Y, Qin R, Wang H, Luo S, Hu D. Urinalysis, but not blood biochemistry, detects the early renal-impairment in patients with COVID-19. 2020. [doi: 10.1101/2020.04.03.20051722]

105 **Hussain M**, Jabeen N, Raza F, Shabbir S, Baig AA, Amanullah A, Aziz B. Structural variations in human ACE2 may influence its binding with SARS-CoV-2 spike protein. *J Med Virol* 2020 [PMID: 32249956 DOI: 10.1002/jmv.25832]

106 **Wang D**, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061-1069 [PMID: 32031570 DOI: 10.1001/jama.2020.1585]

107 **Khwaja A**. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2012; **120**: c179-c184 [PMID: 22890468 DOI: 10.1159/000339789]

108 **Ostermann M**, Joannidis M. Acute kidney injury 2016: diagnosis and diagnostic workup. *Crit Care* 2016; **20**: 299 [PMID: 27670788 DOI: 10.1186/s13054-016-1478-z]

109 **Hsu RK**, Hsu CY. Proteinuria and reduced glomerular filtration rate as risk factors for acute kidney injury. *Curr Opin Nephrol Hypertens* 2011; **20**: 211-217 [PMID: 21455065 DOI: 10.1097/MNH.0b013e3283454f8d]

110 **Patschan D**, Müller GA. Acute Kidney Injury in Diabetes Mellitus. *Int J Nephrol* 2016; **2016**: 6232909 [PMID: 27974972 DOI: 10.1155/2016/6232909]

111 **Izzedine H**, Jhaveri KD, Perazella MA. COVID-19 therapeutic options for patients with kidney disease. *Kidney Int* 2020; **97**: 1297-1298 [PMID: 32317113 DOI: 10.1016/j.kint.2020.03.015]

112 **Beigel JH**, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, Lopez de Castilla D, Finberg RW, Dierberg K, Tapson V, Hsieh L, Patterson TF, Paredes R, Sweeney DA, Short WR, Touloumi G, Lye DC, Ohmagari N, Oh MD, Ruiz-Palacios GM, Benfield T, Fätkenheuer G, Kortepeter MG, Atmar RL, Creech CB, Lundgren J, Babiker AG, Pett S, Neaton JD, Burgess TH, Bonnett T, Green M, Makowski M, Osinusi A, Nayak S, Lane HC; ACTT-1 Study Group Members. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med* 2020 [PMID: 32445440 DOI: 10.1056/NEJMoa2007764]

113 **Adamsick ML**, Gandhi RG, Bidell MR, Elshaboury RH, Bhattacharyya RP, Kim AY, Nigwekar S, Rhee EP, Sise ME. Remdesivir in Patients with Acute or Chronic Kidney Disease and COVID-19. *J Am Soc Nephrol* 2020; **31**: 1384-1386 [PMID: 32513665 DOI: 10.1681/ASN.2020050589]

114 **De Backer D**, Dorman T. Surviving Sepsis Guidelines: A Continuous Move toward Better Care of Patients with Sepsis. *JAMA* 2017; **317**: 807-808 [PMID: 28114630 DOI: 10.1001/jama.2017.0059]

115 **Lee SJ**, Ramar K, Park JG, Gajic O, Li G, Kashyap R. Increased fluid administration in the first three hours of sepsis resuscitation is associated with reduced mortality: a retrospective cohort study. *Chest* 2014; **146**: 908-915 [PMID: 24853382 DOI: 10.1378/chest.13-2702]

116 **Semler MW**, Self WH, Wanderer JP, Ehrenfeld JM, Wang L, Byrne DW, Stollings JL, Kumar AB, Hughes CG, Hernandez A, Guillamondegui OD, May AK, Weavind L, Casey JD, Siew ED, Shaw AD, Bernard GR, Rice TW; SMART Investigators and the Pragmatic Critical Care Research Group. Balanced Crystalloids versus Saline in Critically Ill Adults. *N Engl J Med* 2018; **378**: 829-839 [PMID: 29485925 DOI: 10.1056/NEJMoa1711584]

117 **Self WH**, Semler MW, Wanderer JP, Wang L, Byrne DW, Collins SP, Slovis CM, Lindsell CJ, Ehrenfeld JM, Siew ED, Shaw AD, Bernard GR, Rice TW; SALT-ED Investigators. Balanced Crystalloids versus Saline in Noncritically Ill Adults. *N Engl J Med* 2018; **378**: 819-828 [PMID: 29485926 DOI: 10.1056/NEJMoa1711586]

