ACUTE KIDNEY INJURY: EPIDEMIOLOGY, DIAGNOSIS, PROGNOSIS, AND FUTURE DIRECTIONS

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ABSTRACT

Acute kidney injury (AKI) is a common problem highly associated with hospitalisation. AKI is the cause of harmful short-term consequences: longer hospital stays, greater disability after discharge, and greater risk of in-hospital mortality, as well as adverse long-term outcomes, such as progression to chronic kidney disease, development of cardiovascular disease, and increased risk of long-term mortality. The concept of AKI has changed since the introduction of the 'Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease' (RIFLE) classification. More recently, the 'Kidney Disease Improving Global Outcomes' (KDIGO) classification appears to have provided increased diagnostic sensitivity and outcome-prediction capability. Novel biomarkers and further research on the role of the immune system in AKI may help improve the diagnosis, severity, outcome evaluation, and treatment of the condition. In this review we describe the epidemiology, diagnosis, and prognosis of AKI, as well as possible future directions for its clinical management.

Keywords: Acute kidney injury, biological markers, incidence, mortality, outcome.

INTRODUCTION

Acute kidney injury (AKI) affects one in five hospitalised patients,[1] is associated with high expenditure of resources, and leads to adverse outcomes. Over the last 20 years, great efforts have been made to better unveil and characterise the mechanisms and consequences of AKI. The 'Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease' (RIFLE)[2] criteria were the first consensus criteria for the diagnosis of AKI and have been followed by the Acute Kidney Injury Network (AKIN)[3] and the 'Kidney Disease Improving Global Outcomes' (KDIGO)[4] classifications. These tools have provided more robust knowledge on the epidemiology and outcomes of AKI, especially for the critically ill patient.

A new potential pathway for earlier recognition and better outcome prediction has been opened up by research on more sensitive and specific markers. In addition, the pathogenesis of AKI, namely the role of the immune system, is now less elusive and this knowledge may help further categorise AKI and discover new treatment tools. In this review we discuss the current knowledge on the epidemiology, diagnosis, and prognosis of AKI, and on two fields that we believe will change clinical practice in the future: novel urinary and serum biomarkers, and the role of the immune system in AKI.

EPIDEMIOLOGY

The definition of AKI's epidemiology has been, and is still, limited by the lack of studies evaluating AKI in the community setting, as well as a lack of comparisons between intensive care unit (ICU) patients and non-ICU patients.[1] AKI is more common in the ICU and after cardiac surgery.[1] According to a recently published meta-analysis of 312 studies representing almost 50 million patients, the pooled incidence and mortality of AKI in hospitalised adult patients is 21.6% and 23.9%, respectively.[1] The incidence of AKI in critically ill patients has increased over the years,[5]

as has the incidence of dialysis-requiring AKI, especially among the elderly, the male gender, and the black population.[6] Overall, mortality has declined for the critically ill,[5] but the reverse has occurred for AKI patients who need dialysis.[6]

The typical AKI patient is more complex clinically than they were 30 years ago,[7] and is also more complex than the non-AKI patient;[8-12] AKI tends to affect people of older age, who tend to have a higher rate of comorbidities and a greater likelihood of developing severe disease, multiple organ failure, and sepsis. The leading cause of AKI is sepsis, followed by nephrotoxin use and ischaemia. Septic AKI can be considered a separate clinical entity from non-septic AKI. Septic AKI patients are less likely to have pre-existing renal dysfunction and be dependent on dialysis at discharge, but their disease burden is greater and they are more prone to concomitant non-renal dysfunction, require mechanically assisted ventilation and vasoactive drugs, are prone to longer hospital stays, and their probability of dying is higher during their stay in hospital.[13-15]

Given the growing incidence of AKI and consequent increased healthcare burden,[5] measures to prevent AKI have been sought. Some interventions may help reduce mortality in patients with or at risk of AKI, such as perioperative haemodynamic optimisation, albumin in cirrhotic patients, spontaneous bacterial peritonitis, and terlipressin for Type 1 hepatorenal syndrome.[16] In contrast, positive fluid balance, hydroxyethyl starch, and loop diuretics may have deleterious effects in patients with or at risk of AKI.[16] Unfortunately, prediction of the risk of AKI is difficult or even impossible in many situations today, which limits prophylactic action.

