COVID-19 and Acute Kidney Injury

James Hilton, MBBS, MRCP[a,b], Naomi Boyer, BSc, MBBS[a,b], Mitra K. Nadim, MD, FASN[c], Lui G. Forni, BSc, PhD, MBBS, MRCPI, AFICM, JFCMI[a,b,d,*], John A. Kellum, MD, MCCM[e]

KEYWORDS

- Acute kidney injury • Renal replacement therapy • Blood purification techniques
- COVID-19 • Cytokines

KEY POINTS

- AKI is common in patients with COVID-19.
- Increasing age, diabetes, hypertension and CKD are the major risk factors for developing covid-19 associated AKI.
- No specific therapies are available for treatment of AKI associated with COVID-19 and therefore practitioners should follow accepted local management guidelines.
- The use of blood purification techniques should be adopted with caution although preliminary data shows promise.
- The consequences of COVID-19 associated AKI in the longer term are as yet unknown

INTRODUCTION

In December 2019, a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was discovered in Wuhan, China, the rapid spread of which culminated in a global pandemic and critical pressure on health care resources.[1,2] The presentation of COVID-19 varies considerably from asymptomatic individuals and those presenting with mild respiratory symptoms to the more severe spectrum of disease requiring hospitalization. In more severe cases, the development of multi-organ failure may ensue. Overall, mortality from COVID-19 infection is approximately 1% population-wide but may reach 50% or more in those requiring intensive care.[3,4]

[a] Department of Critical Care, Royal Surrey Hospital, Egerton Road, Guildford, Surrey GU2 7XX, UK; [b] SPACeR Group (Surrey Peri-Operative, Anaesthesia & Critical Care Collaborative Research Group), Royal Surrey Hospital, Egerton Road, Guildford, Surrey GU2 7XX, UK; [c] Division of Nephrology and Hypertension, Department of Medicine, Keck School of Medicine, University of Southern California, 1520 San Pablo Street, Suite 4300, Los Angeles, CA 90033, USA; [d] Department of Clinical & Experimental Medicine, Faculty of Health Sciences, University of Surrey, Stag Hill, Guildford GU2 7XH, UK; [e] Center for Critical Care Nephrology, University of Pittsburgh, 3347 Forbes Avenue #220, Pittsburgh, PA 15213, USA
* Corresponding author. Department of Critical Care, Royal Surrey Hospital, Egerton Road, Guildford, Surrey GU2 7XX, UK.
E-mail address: luiforni@nhs.net

EPIDEMIOLOGY OF COVID-19-ASSOCIATED ACUTE KIDNEY INJURY

Initial reports suggested that acute kidney injury (AKI) as defined by the Kidney Disease Improving Global Outcomes (KDIGO) criteria was uncommon following acute COVID-19 infection.[5,6] However, subsequent data from the US and Europe did not support this finding particularly in the critically ill whereby AKI rates in excess of 40% were reported.[7,8] The incidence of C19-AKI continues to demonstrate regional variability among patients hospitalized for COVID-19. For example, a recent international meta-analysis including 49,048 patients found 28.6% of hospitalized individuals with COVID-19 were diagnosed with AKI in Europe and the USA, compared with only 5.5% of inpatients in China.[9] Similar results have been shown by others,[10] with data from the UK demonstrating C19-AKI rates in intensive care patients of greater than 45% in the period February to July 2020.[11] This disparity, may, in part, be explained by the difference in thresholds dictating hospital admission, for example, in China admission of any suspected COVID-19 infection was mandatory, whereas this was not the case in Europe and the USA.[9]

What is clear is that the development of AKI is a poor prognostic factor for individuals with COVID-19 infection with a risk ratio (RR) of 4.6 for mortality when compared with patients with COVID-19 but without AKI.[9] Cheng and colleagues were able to demonstrate that age over 65, male sex and severe COVID-19 infection were independent risk factors for in-hospital mortality. After adjusting for these, they found a significant increase in mortality with worsening AKI stage, dipstick proteinuria above 1+, and the presence of hematuria.[12]

RISK FACTORS FOR COVID-19-ASSOCIATED ACUTE KIDNEY INJURY

Boxes 1 and 2 outline the main risk factors for the development of AKI in patients with COVID-19 infection. Unsurprisingly, there is considerable overlap with factors known to contribute to the development of AKI in patients without COVID-19 infection.[13] A recent retrospective study from a New York City health system demonstrated a higher incidence of AKI among patients with COVID-19 infection compared with a historical cohort (56.9% vs 25.1%).[14] Factors independently associated with the development of stage 2 or 3 C19-AKI included older age, black race, male sex, diabetes mellitus, nursing home resident, and initial respiratory rate. The median time to development of AKI was 6.5 days in one study in a cohort suffering from severe COVID-19 pneumonitis.[15] Given this delay, predicting those at risk of C19-AKI may influence management and several studies have identified potential candidates for developing C19-AKI including higher levels of α_1-microglobulin excretion.[16]

Box 1
Risk factors for the development of C19-AKI

- Patient factors
  - Obesity[15]
  - Increasing age[15,122,123]
  - Renal transplant recipient[10]
  - Chronic kidney disease[124]

- Disease factors
  - Invasive mechanical ventilation[15,124]
  - Severe COVID-19[122,123]
  - Nephrotoxic drugs exposure[123]
  - Vasopressor requirement[124]

Box 2
Causes of renal impairment in COVID-19 infection

- Hypotension/hypovolemia
- Vascular
  - Macrovascular thrombosis
  - Microthrombi
  - Endothelialitis
  - Thrombotic microangiopathies (atypical hemolytic uremic syndrome, thrombotic thrombocytopenic purpura)
- Acute tubular necrosis
- Viral infection of renal parenchyma
- Collapsing glomerulopathy
- Glomerulonephritis
- Drug-induced acute interstitial nephritis
- Drug-induced acute tubular necrosis

