REVIEW ARTICLE

Renal Disease and Transplantation Forum
2023, vol. 16, no. 2, 33–36

ISSN 2720–2771
e-ISSN: 2720-4189
DOI: 10.5603/RDTF.2023.0012

Katarzyna Kakareko, Irena Głowińska, Alicja Rydzewska-Rosołowska, Tomasz Hryszko

Second Department of Nephrology and Hypertension with Dialysis Unit, Medical University of Bialystok

New aspects in the diagnostics of acute kidney injury

ABSTRACT

Acute kidney injury is a syndrome with a plethora of causes and not fully elucidated pathogenesis. Numerous attempts have been taken for many years to define and reliably diagnose this syndrome. The article reviews recent advances in the diagnostics of acute kidney injury.

Renal Disease and Transplantation Forum 2023, vol. 16, no. 2, 33–36

Key words: acute kidney injury, diagnostics

INTRODUCTION

Acute kidney injury (AKI) is a disease syndrome with a plethora of causes, pathomechanisms, and clinical presentations. As the term is very broad and encompasses many clinical conditions, attempts at formulating a clinical definition of AKI have been made for many years, with more than 30 different definitions proposed over the last half-century. Recent scientific reports indicate that the current definition is also far from being perfect. This article provides an overview of the latest scientific reports on the diagnostics of acute kidney injury.

CHANGES IN THE CLASSIFICATION OF ACUTE KIDNEY INJURY

In recent years, a growing number of reports indicated that creatinine levels may not always be an ideal diagnostic marker for AKI. In 2018, it was observed that an increase in creatinine levels in the course of intensive diuretic therapy in patients treated for acute heart failure was not associated with an increase in the levels of kidney injury markers such as NGAL or KIM-1 and paradoxically translated to better prognosis [1]. A similar lack of association between creatinine and other markers of kidney injury was also observed in two clinical studies: the Systolic Blood Pressure Intervention Trial (SPRINT) [2] and Action to Control Cardiovascular Risk in Diabetes (ACCORD) [3]. As suggested by the results of these studies, an increase in creatinine levels is more likely associated with hemodynamic changes in glomerular perfusion which do not result in structural kidney damage (normal KIM-1 and NGAL concentrations). These reports were used to change the AKI classification by the Acute Disease Quality Initiative (ADQI) [4] consisting in first-stage AKI being subclassified into the following subgrades: 1S — an increase in the concentration of new kidney injury markers is observed without changes in creatinine or diuresis; 1A — an increase in creatinine concentration or reduced diuresis is observed with no changes in the new kidney injury markers; and 1B — an increase in creatinine concentration or reduced diuresis is observed along with an increase in the concentration of new kidney injury markers (Tab. 1). In addition, different forms of stage 1 AKI may change depending on the clinical condition or action taken (Fig. 1).

These changes have significant clinical implications for patients with acute heart failure or exacerbation of chronic heart failure. In these patients, when an increase in creatinine concentration is observed during diuretic therapy with the persistence of fluid retention (swelling, pulmonary circulation stasis) and other causes of AKI (among others, the use of nephrotoxic antibiotics, sepsis, impaired urine outflow) have been excluded, diuretics should not be tapered or discontinued and intravenous fluid therapy should not be initiated.

Address for correspondence:
prof. Tomasz Hryszko,
Second Department of Nephrology and Hypertension with Dialysis Unit,
Medical University of Bialystok,
ul. M. Skłodowskiej-Curie 24A,
15-276 Białystok, Poland,
tel.: 85 831 78 72
e-mail: tomasz.hryszko@umb.edu.pl

Table 1. Novel classification of first-stage acute kidney injury (AKI)

AKI grade	Creatinine level or diuresis	Concentration of biomarkers
1S	Unchanged	Increased
1A	Increased	Unchanged
1B	Increased	Increased

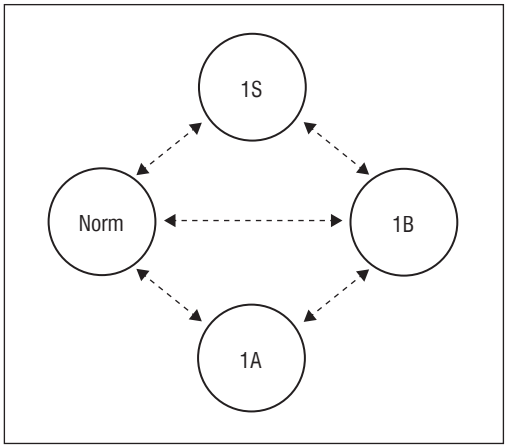

Figure 1. Relationships between the forms of first-stage AKI

A nephrological review is indicated if creatinine levels exceed 3.5 mg/dL or have increased by 100%.

RAPID DIAGNOSTICS AND PREVENTION OF ACUTE KIDNEY INJURY

Along with prevention, early diagnosis of diseases is one of the main principles in modern medicine. Implementation of appropriate therapy at the early stages of the disease reduces organ damage and increases chances for complete recovery. The currently available IT tools allow for the detection of nearly all cases of AKI within about 8 hours [5]. Unfortunately, early diagnosis of AKI does not result in a better prognosis for the affected patients [6]. This may be because the current diagnostic criteria are based on the measurements of creatinine levels or diuresis, both of which are possibly late markers of kidney injury, reflecting damage that has already occurred; the lack of effective AKI treatment methods is another factor contributing to the status quo.