DIAGNOSTIC CLASSIFICATIONS

The first definition of AKI, the RIFLE classification, was published in 2004 (Table 1).[2] This classification categorises AKI into three severity classes (risk, injury, and failure) based on serum creatinine (SCr) or on estimated glomerular filtration rate (eGFR), on urine output changes, and two outcome classes - loss of kidney function and end-stage renal disease based on time of dependence of renal replacement therapy. For AKI to be present, renal function deterioration must occur over a period of 7 days and persist for longer than 24 hours. When baseline SCr is unknown and a previous history of chronic kidney disease (CKD) is absent, a baseline eGFR of 75-100 ml/min/1.73 m^2 should be assumed and the Modification of Diet in Renal Disease equation should be used to calculate baseline SCr.

Because even small increases in SCr are associated with poor outcomes,[17] mathematical formulae that estimate GFR presume a steady state that is absent in AKI, and because the accessibility and indications for starting renal replacement therapy differ between institutions and countries, the AKIN classification, also known as 'modified RIFLE', was published in 2007 (Table 2).[3] Instead of relying on either SCr or eGFR, the AKIN classification depends only on the former and requires at least two measurements taken during a 48-hour period, which removes the need for baseline SCr observations. Also, prior to the diagnosis of AKI, urinary obstruction must be excluded and an adequate hydration status must be attained, and no outcome classes are defined. Despite having higher diagnostic sensitivity, AKIN has not yet been proven to confer any advantages over RIFLE with regard to defining the severity and outcomes of AKI.[10,18-24]

Recently, the RIFLE and AKIN classifications have been merged into the KDIGO classification in order to provide simpler and more unified criteria that can be used in clinical activity, research, and public health surveillance[4] (Table 2). In this classification, disease severity has been staged similarly to AKIN except for a simplification of the criteria needed to be classified as Stage 3. Two recent publications, one from a prospective multi-centre study with 3,107 patients[25] and another from a retrospective single-centre study with 49,518 patients,[26] show that the KDIGO classification has better diagnostic sensitivity than RIFLE and AKIN, and an accuracy for predicting mortality that is at least similar to these two classification systems.[25,26]

The aforementioned AKI classifications rely on SCr, eGFR, and urine output, which are surrogate, unspecific, and often unreliable markers of renal dysfunction. Also, they do not take into account the duration or cause of the disease. However, it is essential when using these tools to recognise AKI in clinical practice and to characterise its epidemiology and outcomes in the research setting.

OUTCOMES

Multiple studies have shown patients with AKI experience poorer early outcomes than patients

without renal dysfunction,[8-12,17-30] namely longer lengths of ICU and hospital stay, higher in-hospital and post-discharge mortality, and increased likelihood of discharge to an extended-care facility. Although AKI patients have more comorbidities than non-AKI patients,[8,11,12] this does not seem to account for all of the increased early AKI-associated mortality.[31] Moreover, if even small increases in SCr lead to worse outcomes,[17] then other factors apart from AKI should probably be taken into consideration. Thus, AKI is increasingly thought of as being part of a systemic disease: underlying mechanisms mediate organ crosstalk, leading to multi-organ dysfunction that includes the kidney.[32,33] These systemic mechanisms, and not just AKI, could help explain the decreased survival observed in AKI patients.

