Raising Awareness of Acute Kidney Injury: Unfolding the Truth

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Acute kidney injury (AKI) is an extremely complex syndrome associated with severe morbidity and mortality.[1] Moreover, AKI may cause loss of kidney function in the long term.[2] Both in developed and developing countries, AKI is common among hospitalized patients, which can be up to 20% of overall patients.[3,4] There is an urgent need to increase knowledge and awareness of AKI, particularly in developing countries, including Indonesia.

AKI is rarely being recognized as it may take place without any apparent symptoms. Severe AKI is commonly found in intensive care unit (ICU) patients. A recent multinational study comprising of thousands of patients from 97 ICUs reported that 57% of patients had developed AKI within 1 week of admission. About 39% of patients had severe AKI (stage 2 or 3), in which 13.5% of them requiring kidney replacement therapy (KRT). AKI in the ICU is an independent risk factor for death, as it may cause systemic effects on other vital organs including the lung, heart, liver, brain and immune system. Some studies have reported that AKI increases susceptibility to infection, doubles the rate of respiratory failure and impairs cardiac function. Common causes of AKI in the ICU are sepsis, cardiac surgery, acute liver failure, intra-abdominal hypertension, hepatorenal syndrome, malignancy, and cardiorenal syndrome.[5]

Considering the substantial impacts of AKI in ICU patients, early implementation of preventive measures should be an essential program which consists of developing AKI risk stratification in the ICU and encouraging the use of novel AKI biomarkers (TIMP-2, IGFBP-7, Cystatin C, IL-18, KIM-1 and NGAL) as well as other risk stratification tools (clinical risk prediction scores, computer algorithms, furosemide stress test). Furthermore, after ICU patients have recovered, AKI survivors are more likely to develop chronic kidney disease (CKD) and end-stage kidney disease (ESKD), imposing significant morbidity in the future. Nephrologist intervention is expected to help patients' recovery, prevent further deterioration of renal function, and mitigate the risk of mortality as well as the development of CKD if patients survive. Recent study has shown that nephrologist intervention was associated with lower risk of starting KRT and progression of AKI.[2,6]

The coronavirus disease 2019 (COVID-19) pandemic has caused more than 800,000 deaths worldwide.[7,8] Kidney involvement in patients with COVID-19 may present as proteinuria or hematuria and may lead to acute kidney injury (AKI). Some initial reports showed that the incidence of AKI in COVID cases was negligible.[9-14] However, later reports suggested that AKI is actually prevalent in patients with COVID-19, particularly in ICU patients. The rate of AKI in COVID-19 patients was more than 20% of hospitalized patients and more than 50% of patients in the ICU.[7,15-18] AKI is now considered as a common complication of COVID-19 and it is also associated with adverse

outcomes, including development or worsening of comorbidities, yet little is known about the pathogenesis or optimal management of COVID-19-associated AKI.

Definition and Classification of AKI (KDIGO 2012)

There was a lack of definition for AKI for quite a long time. At first, the term "acute renal failure (ARF)" was used to describe an acute deterioration in renal function, which usually calls for an emergency KRT.[2] Afterwards, some experts and several specific working groups established the definition and staging of AKI. In 2007, the term ARF was officially replaced by AKI and it was first defined using the RIFLE criteria (Risk, Injury, Failure, Loss, End-Stage).[2,19] The definition has subsequently evolved and currently corresponds to the criteria published in 2012 by KDIGO (Kidney Disease: Improving Global Outcome) working group. KDIGO criteria defines staging of AKI based on serum creatinine level and urine output as follows: (1) AKI stage I with serum creatinine level of 1.5 to 2.0 baseline within 7 days or ≥ 26.4 μmol/L within 48 h and urine output of <0.5 ml/kg/h for 6-12 h; (2) AKI stage II with serum creatinine level of 2.0 to 2.9 times baseline and urine output of <0.5 ml/kg/h for ≥ 12h; and (3) AKI stage III with serum creatinine level of ≥ 3.0 times baseline or an increase in serum creatinine to ≥ 353.6 μmol/L or the initiation of KRT and urine output of < 0.3 ml/kg/h for ≥ 24 h or anuria for ≥ 12 h.[2]