Another approach to reducing AKI progression is to recognize the syndrome as early as in stage 1S, i.e. when serum creatinine level is still normal or before the volume of urine excreted has been reduced. The best studied tool is the NephroCheck kit consisting of two biomarkers: TIMP 2 and IGFBP 7. Unfortunately, studies in populations of patients undergoing intra-abdominal [7] or cardiac surgeries [8] failed to demonstrate a reduction in the frequency of AKI episodes as a result of using this tool. This may be due to two reasons: the biomarker assay kit may identify groups of patients in whom the current methods of AKI prevention have failed, or the current methods of AKI prevention may be too general and thus characterized by low effectiveness. In addition, it appears that, despite their simplicity, the AKI prevention methods proposed by KDIGO are rarely used in hospital settings even in the course of clinical trials. In the studies cited above, only 65% of physicians followed these recommendations in managing their study populations.

At present, the only proven method of AKI prevention is the NINJA (Nephrotoxic Injury Negated by Just-in-time Action) protocol [9]. The protocol consists of a software tool continuously monitoring the medical documentation of hospitalized patients to capture the cases of more than 3 nephrotoxic drugs being administered or aminoglycosides being used for a period longer than 3 days. If such an event is identified, the advisory team analyzes the medical history and results of additional investigations to suggest optimization of therapy to reduce the patient's exposure to nephrotoxins. The NINJA protocol was shown to reduce the frequency of AKI caused by nephrotoxic agents by 24%. Interestingly, the number of AKI episodes in patients who had to be treated with nephrotoxic drugs also decreased. This appears to result from pharmacological surveillance, which most likely reduced the time of exposure to nephrotoxic substances.

IS IT POSSIBLE TO FORESEE THE DEVELOPMENT AND SEVERITY OF ACUTE KIDNEY INJURY?

The possibility to identify patients at high risk of AKI would facilitate implementation of preventive measures which could reduce the risk or even eliminate AKI. Currently, available mathematical models enable identification of patients who will develop in-hospital AKI episodes with efficiency of 56% and identification of episodes of AKI requiring renal replacement therapy within the next 48 hours with efficiency of 90% [10]. Unfortunately, these models have so far worked only in groups

of patients in which they were created; that is, a model working perfectly in hospital A may be completely inefficient in hospital B, even if both hospitals are located within the same city. This is because algorithms developed with the help of modern numerical methods (artificial intelligence) lack a certain degree of flexibility required for different patient populations.

The furosemide test is a simple method facilitating prediction of AKI progression and the necessity of RRT [11]. The test aids in differentiation of patients with acute kidney damage in the prerenal phase from those in whom the renal form of AKI has already developed. The test consists of furosemide administered at a dose of 1 mg/kg of body weight to patients who have not previously taken this diuretic, or 1.5 mg/kg of body weight in patients who have been previously treated with a loop diuretic. Diuresis is measured 2 hours after administration. Diuresis above 200 mL is suggestive of prerenal AKI and potential for therapy optimization (hydration, diuretics in cardiovascular syndrome). On the other hand, values below 200 mL are indicative of the renal form of AKI and potential for disease progression; the need for renal replacement therapy should be taken into account. At present, the furosemide test is the best available tool to help differentiate the two forms of AKI, as shown by the area under the curve value of 87%. The administration of furosemide expedites the assessment of the function of the glomeruli (filtration must be present), proximal tubule (furosemide excretion), ascending arm of the Henle loop (furosemide target site), and patency of the urinary tract.

THE FUTURE OF AKI DIAGNOSTICS

At present, AKI diagnostics are based mainly on data from medical history, laboratory investigations, and imaging studies. In a small percentage of cases, renal biopsy is performed to facilitate description of morphological changes which have occurred in the kidneys. In most cases, presentation corresponds to acute necrosis of renal tubules, which may be due to several factors. In recent years, technological advances have made it possible to use molecular diagnostic techniques in renal biopsy tissues from patients with acute kidney injury. These methods help identify the parts of the nephron that have sustained damage and assess the condition of cells (regeneration, apoptosis, or necrosis) within a particular segment of the nephron [12]. In addition, molecular diagnostics makes it possible to determine the etiology of acute kidney damage (infection, ischemia, or nephrotoxins). Thanks to the Kidney Precision Medicine Project (KPMP), which has been operating for several years now, a molecular atlas has been developed including patterns of injuries in AKI and CKD patients. Thanks to this free online tool, everyone can compare the obtained results with those already in the atlas to try to make a suitable diagnosis. However, one should keep in mind that renal tissue obtained by kidney biopsy is required to use this tool. In recent years, a growing number of reports have been suggesting that similar molecular diagnostics can be pursued in cells obtained from the urine of AKI patients [13]. If those research studies prove capable of complete molecular diagnostics based on material originating from urine, we may witness an emergence of a non-invasive molecular biopsy approach. However, regardless of whether a molecular biopsy is to be carried out using renal biopsy or from the patient's urine, a growing body of data indicates that we will not be able to properly interpret the constellation of activated genes, the degree of protein production, conditions of cells or disturbed metabolic pathways without the help of enormous computing power.