The deleterious effects of AKI persist beyond hospitalisation and AKI patients have a greater risk of long-term mortality than non-AKI patients.[34-39] A large, retrospective, multi-centre study suggests that AKI is an independent risk factor for long-term mortality in critically ill patients[35] and a prospective cohort study showed that even Stage 1 AKI is associated with worse adjusted 10-year survival rates.[36]

If the acute insult is inadequately resolved following AKI, persistent inflammation, increased transformation of pericytes into myofibroblasts in response to tubular injury, and build-up of extracellular matrix and vascular rarefaction[40] lead to permanent changes in renal structure and function,[41,42] and ultimately to CKD. The risk of development or quicker progression of CKD occurs in a stepwise pattern according to the severity of AKI.[43] After AKI there is also an increased risk of proteinuria and arterial hypertension.[44,45] These two signs, and GFR decline, are known risk factors for cardiovascular disease,[46-48] which may contribute to the decrement in survival observed among AKI survivors. In fact, development or progression of CKD contributes to increased long-term mortality, even in ICU AKI patients who did not require dialysis at the time of the acute event.[49] Long-term outcomes appear to be more influenced by pre and post-AKI renal function than by the event itself.[50] In the future, pharmacological interventions with the ability to alter the maladaptive response to injury, such as drugs that affect profibrotic pathways,[40] may provide great impact on morbidity and mortality following AKI. Further understanding of the impact of AKI on long-term outcomes and of the causative mechanisms of AKI will have great impact on treatment and risk stratification during hospitalisation, and will guide follow-up care after hospital discharge.

FUTURE DIRECTIONS

Biomarkers

The RIFLE, AKIN, and KDIGO classifications rely on SCr, eGFR, and urine output, which are surrogate unspecific markers of renal dysfunction. Firstly, SCr can be influenced by factors that regulate its synthesis and elimination, such as age, sex, diet, and muscle mass. Tubular secretion is responsible for up to 40% of creatinine elimination and changes in GFR and certain drugs can modulate this mechanism. Additionally, haemodilution caused by fluid overload and inhibition of creatinine synthesis by sepsis can cause a decrease in SCr.[51]

Table 1: 'Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease' (RIFLE) classification of acute kidney injury.[2]

Class	Glomerular filtration rate	Urine output
Risk	↑ SCr × 1.5 or ↓ GFR >25%	<0.5 ml/kg/h (>6 h)
Injury	↑ SCr × 2 or ↓ GFR >50%	<0.5 ml/kg/h (>12 h)
Failure	↑ SCr × 3 or ↓ GFR >75% or if baseline SCr ≥353.6 µmol/l (≥4 mg/dl) ↑ SCr >44.2 µmol/l (>0.5 mg/dl)	<0.3 ml/kg/h (>24 h) or anuria (>12 h)
Loss of kidney function	Dialysis dependence for at least 4 weeks	
End-stage kidney disease	Dialysis dependence for at least 3 months	

GFR: glomerular filtration rate; SCr: serum creatinine.

Table 2: Acute Kidney Injury Network (AKIN)[3] and Kidney Disease Improving Global Outcomes (KDIGO)[4] classifications of acute kidney injury.

Stage	Serum creatinine		Urine output	
	AKIN	KDIGO	AKIN	KDIGO
1	↑ SCr ≥26.5 µmol/l (≥0.3 mg/dl) or ↑ SCr ≥1.5-2×	↑ SCr ≥26.5 µmol/l (≥0.3 mg/dl) or ↑ SCr ≥1.5-2×	<0.5 ml/kg/h (>6 h)	<0.5 ml/kg/h (>6 h)
2	↑ SCr >2-3×	↑ SCr >2-3×	<0.5 ml/kg/h (>12 h)	<0.5 ml/kg/h (>12 h)
3	↑ SCr >3× or if baseline SCr ≥353.6 µmol/l (≥4 mg/dl) ↑ SCr ≥44.2 µmol/l (≥0.5 mg/dl) or initiation of renal replacement therapy	↑ SCr >3× or ↑ SCr to ≥353.6 µmol/l (≥4 mg/dl) or initiation of renal replacement therapy	<0.3 ml/kg/h (24 h) or anuria (12 h)	<0.3 ml/kg/h (24 h) or anuria (12 h)

SCr: serum creatinine.

The evaluation of SCr can also be mildly compromised by the presence of certain compounds (e.g. acetoacetate accumulation in diabetic ketoacidosis).[52] In the presence of renal injury, there is a time lag until renal function begins to decline.[53] In addition, the percentage rise in SCr needed to establish the diagnosis of AKI occurs later in CKD patients when compared with others without previous renal dysfunction.[53] For this reason, using only SCr delays the diagnosis of AKI with respect to the initial insult and may be insufficient to identify AKI when CKD is present.