PATHOPHYSIOLOGY

Given that AKI, rather than being a distinct phenotype, is often multifactorial in nature, C19-AKI may also be due to a variety of concomitant factors with a number of potential pathophysiological processes implicated. These include direct kidney injury as well as indirect mechanisms leading to C19-AKI (**Fig. 1**).[17,18]
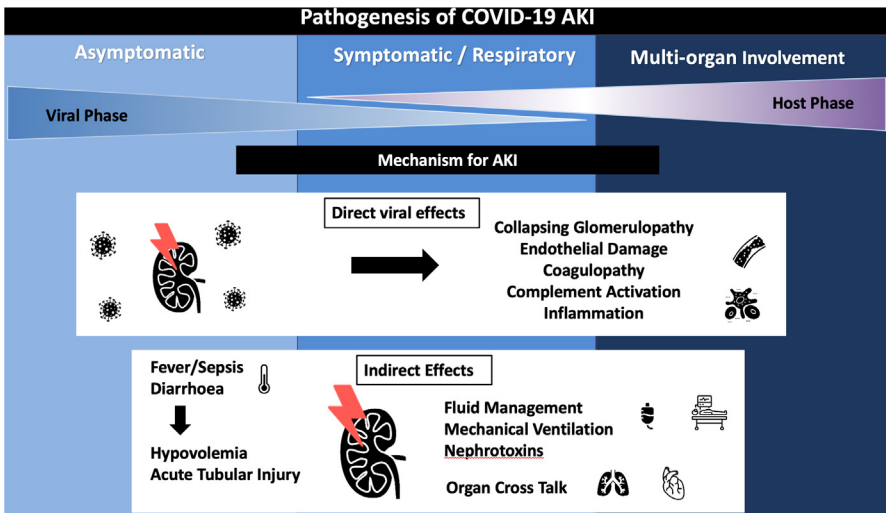
Fig. 1. Pathogenesis of COVID-19 AKI. The pathogenesis of AKI in patients with COVID-19 (COVID-19 AKI) is likely multifactorial, involving both the direct effects of the SARS-CoV-2 virus on the kidney and the indirect mechanisms resulting from systemic consequences of viral infection or effects of the virus on distant organs including the lung, in addition to mechanisms relating to the management of COVID-19. (*From* Acute Disease Quality Initiative 25, www.ADQI.org, CC BY 2.0 (https://creativecommons.org/licenses/by/2.0/).)

Tubular and Glomerular Damage

Acute tubular injury is the most frequent finding on autopsy studies reported in C19-AKI although the findings are often mild despite significant serum creatinine elevation with often evidence of preexisting comorbidities such as hypertensive nephrosclerosis associated with kidney disease.[19,20] In keeping with these findings, proteinuria when demonstrated in C19-AKI has a low molecular weight, pointing to a tubular rather than glomerular injury pattern.[21] In a multicentre study from France including 47 patients who underwent kidney biopsy in those who had severe AKI, the histopathological pattern was almost exclusively tubular injury, whereas none in their comparator group outside the ICU had evidence of acute tubular injury. Interestingly, in those outside the ICU with proteinuria and/or AKI glomerular collapsing glomerulosclerosis characterized by the segmental collapse of the glomerular tuft, parietal cell hypertrophy, or obliteration of the capillary loop or podocyte, was observed. This phenotype has also been described elsewhere predominantly in individuals with high-risk APOL1 genotypes.[22] The APOL1 gene encodes apolipoprotein-1 (apol1), part of high-density lipoprotein complex and genetic variants are common in the peoples of western Africa and carriers of APOL1 variants are at higher risk of chronic kidney disease (CKD) including a 17 times higher risk of developing focal segmental glomerulosclerosis.[23,24]

Viral Tropism in the Kidney

Evidence for direct renal tropism by COVID-19 is controversial. Although a few studies have been able to demonstrate evidence of the presence of viral particles in renal tissue many have not.[25–27] Furthermore, the timing of renal biopsies and autopsy studies are often days to weeks after the onset of the associated AKI, putatively beyond the infectious period of SARS-CoV-2. However, the trimeric spike protein of SARS-CoV-2 is a large molecule at approximately 600 kDa which should preclude its filtration in the healthy glomerulus suggesting the infection of the renal tubular cells, the urothelium or filtration occurring through damaged glomeruli.[28] Similarly to the related virus SARS-CoV, SARS-CoV-2 enters cells expressing ACE2 and seems to be its principal mechanism of infectivity.[29,30] The cell-free and macrophage-phagocytosed virus can spread to other organs and infect ACE2-expressing cells at local sites, causing multiorgan injury.[31] Interestingly, in murine models of ischemic tubular injury ACE2 expression may drop.[32] This would theoretically reduce the further influx of viral material into the renal epithelial cells. Moreover, SARS-CoV-2 is endocytosed by the kidney injury molecule-1 (KIM-1) glycoprotein expressed on pulmonary and renal epithelial cells. This represents an alternative entry mechanism for the virus into already damaged epithelial cells, further prolonging infectivity.[33]

Complement Activation

The immune/inflammatory response to COVID-19 infection has been implicated in the development of C19-AKI. For example, complement activation has been demonstrated within the kidney with evidence of complement deposition and membrane attack complex in nephron vessels and the tubular basement membrane.[34] The activation of the complement cascade has previously been shown to lead to chronic renal inflammation and subsequent tubulointerstitial fibrosis.[35] This has led to studies administering the complement C5a inhibitor eculizumab in patients with COVID-19.[36] Although preliminary results show promise, these are proof of concept studies with insufficient numbers to demonstrate any significant effects on C19-AKI or the need for RRT.

Cytokine Activation

The inflammatory response to COVID-19 infection has been described as a "cytokine storm" contributing to organ dysfunction. Although poorly defined, cytokine storm syndrome (macrophage activation syndrome) is a life-threatening inflammatory response involving high levels of circulating cytokines and immune cell hyperactivation triggered by multiple mechanisms including sepsis. The proinflammatory cytokines interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNFα) are 3 of the most important cytokines of the innate immune system and are implicated in the development of a cytokine storm. Although in COVID-19 elevated levels of monocytes and macrophages have been demonstrated, particularly in the lungs, and are thought to account for the high levels of IL-1, IL-6, and TNFα observed in some individuals other data suggest that levels of circulating cytokines are often lower in patients with COVID-19 than in patients with acute respiratory distress syndrome (ARDS) due to causes other than COVID-19.[37–39] Nevertheless, monoclonal antibodies against IL-6 have been trialed in patients with the RECOVERY trial demonstrating that the anti-IL-6 monoclonal antibody tocilizumab had a positive effect in moderate COVID-19 pneumonitis, contradicting the results of a smaller multicentre Italian study which found no benefit.[40,41] However, in the critically ill, the data are more contentious. The REMAP-CAP trial demonstrated a reduction in the duration of cardiorespiratory support in an intensive care population when administering tocilizumab or sarilumab, another anti-IL-6 monoclonal antibody.[42] The excess cytokine production resulting in ARDS maybe associated with disease severity in COVID-19; however, its role in the contribution toward kidney damage is vague. IL-6 has been implicated in the development of AKI given that elevated IL-6 levels may induce renal endothelium cells to secrete other proinflammatory cytokines and chemokines contributing to microvascular dysfunction.[43] Moreover, in patients with a greater than 100-fold increase in IL-6 levels increased rates of AKI have been observed although this is not a consistent finding.[44,45]