118 **Eisenhut M**. Adverse effects of rapid isotonic saline infusion. *Arch Dis Child* 2006; **91**: 797 [PMID: 16923868 DOI: 10.1136/adc.2006.100123]

119 **Lobo DN**, Awad S. Should chloride-rich crystalloids remain the mainstay of fluid resuscitation to prevent 'pre-renal' acute kidney injury?: con. *Kidney Int* 2014; **86**: 1096-1105 [PMID: 24717302 DOI: 10.1038/ki.2014.105]

120 **Jaber S**, Paugam C, Futier E, Lefrant JY, Lasocki S, Lescot T, Pottecher J, Demoule A, Ferrandière M, Asehnoune K, Dellamonica J, Velly L, Abback PS, de Jong A, Brunot V, Belafia F, Roquilly A, Chanques G, Muller L, Constantin JM, Bertet H, Klouche K, Molinari N, Jung B; BICAR-ICU Study Group. Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): a multicentre, open-label, randomised controlled, phase 3 trial. *Lancet* 2018; **392**: 31-40 [PMID: 29910040 DOI: 10.1016/S0140-6736(18)31080-8]

121 **National Heart,** Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF Jr, Hite RD, Harabin AL. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; **354**: 2564-2575 [PMID: 16714767 DOI: 10.1056/NEJMoa062200]

122 **Grissom CK**, Hirshberg EL, Dickerson JB, Brown SM, Lanspa MJ, Liu KD, Schoenfeld D, Tidswell M, Hite RD, Rock P, Miller RR 3rd, Morris AH; National Heart Lung and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network. Fluid management with a simplified conservative protocol for the acute respiratory distress syndrome\*. *Crit Care Med* 2015; **43**: 288-295 [PMID: 25599463 DOI: 10.1097/CCM.0000000000000715]

123 **Grams ME**, Estrella MM, Coresh J, Brower RG, Liu KD; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network. Fluid balance, diuretic use, and mortality in acute kidney injury. *Clin J Am Soc Nephrol* 2011; **6**: 966-973 [PMID: 21393482 DOI: 10.2215/CJN.08781010]

124 **Liu KD**, Thompson BT, Ancukiewicz M, Steingrub JS, Douglas IS, Matthay MA, Wright P, Peterson MW, Rock P, Hyzy RC, Anzueto A, Truwit JD; National Institutes of Health National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network. Acute kidney injury in patients with acute lung injury: impact of fluid accumulation on classification of acute kidney injury and associated outcomes. *Crit Care Med* 2011; **39**: 2665-2671 [PMID: 21785346 DOI: 10.1097/CCM.0b013e318228234b]

125 **Marts LT**, Kempker JA, Martin GS. Fluid Management in Acute Respiratory Distress Syndrome: Do We Have All the FACTTs to Determine the Effect of Race? *Ann Am Thorac Soc* 2017; **14**: 1391-1392 [PMID: 28862495 DOI: 10.1513/AnnalsATS.201706-501ED]

126 **Gaudry S**, Hajage D, Schortgen F, Martin-Lefevre L, Verney C, Pons B, Boulet E, Boyer A, Chevrel G, Lerolle N, Carpentier D, de Prost N, Lautrette A, Bretagnol A, Mayaux J, Nseir S, Megarbane B, Thirion M, Forel JM, Maizel J, Yonis H, Markowicz P, Thiery G, Tubach F, Ricard JD, Dreyfuss D. Timing of Renal Support and Outcome of Septic Shock and Acute Respiratory Distress Syndrome. A Post Hoc Analysis of the AKIKI Randomized Clinical Trial. *Am J Respir Crit Care Med* 2018; **198**: 58-66 [PMID: 29351007 DOI: 10.1164/rccm.201706-1255OC]

127 **Gaudry S**, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E, Boyer A, Chevrel G, Lerolle N, Carpentier D, de Prost N, Lautrette A, Bretagnol A, Mayaux J, Nseir S, Megarbane B, Thirion M, Forel JM, Maizel J, Yonis H, Markowicz P, Thiery G, Tubach F, Ricard JD, Dreyfuss D; AKIKI Study Group. Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit. *N Engl J Med* 2016; **375**: 122-133 [PMID: 27181456 DOI: 10.1056/NEJMoa1603017]

