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Acute kidney injury in patients with COVID-19: an update on the pathophysiology

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Acute kidney injury (AKI) is common in critically ill patients with coronavirus disease 2019 (COVID-19), affecting ∼20–40% of patients admitted to intensive care, and is considered as a marker of disease severity and a negative prognostic factor for survival [1,2].

AKI appears to result from the interaction of multiple variables, as shown in Figure 1, via various basic pathophysiological mechanisms described below.

Fluid balance disturbances leading to prerenal AKI

It has been reported that 11% of COVID-19 patients experience at least one gastrointestinal symptom (nausea, vomiting or diarrhoea), with significantly higher rates of fever >38.5°C, fatigue, shortness of breath and headache. Cardiomyopathy and acute viral myocarditis can both contribute to renal venous congestion, hypotension and renal hypoperfusion, leading to a reduction in glomerular filtration rate [2].

Toxic tubular damage following cytokine release syndrome or rhabdomyolysis

In cytokine release syndrome, a cytokine storm contributes to hypoperfusion-related injury of the renal tubules. Viral infection in alveolar cells results in massive recruitment of immune cells, which produce large amounts of cytokines that can mediate cytokine-mediated AKI [3]. In a study from New York [1,2], 66% of patients had a urinary sodium level of <35 mEq/L, suggestive of a prerenal state. Urinalysis showed 46% of patients had haematuria and 42% had proteinuria.

Rhabdomyolysis can also occur in patients with COVID-19, with skeletal muscle injury reported in 19.3% of COVID-19-positive patients. Moreover, administration of contrast media also potentiates the risk of tubular toxicity.

Angiotensin II pathway activation

Interaction between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and angiotensin II receptors has been proposed as a potential mechanism contributing to infectivity of the virus. The interaction may facilitate SARS-CoV-2-associated kidney injury [4]. Angiotensin-converting enzyme 1 (ACE1) is characterized by a genetic deletion/insertion (D/I) polymorphism in intron 16, which is associated with alterations in circulating and tissue concentrations of ACE. The D allele is associated with a reduced expression of ACE2. D/I polymorphism shows significant geographical variation, with low D allele frequencies in countries with high COVID-19 prevalence and mortality (Europe, China, Korea). ACE polymorphism and susceptibility to SARS-CoV-2 would explain why the African American population develops more severe forms of COVID-19 compared with Western populations.

A complex process driven by virus-mediated injury

In addition to organ dysfunction related to immune dysregulation, emerging evidence suggests a direct cytopathic effect of SARS-CoV-2. Data from an autopsy series of 27 patients showed that SARS-CoV-2 can be detected in multiple organs, with selective tropism for the kidneys, even in patients without a history of chronic kidney disease or those not critically ill with SARS-CoV-2 infection [4]. Immunofluorescence of kidney specimens showed SARS-CoV-2 protein in areas of glomerular epithelial, endothelial and tubular cells, with preferential targeting of glomerular cells [4].

Early post-mortem examinations confirmed that SARS-CoV-2 directly infects human kidney tubular cells and induces acute tubular damage by a direct cytopathic effect and/or through cytotoxic action of $CD68^{+}$ interstitial macrophages, together with tubular deposition of complement C5b-9. Others studies showed that the viral particles consist of microvesicular bodies.

The most common injury observed in autopsy and biopsy examinations is acute tubular injury. All our kidney biopsies revealed, at least, acute tubular necrosis in all patients [5].

Clinical reports have suggested a high prevalence of proteinuria during the course of COVID-19, with 34% and 63% of patients developing significant proteinuria either at the time of admission or during hospitalization, respectively. Some case reports have described patients with heavy proteinuria associated with collapsing glomerulopathy [6]. As for human immunodeficiency virus–associated nephropathy, a second hit, such as ApoL1 variants, appears necessary for initiation of COVID-19-associated collapsing glomerulopathy [6].

A recent case report found multiple wedge-shaped kidney infarctions as a potential cause of COVID-19-associated AKI [7]. In addition, several cases of pauci-immune vasculitis have emerged as well [5].