COVID-19-Associated Coagulopathy

The extrapulmonary clinical manifestations of COVID-19-infection are likely to be related to associate widespread vascular pathology given prominent pulmonary as well as systemic endotheliitis represents a distinguishable and distinct feature of COVID-19 infection.[46] The prothrombotic nature of COVID-19-associated sepsis has been well described.[47] Platelet-rich thrombi have been observed in the microvasculature of the heart, brain, kidney, and liver and renal infarction secondary to arterial thrombi have also been described.[48,49] Although prophylactic anticoagulation with low-molecular-weight subcutaneous heparin or enoxaparin (a low-molecular-weight heparin) was shown to provide a mortality benefit in inpatients with COVID-19 from the US Veterans database this finding was confirmed only in moderate COVID-19 pneumonitis, failing to show benefit in the critical care population.[50,51] Furthermore, no effect on AKI rates was observed. Thrombotic microangiopathy characterized by thrombocytopenia and microthrombi which may lead to ischemic tissue injury has been observed both in the pulmonary vasculature and kidneys of patients with severe COVID-19.[52–54] In addition, significant alterations of the von Willebrand factor (VWF)-ADAMTS13 axis in patients with COVID-19 have been observed with an elevated VWF:Ag to ADAMTS13 activity ratio being strongly associated with disease severity. Such an imbalance enhances the hypercoagulable state of patients with COVID-19 and their risk of microthrombosis.[55]

Indirect Kidney Injury

Indirect mechanisms include damage from the therapeutic interventions to manage critical illness as well as the systemic effects of COVID-19 infection (see Fig. 1).

Insensible losses leading to hypovolemia and kidney injury, through an increased work of breathing, pyrexia, and gastrointestinal manifestations of infection may be significant in individuals with COVID-19. Moreover, hemodynamic instability and fluid restrictive strategies in patients with ARDS may further exacerbate kidney injury. The relationship between the underlying pulmonary pathology and the kidney may also exacerbate C19-AKI. The consequence of respiratory failure and subsequent hypoxemia on the kidney are well documented with increased renovascular resistance, exacerbated by hypercapnia, leading to a reduction in glomerular filtration rate (GFR).[56] Furthermore, increases in pulmonary artery and intrathoracic pressure may lead to right ventricular dysfunction and renal venous congestion, effects exacerbated by the use of mechanical ventilation and the application of positive end-expiratory pressure (PEEP).[57,58] This effect may be exaggerated in severe COVID-19, whereby high PEEP levels and high peak and plateau pressures are often required to achieve adequate oxygenation in the context of COVID-19 ARDS.[59] Administration of nephrotoxic medications, such as antibiotics, may also contribute to the development of AKI in patients already at high risk.

ASSESSMENT AND INVESTIGATION OF ACUTE KIDNEY INJURY

Initial assessment of any patient with COVID-19 infection should include a full medical history focusing on those comorbidities and patient factors identified as being associated with higher risk for AKI development.[13,46,60] Clinical examination should include the evaluation of volume status and whereby appropriate, hemodynamic assessment. AKI in COVID-19 is defined and classified by the KDIGO criteria-based serum creatinine and urine output changes.[5] Urinalysis is mandatory as it may help to differentiate various causes of AKI and give an indication of potential glomerular involvement, even whereby alterations in kidney function as defined by KDIGO criteria are absent. This has been observed in one study whereby urinalysis was positive for proteinuria in 65.8% and hematuria in 41.7%, while only 4.7% of the patients met KDIGO criteria for AKI.[61]

Biomarkers of Acute Kidney Injury

Novel biomarkers of AKI in the evaluation of C19-AKI have been evaluated in several studies. Neutrophil gelatinase-associated lipocalin (NGAL) is produced in the distal nephron and its synthesis is upregulated in response to kidney injury and may predict the need for RRT requirement and in-hospital mortality.[62,63] A small observational trial of 17 patients with COVID-19-positive admitted to a Japanese ICU showed that elevated urinary NGAL on admission to the ICU was associated with the development of AKI during their stay.[64] Of note, patients with elevated urinary NGAL had a longer duration of mechanical ventilation and ICU length of stay which may reflect the effect of AKI; however, increased NGAL levels have also been observed in ventilator-associated lung injury.[65] The type-1 transmembrane glycoprotein KIM-1 is expressed in proximal tubular epithelial cells and has been shown to be associated with AKI development.[66] A recent study has shown that KIM-1 was significantly elevated in patients with COVID-19 with, compared with those without AKI ($P = .005$) and was significantly elevated in the patients with COVID-19 that had to be transferred to the ICU.[67] The use of other biomarkers such as tissue inhibitor of metaloproteinases-2 (TIMP-2) and insulin-like growth factor binding protein-7 (IGFBP-7) has also been proposed in assessing patients with COVID-19 and a recent study demonstrated that the use of this biomarker combination may identify patients with AKI and infection early.[68,69] Also, increased requirement for RRT in individuals with C19-AKI and high levels of [TIMP-2]x[IGFBP-7], has been observed. While a further study in a cohort of 352

patients found admission soluble urokinase plasminogen activator receptor (suPAR) levels to be predictive of in-hospital AKI and the requirement for RRT.[16,70]

MANAGEMENT OF C19-ACUTE KIDNEY INJURY

As the syndrome of C19-AKI has multiple etiologies, no generalized single management plan can be proposed for use in all cases and there is no evidence that the treatment of C-19 AKI should be managed differently to other causes of AKI in hospitalized patients.[13] Patients admitted with COVID-19 are often intravascularly deplete and fluid resuscitation until euvolemic with vasopressor support whereby required, should be administered according to usual best practice and individualized whereby possible. This is in keeping with recent evidence showing that targeted resuscitation through dynamic hemodynamic assessment reduces the risk of both AKI and respiratory failure.[71] Fluid choice for initial resuscitation should be crystalloid, preferably balanced in those who are critically ill. It has been shown that a composite outcome of death, new RRT, or persistent kidney dysfunction among critically ill patients was reduced with the administration of balanced crystalloids over 0.9% saline. Similar findings in noncritically ill patients were also generated.[72,73] Although subsequent meta-analysis failed to demonstrate a definite benefit for balanced crystalloids over 0.9% saline, other indications, such as hypochloremia or hypernatremia may guide the clinician toward using balanced solutions.[74] Although recent data from a randomized trial on over 11,000 patients in Brazil did not demonstrate a difference in mortality between saline and balanced solutions these data are not directly transferable to severely ill patients with COVID-19 with AKI.[75] These data were from patients with lower acuity (median APACHE II score 12 and SOFA 4) and 40% of the patients were not hypotensive. Median volumes of trial fluid administered were low (mean < 1 L/d) and 68% of all patients received fluid before randomization with significant crossover. Furthermore, following randomization, approximately 30% of the total fluid received by day 3 was nonstudy crystalloid. General management should follow the KDIGO guidelines and include glucose monitoring and control, relevant given the potential association between diabetes, insulin resistance, and COVID-19 infection.[76] Preferably pharmacy lead medication review should be undertaken and pharmacokinetics and drug clearance should be considered as a dose adjustment may be required in AKI for both COVID-19 specific acute therapies as well as other medications. General guidance for nutritional assessment and support in critically ill patients with AKI should be followed especially as COVID-19 infection which is associated with an inflammatory hypercatabolic state, reduced oral intake, and immobilization predisposing to malnutrition and muscle wasting.[77] Where mechanical ventilation is needed lung-protective low tidal volume ventilation strategies as per general ARDS management should be followed.[78–80] Prone ventilation has been reported as beneficial in patients with COVID-19 pneumonitis, and at present no evidence suggests that any effect on intraabdominal pressure and renal blood flow impact on the risk of AKI.[81–83]

