

Acute Kidney Injury: New Definitions and Beyond

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Abstract

Acute kidney injury (AKI) previously known as acute renal failure is a common clinical syndrome, with multiple etiologies and a complex array of clinical and biochemical changes. AKI affecting all age groups with increasing incidence in hospitalized patients and associated with significant morbidity and mortality. It is until 2004, when the Acute Dialysis Quality Initiative (ADQI) group proposed RIFLE (risk, injury, and failure, loss of function and end-stage renal failure) as consensus criteria for AKI definition and staging. Subsequent refinements and modifications had been proposed to increase specificity and sensitivity of diagnosis and prognosis, including pRIFLE (for children), AKIN and KDIGO. This review focuses on the recent advances in AKI definitions and classifications and highlights area of limitations and controversies.

Keywords: Kidney; Acute renal failure; Acute kidney injury; AKI; RIFLE; AKIN; KDIGO

Introduction

Acute kidney injury (previously known as acute renal failure) is an abrupt decline in renal excretory function characterized by a reversible increase in the blood concentration of creatinine and nitrogenous waste products often with decrease in urine output and by the inability of the kidney to regulate fluid and electrolyte homeostasis [1]. Acute kidney injury (AKI) has been reported to be on rise in both developing and developed countries and it is independently associated with increased morbidity and mortality in children and adults, as well as the subsequent development of chronic kidney disease (CKD) [2]. It is estimated that about 2 million people die of AKI every year and mortality increases as kidney function declines [3]. In this review we will focus on the recent consensus definitions, importance of using unify terms, and severity staging of AKI. Shortcomings and some existing controversies are also discussed.

AKI is a disease that has afflicted humans from time immemorial, but early description of a clearer clinical picture for acute renal failure (ARF) was dated back to the year 1802 by William Heberden under the term 'ischuria renalis' suppression of urine flow. Twenty five years later Richard Bright described his eponymous 'acute Bright disease' as a separate renal disorder. Subsequently, during traumatic shock causalities in the World War I the disease was classified as 'War Nephritis' but soon after war elapsed this clinical entity become forgotten. In 1941 Bywaters and Beall during World War II reported detailed description of impaired renal function associated with war crush injury. However, in 1951 Homer Smith in his textbook entitled The Kidney-Structure and Function in Health and Disease was the one who introduced the term ARF. Whereas AKI was coined by William McNider in 1918, in references to mercury intoxication, long before it revived to be used in more universal means [4, 5].

AKI: why a new term?

Heterogeneous definitions for ARF are spread in medical literature with at least 35 definitions has been used, this lack of uniform definition leads to considerable differences in the reported incidence of ARF range (1-30%) and a diversity of patient outcome (mortality 28 - 82%) [6]. Moreover it has been reported that early and small change in kidney function has a significant clinical impact and associated with unfavorable outcome, although affected cases are indiscriminately classified under ARF [7].

AKI is currently recommended to be used in replace to the previously known term ARF. The aim of change in terminology is to

standardized and uniform definition for this complex clinical entity, with attempt to encompass the wide spectrum from minimal elevation in serum creatinine to a full blown anuric renal failure and requirement for renal replacement therapy (RRT). The term is also proposed to emphasize the reversible nature of most acute renal insults. While the concept of renal dysfunction may require just support, injury indicates the need for organ protection and prevent of further damage [8]. Other assumptions are that 'injury' is more accurately conveys the associated pathophysiology than 'failure', and the English word 'kidney' is more readily understood by the public than the Latin-derived word 'renal' [9].

Definitions and staging of AKI

RIFLE: It is until 2004 the Acute Dialysis Quality Initiative (ADQI) has developed the RIFLE classification by expert consensus intended to standardize the definition of AKI in adults. The acronym RIFLE stands for the increasing severity classes from low level (Risk) for renal dysfunction, to an actual kidney (Injury) and to (Failure) with profound decline of kidney function. This new approach includes variation of serum creatinine (SCr) and urine output as basic components, accordingly three severity grades were defined (Table 1). As severity level increases the specificity of this classification system increases while the sensitivity is reduced. The two outcomes criteria, Loss and End-Stage Kidney Disease, are defined by the time frame of persistent loss in kidney function, 4 weeks and 3 months, respectively [10]. The RIFLE criteria have been validated in over 500,000 patients in several multinational studies, and have become a standard way to classify patients with AKI [11].

pRIFLE: The proposed pRIFLE criteria in children are based on a reduction in estimated creatinine clearance (eCCL) while considering urine output based on body weight. A baseline eCCL was calculated using the Schwartz equation ($120 \text{ ml/min}/1.73 \text{ m}^2$), taking in consideration the large variation in body mass in children [12]. The pRIFLE criteria has been found to be a helpful tool for early detection

