International Journal of Research in Health and Allied Sciences

Journal home page: www.ijrhas.com

Official Publication of "Society for Scientific Research and Studies" [Regd.]

ISSN: 2455-7803 Index Copernicus value [ICV] = 68.10;

REVIEW ARTICLE

Management of Acute Kidney Disease in patients with COVID-19

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ABSTRACT:
Acute kidney failure occurs when your kidneys suddenly become unable to filter waste products from your blood. When your kidneys lose their filtering ability, dangerous levels of wastes may accumulate, and your blood's chemical makeup may get out of balance. Severe COVID-19 infection may damage the kidney and cause acute tubular necrosis, leading to proteinuria, hematuria and elevated serum creatinine. Since the SARS-CoV-2 enters the cells by binding to the angiotensin-converting enzyme 2 receptor, some doctors question its ability to increase the risk and severity of developing COVID-19. Neither clinical data nor basic scientific evidence supports this assumption. The present review summarizes the key aspects of management of acute kidney disease in patients with COVID-19.

Key words: COVID, Acute kidney disease.

Received: 8 March, 2020 Accepted: 26 April, 2020

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This article may be cited as: Biswas A, Pandita V, Kaur G, Chakraborty P, Khan R, Das M. Management of Acute Kidney Disease in patients with COVID-19. Int J Res Health Allied Sci 2020; 6(4):15-18.

INTRODUCTION

The concept of Acute Renal Failure (ARF) has undergone significant re-examination in recent years. Traditionally, emphasis was given to the most severe acute reduction in kidney function, as manifested by severe azotaemia and often by oliguria or anuria. However, recent evidence suggests that even relatively mild injury or impairment of kidney function manifested by small changes in serum creatinine (sCr) and/or urine output (UO), is a predictor of serious clinical consequences. Acute Kidney Injury (AKI) is the term that has recently replaced the term ARF. AKI is defined as an abrupt (within hours) decrease in kidney function, which encompasses both injury (structural damage) and impairment (loss of function). It is a syndrome that rarely has a sole and distinct pathophysiology. Many patients with AKI have a mixed aetiology where the presence of sepsis, ischaemia and nephrotoxicity often co-exist and complicate recognition and treatment. Furthermore the syndrome is quite common among patients without critical illness and it is essential that health care professionals, particularly those without specialisation in renal disorders, detect it easily.[1-3]

ETIOLOGY

The primary causes of AKI include ischemia, hypoxia or nephrotoxicity. An underlying feature is a rapid decline in GFR usually associated with decreases in renal blood flow. Inflammation represents an important additional component of AKI leading to the extension phase of injury, which may be associated with insensitivity to vasodilator therapy. It is suggested that targeting the extension phase represents an area potential of treatment with the greatest possible impact. The underlying basis of renal injury appears to be impaired energetics of the highly metabolically active nephron segments (i.e., proximal tubules and thick ascending limb) in the renal outer medulla, which can trigger conversion from transient hypoxia to intrinsic renal failure. Injury to kidney cells can be lethal or sublethal. Sublethal injury represents an important component in AKI, as it may profoundly influence GFR and renal blood flow. The nature of the recovery response is mediated by the degree to which sublethal cells can restore normal function and promote regeneration. The successful recovery from AKI depends on the degree to which these repair processes ensue and these may be compromised in elderly or CKD patients. Recent data suggest that AKI represents a potential link to CKD in surviving patients.[4- 6]

PATHOPHYSIOLOGY OF PRE-RENAL AKI AND ACUTE TUBULAR NECROSIS (ATN)

Well perfused, healthy kidneys will produce on average 180 L of glomerular filtrate per day, the majority of which is reabsorbed leading to a usual excretion of 1.5 - 2 L of urine. Production of this volume of filtrate is dependent on an adequate glomerular capillary pressure which is the driving force for filtration. Normal glomerular capillary pressure is maintained by afferent arteriole vasodilation and efferent vasoconstriction. This mechanism is known as renal autoregulation. The ability to maintain renal haemodynamics becomes impaired at a renal arterial pressure below 70 mmHg. When this occurs the GFR will fall in proportion to further reduction in blood pressure. The GFR will cease when the renal arterial blood pressure is < 50 mmHg.[7]

A reduction in renal perfusion due to hypotension results in prostaglandin mediated dilation of the afferent renal arteriole and constriction of the efferent glomerular capillary mediated by angiotensin II. However in patients with impaired autoregulation the GFR will fall even if the mean arterial pressure remains within the normal range.