COVID-19-SPECIFIC THERAPIES

Several therapeutic agents have emerged as potentially beneficial in COVID-19 infection. Remdesivir, an inhibitor of the viral RNA-dependent RNA polymerase was studied in the Adaptive COVID-19 Treatment Trial (ACTT-1) and demonstrated that compared with placebo, remdesivir shortened the time to recovery although no significant mortality benefit was seen.[84] Of note, however, patients with AKI or CKD were excluded and as such, the clinical effect of remdesivir in C19-AKI remains largely unknown. The RECOVERY trial examined the use of the glucocorticoid dexamethasone at a dose of 6 mg/d for

up to 10 days. The use of dexamethasone reduced the mortality of hospitalized patients receiving invasive mechanical ventilation or oxygen therapy at the time of randomization with further evidence supporting this approach from meta-analysis of systemic corticosteroids in COVID-19.[85,86] The RECOVERY trial also demonstrated a reduced need for RRT in patients not requiring RRT at the time of randomization, with a risk ratio of 0.61 (95% CI 0.48–0.76). More recently a small pilot study from France has also shown a reduction in AKI in COVID-19 infection.[87]

As outlined, there may be significant systemic inflammation complicating COVID-19 infection. This has led to the use of immunomodulatory therapies such as Tocilizumab, an anti-IL-6 receptor monoclonal antibody. The use of Tocilizumab improved survival in critically ill patients receiving organ support in intensive care with an observed reduction in the need for RRT, while the RECOVERY trial demonstrated a reduced 28-day mortality, probability of discharge at 28 days and reduced progression to the composite outcome of mechanical ventilation and death in those not already ventilated in hospitalized patients with hypoxia and systemic inflammation (defined as CRP $\geq$ 75 mg/L).[40,42] Although other therapies have been considered for COVID-19 at the time of writing there is insufficient evidence of clinical efficacy in the management ofC19-AKI.

RENAL REPLACEMENT THERAPY

The indications for RRT in C19-AKI do not differ from AKI complicating other conditions and should consider both patient and disease factors. However, resource limitations in the setting of the pandemic may require further consideration of potential for benefit at the individual patient level.[13] Vascular access should be through the internal jugular and femoral sites with ultrasound directed placement as this increases success rate and reduces complications.[5,13,88,89] Internal jugular access may be associated with lower infection rates compared with femoral in patients with elevated body mass index, but left internal jugular access is associated with higher rates of vascular access dysfunction.[90,91] Internal jugular access may also be preferable in patients whereby prone ventilation is anticipated.[13] In the absence of an emergent indication, multiple trials have failed to demonstrate any impact on mortality using either early/accelerated versus delayed initiation of RRT, and indeed, premature start may be associated with adverse outcomes.[92,93] However, it must be remembered that the ELAIN trial and more recently, the AKIKI2 trial found that an overly delayed strategy may be associated with harm (references) This implies that the exact timing of initiation of RRT in COVID-19 should be on a patient by patient basis considering the full clinical context, not just the degree of kidney dysfunction as measured by conventional means.[94,95] Use of maximal medical management, whereby safe, including loop diuretics, potassium binders, and sodium bicarbonate should be considered before committing to RRT, especially whereby resources may be limited in surge situations. Continuous RRT, prolonged intermittent renal replacement therapy (PIRRT), and intermittent hemodialysis may all be considered depending on local familiarity and resources given there is no evidence for superior outcomes with any one modality of RRT over another. However, continuous RRT may allow more fluid removal and tends to cause less hemodynamic instability, which may be a consideration in critically ill patients with COVID-19.[96] During peak admissions associated with the COVID-19 pandemic, the demand for ICU care and RRT was stretched, and shortages of RRT devices, disposables, and dialysis fluid were described.[97] Approaches to mitigate this included moderating RRT intensity to conserve fluids, running accelerated high clearance RRT or PIRRT to allow machine sharing, in-house preparation of dialysis fluid, and early transition to IHD.[98–100] Peritoneal dialysis (PD) is rarely used in critical care due to concerns regarding unpredictable fluid balance, variable

dialysis adequacy, potential peritoneal infection, and compromised ventilation due to diaphragmatic restriction. Also from a practical standpoint, there may be substantial challenges involved in delivering PD to patients who are ventilated in the prone position and intra-abdominal pressure may be increased. Despite these reservations during surge conditions PD was successfully implemented under certain conditions.[101–103]

Anticoagulation is recommended for RRT unless contra-indicated especially given the proinflammatory and prothrombotic nature of COVID-19 infection. This is especially relevant given that reduced RRT circuit life has been widely reported which has implications on the dose delivered as well as increasing the consumption of consumables and potential exposure of staff to infection risk.[13,104,105] Regional citrate anticoagulation has been shown to be superior to systemic heparin for anticoagulation with RRT and although some centers have reported reduced effectiveness of citrate in patients with COVID-19 others have suggested superiority over heparin.[106,107] Choice of anticoagulation regime is likely to be center dependent, but it is important that if issues with filter lifespan are identified a stepwise approach to optimizing anticoagulation is taken, with the consideration of a shift in modality to IHD, PIRRT, or acute peritoneal dialysis if possible if issues persist.