128 **Barbar SD**, Clere-Jehl R, Bourredjem A, Hernu R, Montini F, Bruyère R, Lebert C, Bohé J, Badie J, Eraldi JP, Rigaud JP, Levy B, Siami S, Louis G, Bouadma L, Constantin JM, Mercier E, Klouche K, du Cheyron D, Piton G, Annane D, Jaber S, van der Linden T, Blasco G, Mira JP, Schwebel C, Chimot L, Guiot P, Nay MA, Meziani F, Helms J, Roger C, Louart B, Trusson R, Dargent A, Binquet C, Quenot JP; IDEAL-ICU Trial Investigators and the CRICS TRIGGERSEP Network. Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis. *N Engl J Med* 2018; **379**: 1431-1442 [PMID: 30304656 DOI: 10.1056/NEJMoa1803213]

129 **Ahmed AR**, Obilana A, Lappin D. Renal Replacement Therapy in the Critical Care Setting. *Crit Care Res Pract* 2019; **2019**: 6948710 [PMID: 31396416 DOI: 10.1155/2019/6948710]

130 **Han F**, Sun R, Ni Y, Hu X, Chen X, Jiang L, Wu A, Ma L, Chen M, Xv Y, Tu Y. Early initiation of continuous renal replacement therapy improves clinical outcomes in patients with acute respiratory distress syndrome. *Am J Med Sci* 2015; **349**: 199-205 [PMID: 25494217 DOI: 10.1097/MAJ.0000000000000379]

131 **Garzia F**, Todor R, Scalea T. Continuous arteriovenous hemofiltration countercurrent dialysis (CAVH-D) in acute respiratory failure (ARDS). *J Trauma* 1991; **31**: 1277-84; discussion 1284-5 [PMID: 1920560 DOI: 10.1097/00005373-199109000-00013]

132 **Jin ZC**, Yu ZX, Ji MS, Zhou H. [Application of continuous veno-venous hemofiltration in patients with acute respiratory distress syndrome]. *Zhonghua Yi Xue Za Zhi* 2008; **88**: 2274-2277 [PMID: 19087678]

133 **Helms J**, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, Merdji H, Clere-Jehl R, Schenck M, Fagot Gandet F, Fafi-Kremer S, Castelain V, Schneider F, Grunebaum L, Anglés-Cano E, Sattler L, Mertes PM, Meziani F; CRICS TRIGGERSEP Group (Clinical Research in Intensive Care and Sepsis Trial Group for Global Evaluation and Research in Sepsis). High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med* 2020; **46**: 1089-1098 [PMID: 32367170 DOI: 10.1007/s00134-020-06062-x]

134 **Ronco C**, Reis T. Kidney involvement in COVID-19 and rationale for extracorporeal therapies. *Nat Rev Nephrol* 2020; **16**: 308-310 [PMID: 32273593 DOI: 10.1038/s41581-020-0284-7]

135 **Ronco C**, Reis T, De Rosa S. Coronavirus Epidemic and Extracorporeal Therapies in Intensive Care: si vis pacem para bellum. *Blood Purif* 2020; **49**: 255-258 [PMID: 32172242 DOI: 10.1159/000507039]

136 **Bottari G**, Guzzo I, Marano M, Stoppa F, Ravà L, Di Nardo M, Cecchetti C. Hemoperfusion with Cytosorb in pediatric patients with septic shock: A retrospective observational study. *Int J Artif Organs* 2020; **43**: 587-593 [PMID: 32003289 DOI: 10.1177/0391398820902469]

137 **Kellum JA**, Song M, Venkataraman R. Hemoadsorption removes tumor necrosis factor, interleukin-6, and interleukin-10, reduces nuclear factor-kappaB DNA binding, and improves short-term survival in lethal endotoxemia. *Crit Care Med* 2004; **32**: 801-805 [PMID: 15090965 DOI: 10.1097/01.ccm.0000114997.39857.69]

138 **Houschyar KS**, Pyles MN, Rein S, Nietzschmann I, Duscher D, Maan ZN, Weissenberg K, Philipps HM, Strauss C, Reichelt B, Siemers F. Continuous hemoadsorption with a cytokine adsorber during sepsis - a review of the literature. *Int J Artif Organs* 2017; **40**: 205-211 [PMID: 28525674 DOI: 10.5301/ijao.5000591]