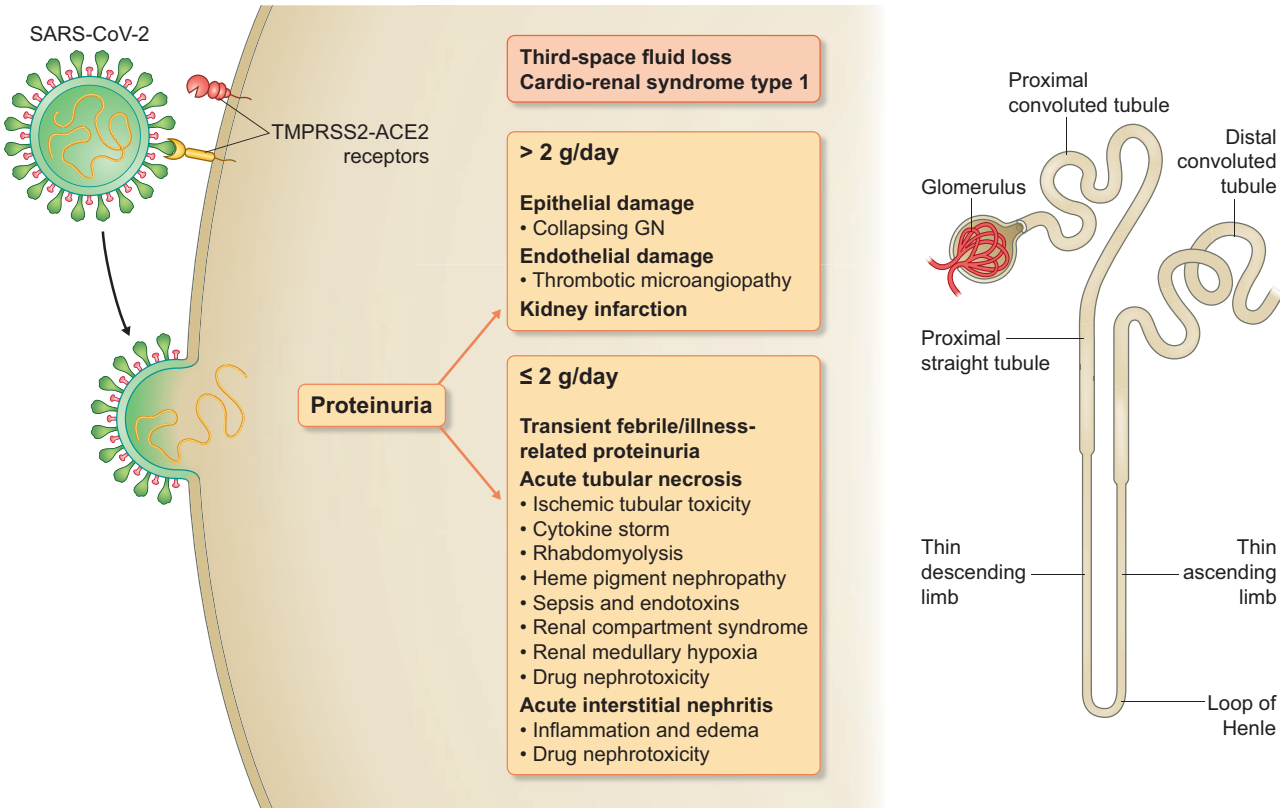

FIGURE 1: AKI results from the interaction of multiple variables.

Endotheliitis, thrombotic events and intravascular coagulation

Disseminated intravascular coagulation (DIC) has been recognized as a life-threatening complication in sepsis. DIC is characteristic of severe COVID-19 illness, with a mortality rate of 71.4%, compared with only a 0.6% survival rate [8]. Further, a post-mortem histopathological analysis of patients with COVID-19 showed prominent erythrocyte aggregates obstructing the lumen of capillaries without platelet or fibrinoid material. However, a recent case report described a patient with signs and symptoms of severe COVID-19 infection that better reflected the pathophysiology and phenotype of complement-mediated thrombotic microangiopathy [9] rather than sepsis-induced coagulopathy or DIC. Indeed, unrestrained complement activation induced by the virus plays a major role in inflammation, endothelial cell dysfunction, thrombus formation and intravascular coagulation, and ultimately contributes to multiple organ failure and death [9].

Organ crosstalk

In the lung–kidney axis, a close bidirectional relationship between alveolar and tubular damage as a consequence of toxic overproduction of cytokines in SARS-CoV-2 has been reported [2]. Acute respiratory distress syndrome may also cause renal medullary hypoxia, which is an additional insult to tubular cells [2].

The heart–kidney axis, or cardiorenal syndrome, can also contribute to AKI in COVID-19 patients with cardiomyopathy and/or acute viral myocarditis [2]. It was found that AKI developed, on average, 9 days after admission, along with secondary infections and acute cardiac damage.

Drug nephrotoxicity

A large proportion of COVID-19 patients will use antibiotics at some point during their treatment period, while various drug trials against SARS-CoV-2, including lopinavir/ritonavir, nucleoside analogues, remdesivir, tenofovir, chloroquine phosphate and hydroxychloroquine sulfate, are currently under way. According to some reports, these patients are at risk of liver and kidney damage, with an increasing risk of renal adverse drug reactions [10].

In conclusion, there is a higher prevalence of AKI in patients with more severe forms of COVID-19. AKI develops early during hospitalization and is concurrent with intubation. The need for dialysis is considered to be a negative survival prognostic factor. Knowledge of AKI can lead to better optimization and prognostication of patients with COVID-19.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no relevant financial interests. K.D.J. serves as a consultant for Astex Pharmaceuticals and Natera.

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