Renal hypoperfusion reduces glomerular capillary pressure and the GFR. The post-glomerular capillary bed which perfuses the tubules will also have diminished blood flow leading to a subsequent ischaemic structural injury to the renal tubules often referred to as ischaemic Acute Tubular Necrosis (ATN). This state is characterized by a rising serum creatinine and a reduced urine volume refractory to further increases in intravascular volume and renal perfusion pressure. Management of this state includes avoidance of fluid overload, maintenance of an adequate mean arterial pressure (> 65 mmHg), correction of electrolyte disorders (potassium) and treatment of the underlying precipitating condition. Such patients may require a temporary period of dialysis support.[8, 9]

COVID19

The CoVs have become the major pathogens of emerging respiratory disease outbreaks. They are a large family of single-stranded RNA viruses (+ssRNA) that can be isolated in different animal species. For reasons yet to be explained, these viruses can cross species barriers and can cause, in humans, illness ranging from the common cold to more severe diseases such as MERS and SARS. Interestingly, these latter viruses have probably originated from bats and then moving into other mammalian hosts — the Himalayan palm civet for SARS-CoV, and the dromedary camel for MERS-CoV — before jumping to humans. The dynamics of SARS-Cov-2 are currently unknown, but there is speculation that it also has an animal origin. The potential for these viruses to grow to become a pandemic worldwide represents a serious public health risk. Concerning COVID-19, the WHO raised the threat to the CoV epidemic to the "very high" level, on February 28, 2020. On March 11, as the number of COVID-19 cases outside China has increased 13 times and the number of countries involved has tripled with more than 118,000 cases in 114 countries and over 4,000 deaths, WHO declared the COVID-19 a pandemic.[8- 10]

EPIDEMIOLOGY AND PATHOGENESIS OF COVID

All ages are susceptible. Infection is transmitted through large droplets generated during coughing and sneezing by symptomatic patients but can also occur from asymptomatic people and before onset of symptoms. Studies have shown higher viral loads in the nasal cavity as compared to the throat with no difference in viral burden between symptomatic and asymptomatic people. Patients can be infectious for as long as the symptoms last and even on clinical recovery. Some people may act as super spreaders; a UK citizen who attended a conference in Singapore infected 11 other people while staying in a resort in the French Alps and upon return to the UK. These infected droplets can spread 1–2 m and deposit on surfaces. The virus can remain viable on surfaces for days in favourable atmospheric conditions but are destroyed in less than a minute by common disinfectants like sodium hypochlorite, hydrogen peroxide etc. Infection is acquired either by inhalation of these droplets or touching surfaces contaminated by them or then touching the nose, mouth and eyes. The virus is also present in the stool and contamination of the water supply and subsequent transmission via aerosolization/feco oral route is also hypothesized. However, neonatal disease due to post natal transmission is described. The incubation period varies from 2 to 14 d. Studies have identified angiotensin receptor 2 (ACE2) as the receptor through which the virus enters the respiratory mucosa. The basic case reproduction rate (BCR) is estimated to range from 2 to 6.47 in various modelling studies. In comparison, the BCR of SARS was 2 and 1.3 for pandemic flu H1N1 2009.[11- 13]