139 **Monard C**, Rimmelé T, Ronco C. Extracorporeal Blood Purification Therapies for Sepsis. *Blood Purif* 2019; **47 Suppl 3**: 1-14 [PMID: 30974444 DOI: 10.1159/000499520]

140 **Schädler D**, Pausch C, Heise D, Meier-Hellmann A, Brederlau J, Weiler N, Marx G, Putensen C, Spies C, Jörres A, Quintel M, Engel C, Kellum JA, Kuhlmann MK. The effect of a novel extracorporeal cytokine hemoadsorption device on IL-6 elimination in septic patients: A randomized controlled trial. *PLoS One* 2017; **12**: e0187015 [PMID: 29084247 DOI: 10.1371/journal.pone.0187015]

141 **Borthwick EM**, Hill CJ, Rabindranath KS, Maxwell AP, McAuley DF, Blackwood B. High-volume haemofiltration for sepsis in adults. *Cochrane Database Syst Rev* 2017; **1**: CD008075 [PMID: 28141912 DOI: 10.1002/14651858.CD008075.pub3]

142 **Klein DJ**, Foster D, Schorr CA, Kazempour K, Walker PM, Dellinger RP. The EUPHRATES trial (Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized controlled trial of Adults Treated for Endotoxemia and Septic shock): study protocol for a randomized controlled trial. *Trials* 2014; **15**: 218 [PMID: 24916483 DOI: 10.1186/1745-6215-15-218]

143 **Klein DJ**, Foster D, Walker PM, Bagshaw SM, Mekonnen H, Antonelli M. Polymyxin B hemoperfusion in endotoxemic septic shock patients without extreme endotoxemia: a post hoc analysis of the EUPHRATES trial. *Intensive Care Med* 2018; **44**: 2205-2212 [PMID: 30470853 DOI: 10.1007/s00134-018-5463-7]

144 **Alberici F**, Delbarba E, Manenti C, Econimo L, Valerio F, Pola A, Maffei C, Possenti S, Zambetti N, Moscato M, Venturini M, Affatato S, Gaggiotti M, Bossini N, Scolari F. A single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia. *Kidney Int* 2020; **97**: 1083-1088 [PMID: 32354634 DOI: 10.1016/j.kint.2020.04.002]

145 **Akalin E**, Azzi Y, Bartash R, Seethamraju H, Parides M, Hemmige V, Ross M, Forest S, Goldstein YD, Ajaimy M, Liriano-Ward L, Pynadath C, Loarte-Campos P, Nandigam PB, Graham J, Le M, Rocca J, Kinkhabwala M. Covid-19 and Kidney Transplantation. *N Engl J Med* 2020; **382**: 2475-2477 [PMID: 32329975 DOI: 10.1056/NEJMc2011117]

146 **Banerjee D**, Popoola J, Shah S, Ster IC, Quan V, Phanish M. COVID-19 infection in kidney transplant recipients. *Kidney Int* 2020; **97**: 1076-1082 [PMID: 32354637 DOI: 10.1016/j.kint.2020.03.018]

147 **Columbia University Kidney Transplant Program.** Early Description of Coronavirus 2019 Disease in Kidney Transplant Recipients in New York. *J Am Soc Nephrol* 2020; **31**: 1150-1156 [PMID: 32317402 DOI: 10.1681/ASN.2020030375]

148 **Guillen E**, Pineiro GJ, Revuelta I, Rodriguez D, Bodro M, Moreno A, Campistol JM, Diekmann F, Ventura-Aguiar P. Case report of COVID-19 in a kidney transplant recipient: Does immunosuppression alter the clinical presentation? *Am J Transplant* 2020; **20**: 1875-1878 [PMID: 32198834 DOI: 10.1111/ajt.15874]

149 **Fernández-Ruiz M**, Andrés A, Loinaz C, Delgado JF, López-Medrano F, San Juan R, González E, Polanco N, Folgueira MD, Lalueza A, Lumbreras C, Aguado JM. COVID-19 in solid organ transplant recipients: A single-center case series from Spain. *Am J Transplant* 2020; **20**: 1849-1858 [PMID: 32301155 DOI: 10.1111/ajt.15929]

150 **Zhu L**, Xu X, Ma K, Yang J, Guan H, Chen S, Chen Z, Chen G. Successful recovery of COVID-19 pneumonia in a renal transplant recipient with long-term immunosuppression. *Am J Transplant* 2020; **20**: 1859-1863 [PMID: 32181990 DOI: 10.1111/ajt.15869]