EXTRACORPOREAL BLOOD PURIFICATION

There has been considerable interest in the use of extracorporeal blood purification (EBP) therapies to modify or remove circulating inflammatory mediators with the aim of mitigating organ damage, including AKI.[108] Given the inflammatory profile associated with COVID-19 this provides the rationale for such a treatment, but, as discussed earlier, the degree of cytokine production is generally not as pronounced in COVID-19 infection as in other causes of ARDS or bacterial sepsis which may confound this approach. Despite these reservations, several extracorporeal blood purification filters received emergency use authorization from the US FDA for the treatment of severe COVID-19 pneumonia in patients with respiratory failure not specifically for AKI. To-date, several single-center case series have been produced with variable results. In a time-series analysis of 44 consecutive COVID-19 cases treated with the AN69ST (oXiris) cytokine adsorbing hemodiafilter a decrease in acute phase proteins was demonstrated with a reduction in IL-6 levels and an observed mortality of 36.3% across the cohort.[109] In a further study on 5 patients using the AN69ST filter a reduction in cytokines levels and improvement of hemodynamic status was also observed and similarly in 37 patients in a further single-center study a reduction in expected mortality was also seen (8.3% compared with the expected rate as calculated by APACHE IV).[110,111] Several studies have reported benefits on the use of the hemadsorption filter Cytosorb whereby improvements in catecholamine use as well as decreases in inflammatory markers were seen.[112] A multi-centre study enrolled 61 patients with COVID-19 treated with the Seraph 100 microbind affinity sorbent hemoperfusion filter which contains polyethylene beads coated with immobilized heparin and allows for broad-spectrum pathogen removal.[113] An overall mortality of 37.3% was observed compared with 67.4% in historical controls ($P = .003$). In addition, multivariable logistic regression analysis yielded an odds ratio of 0.27 (95% confidence interval 0.09–0.79, $P = .016$) in favor of the treatment. However, there are important caveats principally that this was a retrospective analysis with differing local criteria for initiating extracorporeal blood purification therapy and hence the potential for significant selection bias.[114] However, not all EBP interventions have demonstrated such positive findings as a recent randomized controlled pilot study examined cytokine adsorption during the first 72 h after the initiation of venovenous ECMO in severe

COVID-19 demonstrates. Of the 34 patients assessed for eligibility, 17 (50%) were treated with cytokine adsorption but cytokine adsorption did not result in reduced interleukin-6 concentrations after 72 h, compared with the control group. One patient in each group died before 72 h. Survival after 30 days was 3 (18%) of 17 with cytokine adsorption and 13 (76%) of 17 without cytokine adsorption ($P = 0·0016$) These findings were in contrast with the hypothesis of a treatment benefit for patients in the cytokine adsorption group although the study was not powered to detect a mortality benefit, the results are of interest.[115,116] These variable results show that although control of inflammation in the critically ill through immunomodulation may hold promise, more data from large, multicentre trials with robust yet pragmatic endpoints are required.

LONG-TERM OUTCOMES

Early observational data suggest that approximately 50% of patients who have had AKI associated with COVID-19 infection had not recovered to baseline by the time of hospital discharge.[61,117] Similarly, emerging data suggest that C19-AKI may be associated with an increased decline in GFR postdischarge than patients who had AKI from other causes.[118] Data from New York showed that in survivors from AKI who required RRT, 30.6% remained dialysis dependent on discharge with a history of CKD being the only independent risk factor for this association (adjusted OR, 9.3 [95% CI, 2.3–37.8]).[119] In another US-based cohort study from 67 hospitals, 1 in 5 patients developed AKI-RRT, 63% of whom died during hospitalization. Among those who survived to discharge, 1 in 3 remained dialysis dependent at discharge, and 1 in 6 remained dialysis dependent 60 days after ICU admission.[120] Similar results were observed in a German study whereby 67% of patients who had required RRT were dialysis free at hospital discharge and encouragingly at a mean follow-up of 151 days over 90% were dialysis independent.[121]

SUMMARY

Despite early reports, AKI complicating COVID-19 infection is common in hospitalized patients. The development of AKI increases the risk of mortality significantly and therefore, efforts should be made to minimize the occurrence of AKI and limit the progression to more severe stages. Treatment should follow accepted practice guidelines for the general management of AKI given the heterogeneous nature of the potential causes of AKI in this group. To-date, no specific therapies have demonstrated a benefit for patients with C19-AKI. Extracorporeal blood therapies show promise but should be adopted with caution and preferably within a clinical trial. Long-term outcomes from C19-AKI may not be as poor as initially suggested although data are still accumulating.

CLINICS CARE POINTS

- COVID-19 associated AKI resembles AKI due to other causes and therefore these should be excluded where possible.
- Although no specific therapies are available for the treatment of AKI associated with COVID-19 practitioners should follow accepted management guidelines for the treatment of AKI.
- Where possible follow up of patients who have sustained severe AKI should occur to minimise longer term sequelae such as CKD.

DISCLOSURE

The authors have nothing to disclose.

REFERENCES

1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382(8):727–33.
2. Tangcharoensathien V, Bassett MT, Meng Q, et al. Are overwhelmed health systems an inevitable consequence of COVID-19? Experiences from China, Thailand, and New York State. BMJ 2021;372:n83.
3. Wang C, Wang Z, Wang G, et al. COVID-19 in early 2021: current status and looking forward. Signal Transduct Target Ther 2021;6(1):114.
4. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA 2020; 323(11):1061–9.
5. Acute Kidney Injury Work G. Kidney disease: improving global outcomes (KDIGO). Kidney Int Suppl 2012;2:1–138.
6. Wang L, Li X, Chen H, 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(5):343–8.
7. Hirsch JS, Ng JH, Ross DW, et al. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int 2020;98(1):209–18.
8. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area. JAMA 2020;323(20):2052.
9. Fu EL, Janse RJ, de Jong Y, et al. Acute kidney injury and kidney replacement therapy in COVID-19: a systematic review and meta-analysis. Clin Kidney J 2020;13(4):550–63.
10. Yang X, Tian S, Guo H. Acute kidney injury and renal replacement therapy in COVID-19 patients: a systematic review and meta-analysis. Int Immunopharmacol 2021;90:107159.
11. Doidge JC, Gould DW, Ferrando-Vivas P, et al. Trends in intensive care for patients with COVID-19 in England, Wales, and Northern Ireland. Am J Respir Crit Care Med 2021;203(5):565–74.
12. Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int 2020;97(5):829–38.
13. Nadim MK, Forni LG, Mehta RL, et al. COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. Nat Rev Nephrol 2020;16(12):747–64.
14. Fisher M, Neugarten J, Bellin E, et al. AKI in hospitalized patients with and without COVID-19: a comparison study. J Am Soc Nephrol 2020;31(9):2145–57.
15. Casas-Aparicio GA, Leon-Rodriguez I, Alvarado-de la Barrera C, et al. Acute kidney injury in patients with severe COVID-19 in Mexico. PLoS One 2021; 16(2):e0246595.
16. Husain-Syed F, Wilhelm J, Kassoumeh S, et al. Acute kidney injury and urinary biomarkers in hospitalized patients with coronavirus disease-2019. Nephrol Dial Transplant 2020;35(7):1271–4.
17. Sharma P, Ng JH, Bijol V, et al. Pathology of COVID-19-associated acute kidney injury. Clin Kidney J 2021;14(Suppl 1):i30–9.
18. Legrand M, Bell S, Forni L, et al. Pathophysiology of COVID-19-associated acute kidney injury. Nat Rev Nephrol 2021;17(11):751–64.

19. Santoriello D, Khairallah P, Bomback AS, et al. Postmortem kidney pathology findings in patients with COVID-19. J Am Soc Nephrol 2020;31(9):2158–67.