Secondly, large changes in GFR can be associated with only small changes in SCr[53] and using formulae to estimate GFR is inadequate since they presume a steady state that is absent in patients with AKI. Thirdly, urine output is highly influenced by diuretics. There are nonoliguric forms of AKI: calculating diuresis as a function of body weight can induce diagnostic error in obesity and in cachexia, so a urinary catheter is needed for its accurate measurement and most studies do not evaluate this parameter.[54]

To surpass the limitations of known functional markers, novel biomarkers have been studied: cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), interleukin 18, urinary kidney injury molecule 1, clusterin, liver-type fatty-acid binding protein, and osteopontin. Some of these have been shown to offer great advantages over the clinical classifications: earlier diagnosis of AKI (1-3 days),[55] identification of the probable aetiology of injury,[56] monitoring of treatment,[57] and prediction of outcome.[58] Subclinical AKI, an entity whose diagnosis depends on the rise of these novel biomarkers without changes in SCr and urine output, has been previously associated with poor prognosis,[59] unravelling the potential of outperformance of functional markers.

Nonetheless, strong evidence for the clinical applicability of single biomarkers is still lacking, proper cut-offs remain to be defined, and their specificity may be compromised by concomitant conditions, for example, plasma NGAL is also elevated in sepsis and in cardiac failure.[60,61] The development of studies using biochemical patterns of markers that could anticipate the diagnosis of AKI, assist with differential diagnosis, and predict outcomes was proposed at the 10th Acute Dialysis Quality Initiative (ADQI) meeting.[62] In fact, a study using the relative changes in different urinary biomarkers over time demonstrated that such a combination could help predict short-term outcomes.[63] To date, biomarkers are still not recommended for clinical decision making.[62] However, biomarkers show great promise for changing the course of AKI through early detection of injury and implementation of therapy, which may help decrease the associated health burden.

The Immune System in AKI

Purely haemodynamic or toxic actions appear to be insufficient to explain the pathogenesis of AKI in most cases. Especially in the critically ill, multifactorial mechanisms take place and non-haemodynamic factors such as neurohormonal

pathways and immune activation play an active and important role in AKI and associated multi-organ dysfunction.[33] For example, septic AKI results from an interaction between inflammatory pathways, microcirculatory changes, cellular energetic responses, and tubular cell adaptation to injury.[64]

Multiple key players of innate immunity have been shown to participate in AKI[65] and this may explain why AKI patients are more prone to infection.[9,29] After acute injury, inflammation mediates further renal damage and dendritic cells appear to be key players in summoning action from other immune cells.[66] During resolution after injury, cytokines, growth factors, and peptide molecules regulate M1 and M2 macrophages to cause either regeneration of renal tissue or evolution to fibrosis.[66]

T cells also have a role in AKI: CD4+ cells during the early stages of injury, and CD4+/CD25+/FoxP3− regulatory cells and the newly discovered kidney CD4−/CD8− cells apparently through protective mechanisms.[67] Finally, immune activation following AKI, among other mechanisms, appears to negatively influence function of other organs, such as the lungs, the liver, and the heart.[32,33] The modulation of the immune system could provide a therapeutic route to decrease the severity and improve the outcomes of AKI,[67,68] and potential therapeutic targets are already being sought.

CONCLUSION

Over recent decades, landmark studies and consensus criteria have helped improve our knowledge of AKI and understand its clinical relevance. In the future, the key research priorities must be focussed on earlier diagnosis, better prediction of outcomes, and new treatment modalities. The KDIGO classification aims to unify practice and has been shown to represent an improvement over the previous classifications. Nevertheless, novel biomarkers hold the promise of change from a renal function-based diagnosis towards an injury-defined, subclinical diagnosis, which could help improve outcomes. In addition, these markers could represent more accurate tools for outcome prediction. Further research on the role of the immune system might provide insights into the pathogenic steps behind the acute injury and its consequent resolution, which can become targets for disease and outcome-modifying treatment tools.

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