PATHOPHYSIOLOGY OF AKI IN COVID-19

The cause of kidney involvement in COVID-19 is likely to be multifactorial, with cardiovascular comorbidity and predisposing factors (eg, sepsis, hypovolaemia, and nephrotoxins) as important contributors. Cardiorenal syndrome, particularly right ventricular failure secondary to COVID-19 pneumonia, might lead to kidney congestion and subsequent AKI. Similarly, left ventricular dysfunction might lead to low cardiac output, arterial underfilling, and kidney hypoperfusion. Autopsy data indicate that the endothelium is affected in the lung and in the kidney, where it is probably responsible for proteinuria. Furthermore, virus particles were reported to be present in renal endothelial cells, indicating viraemia as a possible cause of endothelial damage in the kidney and a probable contributor to AKI.7 Additionally, SARS-CoV-2 can directly infect the renal tubular epithelium and podocytes through an angiotensin-converting enzyme 2 (ACE2)-dependent pathway and cause mitochondrial dysfunction, acute tubular necrosis, the formation of protein reabsorption vacuoles, collapsing glomerulopathy, and protein leakage in Bowman's capsule.[14- 16]

TREATMENT OF COVID-19-INDUCED AKI

To date, there is no specific treatment for COVID-19-induced AKI. A number of investigational agents are being explored for treatment of COVID-19. However, there are no controlled data supporting the use of any specific treatment (antiviral drugs or immunomodulatory drugs), and their efficacy for COVID-19 is still unknown. Concerning RRT, there are no data supporting the use of different strategies than those used in the context of sepsis. The timing of RRT, modality (intermittent versus continuous) and dose may therefore rely on non-COVID-19 data. Of note, Helms et al. found a high incidence of filter clotting during RRT (especially during continuous veno-venous hemofiltration, with up to 96.6% of filter clotting). If possible, citrate regional anticoagulation (in addition to systemic anticoagulation) should then be preferred. If not, special attention should be paid to administer efficient heparin anticoagulation. To date, there is no evidence for clinically important cytokine removal with RRT during sepsis-induced AKI and no data are available in the setting of COVID-19. In case of persistent proteinuria or hematuria at ICU discharge, COVID-19 patients may benefit from follow-up by a nephrologist.[15- 18]

Implementation of the Kidney Disease: Improving Global Outcomes (KDIGO) supportive care guideline (eg, avoidance of nephrotoxins, regular monitoring of serum creatinine and urine output, consideration of haemodynamic monitoring) in critically ill patients with kidney involvement is likely to reduce the occurrence and severity of AKI in COVID-19, but requires validation. Mitigation of volutrauma and barotrauma through the application of lung-protective ventilation lowers the risk of new or worsening AKI by limiting ventilation-induced haemodynamic effects and the cytokine burden on the kidney. Novel tubular damage biomarkers should be incorporated in future randomised clinical trials to investigate their value in AKI prediction and management. Another important option is to adjust fluid balance according to volume responsiveness and tolerance assessment. This strategy aims to restore normal volume status to avoid volume overload and reduce the risk of pulmonary oedema, right ventricular overload, congestion, and subsequent AKI. Volume depletion at admission might be common in patients with COVID-19, as they typically present with fever and pre-hospital fluid resuscitation is rarely performed. In these cases, hypovolaemia should be corrected to prevent AKI. Relatively high positive end-expiratory pressure strategies and recruitment manoeuvres have been used in ARDS secondary to COVID-19;14 these strategies could further compromise cardiac output in the setting of relative hypovolaemia.[18- 20]

If conservative management fails, RRT should be considered in patients with volume overload, especially those with refractory hypoxaemia. In patients with COVID-19 and AKI, early initiation of RRT and sequential extracorporeal organ support (ECOS) seem to provide adequate organ support and prevent progression of disease severity. This approach, however, should be tested in future clinical trials. Continuous RRT (CRRT) is the preferred modality in haemodynamically unstable patients with COVID-19.[21]

CONCLUSION

To date, there is no specific treatment for COVID-19-induced AKI. A number of investigational agents are being explored for treatment of COVID-19. However, there are no controlled data supporting the use of any specific treatment (antiviral drugs or immunomodulatory drugs), and their efficacy for COVID-19 is still unknown. Concerning RRT, there are no data supporting the use of different strategies than those used in the context of sepsis. The timing of RRT, modality (intermittent versus continuous) and dose may therefore rely on non-COVID-19 data.

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