SUMMARY

In daily clinical practice, it is worth remembering that an increase in creatinine levels in the course of cardiorenal syndrome during diuretic therapy does not necessarily result in acute kidney injury. The furosemide test is also worth considering in AKI patients so that patients potentially requiring renal replacement therapy can be identified. As suggested by the literature reports, the furosemide test is currently the best tool to predict severity of acute kidney injury.

CONFLICT OF INTEREST

None to declared.

References

1. Ahmad T, Jackson K, Rao VS, et al. Worsening Renal Function in Patients With Acute Heart Failure Undergoing Aggressive Diuresis Is Not Associated With Tubular Injury. Circulation. 2018; 137(19): 2016–2028, doi: 10.1161/CIRCULATIONAHA.117.030112, indexed in Pubmed: 29352071.
2. Malhotra R, Craven T, Ambrosius WT, et al. SPRINT Research Group. Effects of Intensive Blood Pressure Lowering on Kidney Tubule Injury in CKD: A Longitudinal Subgroup Analysis in SPRINT. Am J Kidney Dis. 2019; 73(1): 21–30, doi: 10.1053/j.ajkd.2018.07.015, indexed in Pubmed: 30291012.
3. Nadkarni GN, Chauhan K, Rao V, et al. Effect of Intensive Blood Pressure Lowering on Kidney Tubule Injury: Findings From the ACCORD Trial Study Participants. Am J Kidney Dis. 2019; 73(1): 31–38, doi: 10.1053/j.ajkd.2018.07.016, indexed in Pubmed: 30291011.
4. Ostermann M, Zarbock A, Goldstein S, et al. Recommendations on Acute Kidney Injury Biomarkers From the Acute Disease Quality Initiative Consensus Conference: A Consensus Statement. JAMA Netw Open. 2020; 3(10): e2019209, doi: 10.1001/jamanetworkopen.2020.19209, indexed in Pubmed: 33021646.
5. Connell A, Montgomery H, Martin P, et al. Evaluation of a digitally-enabled care pathway for acute kidney injury management in hospital emergency admissions. NPJ Digit Med. 2019; 2: 67, doi: 10.1038/s41746-019-0100-6, indexed in Pubmed: 31396561.
6. Wilson FP, Martin M, Yamamoto Yu, et al. Electronic health record alerts for acute kidney injury: multicenter, randomized clinical trial. BMJ. 2021; 372: m4786, doi: 10.1136/bmj.m4786, indexed in Pubmed: 33461986.
7. Göcze I, Jauch D, Götz M, et al. Biomarker-guided Intervention to Prevent Acute Kidney Injury After Major Surgery: The Prospective Randomized BigpAK Study. Ann Surg. 2018; 267(6): 1013–1020, doi: 10.1097/SLA.0000000000002485, indexed in Pubmed: 28857811.
8. Zarbock A, Küllmar M, Ostermann M, et al. Prevention of Cardiac Surgery-Associated Acute Kidney Injury by Implementing the KDIGO Guidelines in High-Risk Patients Identified by Biomarkers: The PrevAKI-Multicenter Randomized Controlled Trial. Anesth Analg. 2021; 133(2): 292–302, doi: 10.1213/ANE.0000000000005458, indexed in Pubmed: 33684086.
9. Goldstein SL, Dahale D, Kirkendall ES, et al. A prospective multi-center quality improvement initiative (NINJA) indicates a reduction in nephrotoxic acute kidney injury in hospitalized children. Kidney Int. 2020; 97(3): 580–588, doi: 10.1016/j.kint.2019.10.015, indexed in Pubmed: 31980139.
10. Tomašev N, Glorot X, Rae JW, et al. A clinically applicable approach to continuous prediction of future acute kidney injury. Nature. 2019; 572(7767): 116–119, doi: 10.1038/s41586-019-1390-1, indexed in Pubmed: 31367026.
11. Rewa OG, Bagshaw SM, Wang X, et al. The furosemide stress test for prediction of worsening acute kidney injury in critically ill patients: A multicenter, prospective, observational study. J Crit Care. 2019; 52: 109–114, doi: 10.1016/j.jcrc.2019.04.011, indexed in Pubmed: 31035185.
12. Menon R, Bomback A, Lake B, et al. Integrated single-cell sequencing and histopathological analyses reveal diverse injury and repair responses in a participant with acute kidney injury: a clinical-molecular-pathologic correlation. Kidney International. 2022; 101(6): 1116–1125, doi: 10.1016/j.kint.2022.03.011.
13. Klocke J, Kim SJ, Skopnik CM, et al. Urinary single-cell sequencing captures kidney injury and repair processes in human acute kidney injury. Kidney Int. 2022; 102(6): 1359–1370, doi: 10.1016/j.kint.2022.07.032, indexed in Pubmed: 36049643.