20. Sharma P, Uppal NN, Wanchoo R, et al. COVID-19-Associated kidney injury: a case series of kidney biopsy findings. J Am Soc Nephrol 2020;31(9):1948–58.

21. Ferlicot S, Jamme M, Gaillard F, et al. The spectrum of kidney biopsies in hospitalized patients with COVID-19, acute kidney injury, and/or proteinuria. Nephrol Dial Transplant 2021. https://doi.org/10.1093/ndt/gfab042.

22. Shetty AA, Tawhari I, Safar-Boueri L, et al. COVID-19-associated glomerular disease. J Am Soc Nephrol 2021;32(1):33–40.

23. Kopp JB, Nelson GW, Sampath K, et al. APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. J Am Soc Nephrol 2011;22(11):2129–37.

24. Foster MC, Coresh J, Fornage M, et al. APOL1 variants associate with increased risk of CKD among African Americans. J Am Soc Nephrol 2013;24(9):1484–91.

25. Hassler L, Reyes F, Sparks M, et al. Evidence for and against direct kidney infection by SARS-CoV-2 in Patients with COVID-19. Clin J Am Soc Nephrol 2021;16(11):1755–65.

26. Puelles VG, Lutgehetmann M, Lindenmeyer MT, et al. Multiorgan and renal tropism of SARS-CoV-2. N Engl J Med 2020;383(6):590–2.

27. Westhoff TH, Seibert FS, Bauer F, et al. Allograft infiltration and meningoencephalitis by SARS-CoV-2 in a pancreas-kidney transplant recipient. Am J Transplant 2020;20(11):3216–20.

28. Yao H, Song Y, Chen Y, et al. Molecular architecture of the SARS-CoV-2 virus. Cell 2020;183(3):730–8.e3.

29. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579(7798):270–3.

30. Walls AC, Park YJ, Tortorici MA, et al. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell 2020;183(6):1735.

31. Ni W, Yang X, Yang D, et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. Crit Care 2020;24(1):422.

32. Nath KA, Grande JP, Garovic VD, et al. Expression of ACE2 in the intact and acutely injured kidney. Kidney360 2021;2:1095–106.

33. Ichimura T, Mori Y, Aschauer P, et al. KIM-1/TIM-1 is a receptor for SARS-CoV-2 in lung and kidney. medRxiv 2020. https://doi.org/10.1101/2020.09.16.20190694.

34. Pfister F, Vonbrunn E, Ries T, et al. Complement activation in kidneys of patients with COVID-19. Front Immunol 2020;11:594849.

35. Choudhry N, Li K, Zhang T, et al. The complement factor 5a receptor 1 has a pathogenic role in chronic inflammation and renal fibrosis in a murine model of chronic pyelonephritis. Kidney Int 2016;90(3):540–54.

36. Annane D, Heming N, Grimaldi-Bensouda L, et al. Eculizumab as an emergency treatment for adult patients with severe COVID-19 in the intensive care unit: a proof-of-concept study. EClinicalMedicine 2020;28:100590.

37. Sinha P, Matthay MA, Calfee CS. Is a "cytokine storm" relevant to COVID-19? JAMA Intern Med 2020;180(9):1152.

38. Ragab D, Salah Eldin H, Taeimah M, et al. The COVID-19 cytokine storm; what we know so far. Front Immunol 2020;11:1446.

39. Soy M, Keser G, Atagunduz P, et al. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. Clin Rheumatol 2020;39(7):2085–94.

40. Abani O, Abbas A, Abbas F, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 2021;397(10285):1637–45.

41. Salvarani C, Dolci G, Massari M, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial. JAMA Intern Med 2021;181(1):24–31.

42. The REMAP-CAP investigatorsInterleukin-6 receptor antagonists in critically ill patients with covid-19. New England Journal of Medicine 2021;384(16):1491–502.

43. Desai TR, Leeper NJ, Hynes KL, et al. Interleukin-6 causes endothelial barrier dysfunction via the protein kinase C pathway. J Surg Res 2002;104(2):118–23.

44. Li XQ, Liu H, Meng Y, et al. Critical roles of cytokine storm and secondary bacterial infection in acute kidney injury development in COVID-19: a multi-center retrospective cohort study. J Med Virol 2021;93(12):6641–52.

45. Fajgenbaum DC, June CH. Cytokine storm. N Engl J Med 2020;383(23):2255–73.

46. Cottam D, Nadim MK, Forni LG. Management of acute kidney injury associated with COVID-19: what have we learned? Curr Opin Nephrol Hypertens 2021;30(6):563–70.

47. Klok FA, Kruip M, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020;191:145–7.

48. Rapkiewicz AV, Mai X, Carsons SE, et al. Megakaryocytes and platelet-fibrin thrombi characterize multi-organ thrombosis at autopsy in COVID-19: a case series. EClinicalMedicine 2020;24:100434.

49. Post A, den Deurwaarder ESG, Bakker SJL, et al. Kidney infarction in patients with COVID-19. Am J Kidney Dis 2020;76(3):431–5.

50. Rentsch CT, Beckman JA, Tomlinson L, et al. Early initiation of prophylactic anticoagulation for prevention of coronavirus disease 2019 mortality in patients admitted to hospital in the United States: cohort study. BMJ 2021;372:n311.

51. Investigators R-C, Investigators AC-a, Investigators A, et al. Therapeutic anticoagulation with heparin in critically ill patients with COVID-19. N Engl J Med 2021;385(9):777–89.

52. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. N Engl J Med 2020;383(2):120–8.

53. Akilesh S, Nast CC, Yamashita M, et al. Multicenter clinicopathologic correlation of kidney biopsies performed in COVID-19 patients presenting with acute kidney injury or proteinuria. Am J Kidney Dis 2021;77(1):82–93.e81.

54. Bascunana A, Mijaylova A, Vega A, et al. Thrombotic microangiopathy in a kidney transplant patient with COVID-19. Kidney Med 2021;3(1):124–7.

55. Mancini I, Baronciani L, Artoni A, et al. The ADAMTS13-von Willebrand factor axis in COVID-19 patients. J Thromb Haemost 2021;19(2):513–21.

56. Sharkey RA, Mulloy EM, O'Neill SJ. Acute effects of hypoxaemia, hyperoxaemia and hypercapnia on renal blood flow in normal and renal transplant subjects. Eur Respir J 1998;12(3):653–7.

57. Koyner JL, Murray PT. Mechanical ventilation and the kidney. Blood Purif 2010;29(1):52–68.

58. Joannidis M, Forni LG, Klein SJ, et al. Lung–kidney interactions in critically ill patients: consensus report of the Acute Disease Quality Initiative (ADQI) 21 Workgroup. Intensive Care Med 2020;46(4):654–72.