Etiology and Pathophysiology of AKI

AKI is a sudden loss in renal function that may be caused by a wide variety of clinical conditions. However, the causal relationship between AKI and those clinical conditions, whether as the cause or adverse outcomes remains controversial in most studies.[20-23] Etiologies of AKI are very heterogenous and may initiate multiple pathophysiological pathways. These etiologies can be classified into three main categories: pre-renal, intrinsic and post-renal. Pre-renal AKI is caused by renal hypoperfusion that leads to a decreased GFR without any damage to the renal parenchyma, such as hypovolemia (bleeding, volume depletion, etc), impaired cardiac function, or increased vascular resistance. Intrinsic AKI is due to a variety of injury that occurs in the kidney structures (tubules, glomeruli, interstitium or renal blood vessels). Whereas, post-renal AKI etiologies include any acute obstruction of the urinary flow that increases intra-tubular pressure and thus decreases the glomerular filtration rate (GFR).

In the pathophysiological point of view, these etiologies usually cause imbalance of oxygen supply and demand that activates cascade of responses to hypoxemia and oxidative stress. Subsequently, this may lead to persistent inflammation, hyperfiltration, progressive tubular damage, glomerulosclerosis and tubulointerstitial fibrosis, eventually leading to CKD, ESKD, and other associated complications.[24-26] Currently, the pathophysiology of AKI is not completely understood and is known to be mediated by a complex interplay of multiple pathophysiological process.[2] This process will ultimately end up as irreversible renal damage. Based on such pathophysiological perspective, the long-term impact of AKI outcomes depends on the residual renal function and repair capacity after surviving renal stress.[2]

Multiple Impacts of AKI, Prevention and Early Diagnosis

AKI may have multiple clinical impacts, high risk of mortality, and risk of progressive deterioration of renal function, leading to CKD as well as ESKD. Consequently, AKI decreases the quality of life and may contribute to the increasing medical costs and becomes national financial burden covered in the universal health coverage (BPJS Kesehatan).[27,28]

Some recent studies have also identified AKI as risk factor for other adverse outcomes, including stroke, cardiovascular disease, sepsis, malignancy, bone fracture and upper gastrointestinal hemorrhage.[29,30] In a general sense, AKI-related adverse outcomes depend on the presence of preexisting comorbidities, namely cardiovascular disease, hypertension, diabetes mellitus, and most importantly, preexisting CKD.[2] It can be said that presence of comorbidities is a key player in the long-term impact of AKI. Tight control of these comorbidities should prevent the progression of AKI into CKD.[31,32] It is important to preserve

renal function as much as possible to halt further renal deterioration.

Despite great advances in the understanding of risk factors, diagnosis and management of AKI, mortality risk remains high.[33,34] Surprisingly, majority of patients had delayed consultation to nephrologists, which is known to be associated with higher mortality.[35,36] Further prevention measures may include improvement of tools used for early detection and diagnosis, identification of high-risk patients (the elderlies, patients with preexisting comorbidities and preexisting renal impairment), optimization of fluid management, proper antibiotic dosing, nutritional adjustments, withdrawal of nephrotoxic drugs, removal of hyperchloremic solutions and others.[37] Nephrologist intervention is an essential part of entire care in patients with AKI and can influence progression of AKI as well as AKI-associated mortality. Various efforts, specifically fluid adjustment, may prevent the need for KRT and decrease the progression of AKI. Considering the multifactorial nature of AKI, besides nephrologist intervention, AKI demands for multidisciplinary approach as needed, in order to provide best quality of care for patients.[6]

CONCLUSION

AKI is an important complex syndrome with multiple adverse outcomes in hospitalized patients, particularly in ICU patients. The COVID-19 pandemic has increased its complexity and thus proper treatment is vital to reduce morbidity, mortality and medical costs. Some pivotal approaches in managing AKI patients are (1) consideration of multiple risk factors and comorbidities, (2) use of early detection tools and diagnosis, and (3) implementation of preventive and therapeutic intervention as well as early nephrologist intervention as a part of multidisciplinary spectrum that lowers the risk of starting KRT and AKI progression.

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