151 **Alberici F**, Del Barba E, Manenti C, Econimo L, Valerio F, Pola A, Maffei C, Possenti S, Gaggia P, Movilli E, Bove S, Malberti F, Farina M, Bracchi M, Costantino EM, Bossini N, Gaggiotti M, Scolari F; Brescia Renal Covid Task Force. [Managing patients in dialysis and with kidney transplant infected with Covid-19]. *G Ital Nefrol* 2020; **37** [PMID: 32281754]

**Footnotes**

**Conflict-of-interest statement:** No potential conflicts of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Unsolicited manuscript

**Peer-review started:** June 25, 2020

**First decision:** August 22, 2020

**Article in press:** October 20, 2020

**Specialty type:** Urology and Nephrology

**Country/Territory of origin:** Ireland

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Omar AS **S-Editor:** Zhang L **L-Editor:** Filipodia **P-Editor:** Wang LL

**Table 1 Summary of acute kidney injury incidence in coronavirus disease 2019 patients**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Zhou *et al***[2] | **Yang *et al***[8] | **Guan *et al***[4] | **Wan *et al***[16] | **Arentz *et al***[6] | **Cheng *et al***[10] | **Italian data March 20, 2020**[7] | **Combined results without Italian data** | **Combined results with Italian data** |
| Total patients | 191 | 52 | 1099 | 135 | 21 | 701 | 47021 | 2199 | 49220 |
| Critically Ill1 | 50 | 52 | 55 | 40 | 21 | 73 | N/A | 291 |  |
| ARDS | 59 (30.1%) | 35 (67%) | 37 (3.4%) | 20 (14.8%) | 20 (95.2%) | 974 (13%) | N/A | 268 (12.2%) |  |
| AKI | 28 (14.7%) | 15 (28.8%) | 6 (0.5%) | 5 (3.7%) | 4 (19%) | 36 (5.1%) | N/A | 94 (4.2%) |  |
| RRT | 10 (5%) | 9 (17.3%) | 9 (0.85) | 5 (3.7%) | N/A | N/A | N/A | 33 (1.5%) |  |
| Non survivors (NS)2 | 54 (28.3%) | 32 (61.5%) | 672 (6.1%) | 1 (0.7%) | 11 (52.4%) | 113 (16.1%) | 3200 (6.8%) | 278 (154)5 (12.6%) | 3478 (3354) (7%) |
| AKI in NS2,3 | 27 (50%) | 12 (37.5%) | 42 (6%) | 43 (10%) | N/A | N/A | 944 (29.5%) | 47 (30.5%) | 991 (29.5%) |
| RRT in NS2,3 | 10 (18.5%) | 8 (25%) | 82 (11.9%) | 43 (10%) | N/A | N/A | N/A | 1. (19.5%) |  |

1Critically ill is defined as intensive care unit (ICU) admitted or categorised as a severe case where separate ICU data are not provided by the primary authors.

2The study by Guan *et al*[4] (NEJM) includes patients in ICU admission, on mechanical ventilation and non-survivors.

3The study by Wan *et al*[16] includes patients with critical illness.

4Patients on mechanical ventilation.

5Excluding data from Arentz *et al*[6] and Cheng *et al*[10] as acute kidney injury incidence was not provided in non-survivors. AKI: Acute kidney injury; ARDS: Acute respiratory distress syndrome; RRT: Renal replacement therapy.

**Table 2 Summary of the mechanism of kidney injury in coronavirus disease 2019**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Mechanism of kidney injury** | **Hypovolaemia** | **ARDS related AKI** | **Cytokine storm syndrome associated AKI** | **Direct viral invasion** |
| Pre-renal | Fever causing insensible losses; Gastrointestinal volume losses | Haemodynamic instability; High positive end expiratory pressure /intrathoracic pressure; Right heart failure | Haemodynamic instability |  |
| Renal1 |  | Inflammation; Hypoxia/hypercapnia; Acid-base dysregulation; Tubular injury | Inflammation; Possible glomerulopathy and TMA ( hypercoagulability) | Inflammation; Possible Tubulopathy; Podocytopathy; Interstitial inflammation |
| Post renal |  |  |  |  |

1The most common intrinsic renal lesion observed is acute tubular necrosis. AKI: Acute kidney injury; ARDS: Acute respiratory distress syndrome; TMA: Thrombotic microangiopathy.