59. Swenson KE, Swenson ER. Pathophysiology of acute respiratory distress syndrome and COVID-19 lung injury. Crit Care Clin 2021;37(4):749–76.
60. Alvarez-Belon L, Sarnowski A, Forni LG. COVID-19 infection and the kidney. Br J Hosp Med (Lond) 2020;81(10):1–8.
61. Pei G, Zhang Z, Peng J, et al. Renal involvement and early prognosis in patients with COVID-19 pneumonia. J Am Soc Nephrol 2020;31(6):1157–65.
62. Haase M, Bellomo R, Devarajan P, et al. Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis 2009;54(6):1012–24.
63. Albert C, Zapf A, Haase M, et al. Neutrophil gelatinase-associated lipocalin measured on clinical laboratory platforms for the prediction of acute kidney injury and the associated need for dialysis therapy: a systematic review and meta-analysis. Am J Kidney Dis 2020;76(6):826–41.e1.
64. Komaru Y, Doi K, Nangaku M. Urinary neutrophil gelatinase-associated lipocalin in critically ill patients with coronavirus disease 2019. Crit Care Explor 2020;2(8): e0181.
65. Xiao R, Chen R. Neutrophil gelatinaseassociated lipocalin as a potential novel biomarker for ventilatorassociated lung injury. Mol Med Rep 2017;15(6): 3535–40.
66. Han WK, Bailly V, Abichandani R, et al. Kidney Injury Molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. Kidney Int 2002;62(1):237–44.
67. Vogel MJ, Mustroph J, Staudner ST, et al. Kidney injury molecule-1: potential biomarker of acute kidney injury and disease severity in patients with COVID-19. J Nephrol 2021;34(4):1007–18.
68. Fanelli V, Fiorentino M, Cantaluppi V, et al. Acute kidney injury in SARS-CoV-2 infected patients. Crit Care 2020;24(1):155.
69. Kellum JA, Artigas A, Gunnerson KJ, et al. Use of biomarkers to identify acute kidney injury to help detect sepsis in patients with infection. Crit Care Med 2021;49(4):e360–8.
70. Azam TU, Shadid HR, Blakely P, et al. Soluble urokinase receptor (SuPAR) in COVID-19-related AKI. J Am Soc Nephrol 2020;31(11):2725–35.
71. Douglas IS, Alapat PM, Corl KA, et al. Fluid response evaluation in sepsis hypotension and shock: a randomized clinical trial. Chest 2020;158(4):1431–45.
72. Self WH, Semler MW, Wanderer JP, et al. Balanced crystalloids versus saline in noncritically ill adults. N Engl J Med 2018;378(9):819–28.
73. Semler MW, Self WH, Wanderer JP, et al. Balanced crystalloids versus saline in critically ill adults. N Engl J Med 2018;378(9):829–39.
74. Antequera Martín AM, Barea Mendoza JA, Muriel A, et al. Buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children. Cochrane Database Syst Rev 2019;7:CD012247.
75. Zampieri FG, Machado FR, Biondi RS, et al. Effect of intravenous fluid treatment with a balanced solution vs 0.9% saline solution on mortality in critically ill patients: the BaSICS randomized clinical trial. JAMA 2021;326(9):1–12.
76. Santos A, Magro DO, Evangelista-Poderoso R, et al. Diabetes, obesity, and insulin resistance in COVID-19: molecular interrelationship and therapeutic implications. Diabetology Metab Syndr 2021;13(1):23.
77. Thibault R, Seguin P, Tamion F, et al. Nutrition of the COVID-19 patient in the intensive care unit (ICU): a practical guidance. Crit Care 2020;24(1):447.
78. Acute Respiratory Distress Syndrome N, Brower RG, Matthay MA, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute

lung injury and the acute respiratory distress syndrome. N Engl J Med 2000; 342(18):1301–8.

79. Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. JAMA 2010;303(9):865–73.

80. Griffiths M, Meade S, Summers C, et al. RAND appropriateness panel to determine the applicability of UK guidelines on the management of acute respiratory distress syndrome (ARDS) and other strategies in the context of the COVID-19 pandemic. Thorax 2021. https://doi.org/10.1136/thoraxjnl-2021-216904.

81. Shelhamer MC, Wesson PD, Solari IL, et al. Prone positioning in moderate to severe acute respiratory distress syndrome due to COVID-19: a cohort study and analysis of physiology. J Intensive Care Med 2021;36(2):241–52.

82. Weiss TT, Cerda F, Scott JB, et al. Prone positioning for patients intubated for severe acute respiratory distress syndrome (ARDS) secondary to COVID-19: a retrospective observational cohort study. Br J Anaesth 2021;126(1):48–55.

83. Hering R, Wrigge H, Vorwerk R, et al. The effects of prone positioning on intra-abdominal pressure and cardiovascular and renal function in patients with acute lung injury. Anesth Analg 2001;92(5):1226–31.

84. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of covid-19 — final report. New England Journal of Medicine 2020;383(19):1813–26.

85. Group TRC. Dexamethasone in hospitalized patients with COVID-19. N Engl J Med 2020.

86. Group WHOREAfC-TW, Sterne JAC, Murthy S, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. JAMA 2020;324(13):1330–41.

87. Orieux A, Khan P, Prevel R, et al. Impact of dexamethasone use to prevent from severe COVID-19-induced acute kidney injury. Crit Care 2021;25(1):249.

88. Brass P, Hellmich M, Kolodziej L, et al. Ultrasound guidance versus anatomical landmarks for internal jugular vein catheterization. Cochrane Database Syst Rev 2015;1:CD006962.

89. Brass P, Hellmich M, Kolodziej L, et al. Ultrasound guidance versus anatomical landmarks for subclavian or femoral vein catheterization. Cochrane Database Syst Rev 2015;2015(1):CD011447.

90. Parienti J-J, Mégarbane B, Fischer M-O, et al. Catheter dysfunction and dialysis performance according to vascular access among 736 critically ill adults requiring renal replacement therapy: a randomized controlled study. Crit Care Med 2010;38(4):1118–25.

91. Parienti J-J, Thirion M, Mégarbane B, et al. Femoral vs jugular venous catheterization and risk of nosocomial events in adults requiring acute renal replacement therapy: a randomized controlled trial. JAMA 2008;299(20):2413.

92. Gaudry S, Hajage D, Benichou N, et al. Delayed versus early initiation of renal replacement therapy for severe acute kidney injury: a systematic review and individual patient data meta-analysis of randomised clinical trials. Lancet 2020; 395(10235):1506–15.

93. STARRT-AKI Investigators; Canadian Critical Care Trials Group; Australian and New Zealand Intensive Care Society Clinical Trials Group; United Kingdom Critical Care Research Group; Canadian Nephrology Trials Network; Irish Critical Care Trials Group, Bagshaw SM, Wald R, Adhikari NKJ, et al. Timing of initiation of renal-replacement therapy in acute kidney injury. N Engl J Med 2020;383(3): 240–51.

94. Gaudry S, Hajage D, Martin-Lefevre L, et al. Comparison of two delayed strategies for renal replacement therapy initiation for severe acute kidney injury (AKIKI 2): a multicentre, open-label, randomised, controlled trial. Lancet 2021; 397(10281):1293–300.

95. Zarbock A, Kellum JA, Schmidt C, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial. JAMA 2016;315(20):2190–9.

96. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012;120(4):c179–84.

97. Chua H-R, MacLaren G, Choong LH-L, et al. Ensuring sustainability of continuous kidney replacement therapy in the face of extraordinary demand: lessons from the COVID-19 pandemic. Am J Kidney Dis 2020;76(3):392–400.

98. Burgner A, Ikizler TA, Dwyer JP. COVID-19 and the inpatient dialysis unit: managing resources during contingency planning pre-crisis. Clin J Am Soc Nephrol 2020;15(5):720–2.

99. Adapa S, Aeddula NR, Konala VM, et al. COVID-19 and renal failure: challenges in the delivery of renal replacement therapy. J Clin Med Res 2020;12(5):276–85.

100. Lumlertgul N, Tunstell P, Watts C, et al. In-house production of dialysis solutions to overcome challenges during the coronavirus disease 2019 pandemic. Kidney Int Rep 2021;6(1):200–6.

101. Shamy OE, Patel N, Abdelbaset MH, et al. Acute start peritoneal dialysis during the COVID-19 pandemic: outcomes and experiences. J Am Soc Nephrol 2020; 31(8):1680–2.

102. Srivatana V, Aggarwal V, Finkelstein FO, et al. Peritoneal dialysis for acute kidney injury treatment in the United States: Brought to You by the COVID-19 Pandemic. Kidney360 2020;1(5):410–5.

103. Bowes E, Joslin J, Braide-Azikiwe DCB, et al. Acute peritoneal dialysis with percutaneous catheter insertion for COVID-19–associated acute kidney injury in intensive care: experience from a UK Tertiary Center. Kidney Int Rep 2021; 6(2):265–71.

104. Wen Y, LeDoux JR, Mohamed M, et al. Dialysis filter life, anticoagulation, and inflammation in COVID-19 and acute kidney injury. Kidney360. 2020;1(12): 1426–31.

105. Shankaranarayanan D, Muthukumar T, Barbar T, et al. Anticoagulation Strategies and Filter Life in COVID-19 patients receiving continuous renal replacement therapy: a single-center experience. Clin J Am Soc Nephrol 2021;16(1):124–6.

106. Zarbock A, Küllmar M, Kindgen-Milles D, et al. Effect of regional citrate anticoagulation vs systemic heparin anticoagulation during continuous kidney replacement therapy on dialysis filter life span and mortality among critically ill patients with acute kidney injury: a randomized clinical trial. JAMA 2020; 324(16):1629–39.

107. Arnold F, Westermann L, Rieg S, et al. Comparison of different anticoagulation strategies for renal replacement therapy in critically ill patients with COVID-19: a cohort study. BMC Nephrol 2020;21(1):486.

108. Ronco C, Reis T. Kidney involvement in COVID-19 and rationale for extracorporeal therapies. Nat Rev Nephrol 2020;16(6):308–10.

109. Rosalia RA, Ugurov P, Neziri D, et al. Extracorporeal Blood Purification in moderate and severe COVID-19 patients: a prospective cohort study. medRxiv 2020. 2020.10.10.20210096.

110. Zhang H, Zhu G, Yan L, et al. The absorbing filter Oxiris in severe coronavirus disease 2019 patients: a case series. Artif Organs 2020;44(12):1296–302.

111. Villa G, Romagnoli S, De Rosa S, et al. Blood purification therapy with a hemodiafilter featuring enhanced adsorptive properties for cytokine removal in patients presenting COVID-19: a pilot study. Crit Care 2020;24(1):605.

112. Nassiri AA, Hakemi MS, Miri MM, et al. Blood purification with CytoSorb in critically ill COVID-19 patients: a case series of 26 patients. Artif Organs 2021; 45(11):1338–47.

113. Seffer MT, Cottam D, Forni LG, et al. Heparin 2.0: a new approach to the infection crisis. Blood Purif 2021;50(1):28–34.

114. Chitty SA, Mobbs S, Rifkin BS, et al. A multicenter evaluation of blood purification with seraph 100 microbind affinity blood filter for the treatment of severe COVID-19: a preliminary report. medRxiv 2021. 2021.2004.2020.21255810.

115. Rieder M, Duerschmied D, Zahn T, et al. Cytokine adsorption in severe acute respiratory failure requiring veno-venous extracorporeal membrane oxygenation. ASAIO J 2021;67(3):332–8.

116. Supady A, Weber E, Rieder M, et al. Cytokine adsorption in patients with severe COVID-19 pneumonia requiring extracorporeal membrane oxygenation (CY-COV): a single centre, open-label, randomised, controlled trial. Lancet Respir Med 2021;9(7):755–62.

117. Bowe B, Cai M, Xie Y, et al. Acute kidney injury in a national cohort of hospitalized US veterans with COVID-19. Clin J Am Soc Nephrol 2020;16(1):14–25.

118. Nugent J, Aklilu A, Yamamoto Y, et al. Assessment of acute kidney injury and longitudinal kidney function after hospital discharge among patients with and without COVID-19. JAMA Netw Open 2021;4(3):e211095.

119. Ng JH, Hirsch JS, Hazzan A, et al. Outcomes among patients hospitalized with COVID-19 and acute kidney injury. Am J Kidney Dis 2021;77(2):204–15.e201.

120. Gupta S, Coca SG, Chan L, et al. AKI treated with renal replacement therapy in critically ill patients with COVID-19. J Am Soc Nephrol 2021;32(1):161.

121. Stockmann H, Hardenberg JB, Aigner A, et al. High rates of long-term renal recovery in survivors of coronavirus disease 2019-associated acute kidney injury requiring kidney replacement therapy. Kidney Int 2021;99(4):1021–2.

122. Lin L, Wang X, Ren J, et al. Risk factors and prognosis for COVID-19-induced acute kidney injury: a meta-analysis. BMJ Open 2020;10(11):e042573.

123. See YP, Young BE, Ang LW, et al. Risk factors for development of acute kidney injury in COVID-19 patients: a retrospective observational cohort study. Nephron 2021;145(3):256–64.

124. Geri G, Darmon M, Zafrani L, et al. Acute kidney injury in SARS-CoV2-related pneumonia ICU patients: a retrospective multicenter study. Ann Intensive Care 2021;11(1):86.