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Scheme	Stage	Creatinine Criteria	Urine Output Criteria
RIFLE [10]	R	SCr increase to 1.5-fold or GFR decrease >25% from baseline	<0.5 ml/kg/h for 6 h
	I	SCr increase to 2.0-fold or GFR decrease >50% from baseline	<0.5 ml/kg/h for 12 h
	F	SCr increase to 3.0-fold or GFR decrease >75% from baseline or SCr ≥354 μmol/l (≥4 mg/dl) with an acute increase of at least 44 μmol/l (0.5 mg/dl)	anuria for 12 h
	L	Persistent failure>4 weeks	
	E	Persistent failure>3 months)	
pRIFLE [12]	R	eCCL decrease by 25 %	<0.5 ml/(kg/h) for 8 h
	I	eCCL decrease by 50 %	<0.5 ml/(kg/h) for 16 h
	F	eCCL decrease by 75% or eCCI <35 ml/min/1.73 m ²	<0.3 ml/kg/h for 24 h or anuria for 12 h
	L	Persistent failure>4 weeks	
	E	Persistent failure>3 months)	
AKIN [13]	1	SCr increase ≥26.5 μmol/l (≥0.3 mg/dl) or increase to 1.5–2.0-fold from baseline	<0.5 ml/kg/h for 6 h
	2	SCr increase >2.0–3.0-fold from baseline	<0.5 ml/kg/h for 12 h
	3	SCr increase >3.0-fold from baseline or SCr ≥354 μmol/l (≥4.0 mg/dl) with an acute increase of at least 44 μmol/l (0.5 mg/dl) or need for RRT	<0.3 ml/kg/h for 24 h or anuria for 12 h or need for RRT
KDIGO [14]	1	1.5 to 1.9 times baseline or ≥0.3 mg/dl (≥26.5 μmol/l) increase	<0.5 ml/kg/h for 6 to 12 h
	2	2.0 to 2.9 times baseline	<0.5 ml/kg/h for ≥12 h
	3	3.0 times baseline or increase in SCr to ≥4.0 mg/dl (≥353.6 μmol/l) or initiation of RRT or in patients <18 years a decrease in eGFR to <35 ml/minute per 1.73 m ²	<0.3 ml/kg/h for ≥24 h or anuria for ≥12 h

RIFLE: risk, injury, failure, loss, end stage; pRIFLE: pediatric RIFLE; AKIN: Acute Kidney Injury Network; KDIGO: kidney disease improving global outcomes; SCr: serum creatinine; GFR: glomerular filtration rate; eGFR: estimated GFR; eCCL, estimated creatinine clearance; RRT: renal replacement therapy.

Table 1: Diagnostic criteria and staging of acute kidney injury

of AKI, being sensitive and specific and related to length of hospital stay, the need for renal replacement therapy and higher mortality rate in pediatric ICU setting [13].

AKIN: The Acute Kidney Injury Network (AKIN) criteria proposed some relevant modifications to the RIFLE criteria. These modifications involved a broadening of the ‘risk’ category of RIFLE to include small increment in serum creatinine of at least 0.3 mg/dl even if this does not reach the 50% threshold but provided that it is reached in a 48-hours window. AKIN also categorizing individuals who receive RRT as stage 3 regardless of what their serum creatinine or urine output is at the point of initiation and the estimated glomerular filtration rate (eGFR) criteria have been eliminated. AKIN proposed that stages 1, 2, and 3 be used instead of R, I, F and omitted the L and E stages from RIFLE, which are considered measures of outcome rather than a part of diagnosis [14].

KDIGO: In 2012, a modified definition that merge RIFLE criteria and AKIN has been proposed by the Kidney Disease Improving Global Outcomes (KDIGO) work group. This aimed to establish uniform definition and classification of AKI expected to be adopted in research and public health settings [14,15]. AKI was defined as any of the following: increase in SCr by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 hours; or increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume <0.5 ml/kg/hour for 6 hours. AKI can be caused by sepsis, hypoperfusion, drugs and toxins among many others [16]. The causes and individual risk profile should be determined whenever possible according to KDIGO recommendations (Table 2) [14].

Limitations and Controversies

RIFLE criteria and its modifications are widely accepted as a worldwide standard for defining and staging AKI and their clinical application can be used easily in many patients and mostly requires little clinical interpretation [17]. These universal criteria help researchers from different localities and populations to reduced variation in reporting of incidence, staging and patient outcomes, and facilitate comparison between results. However, the new criteria are not totally perfect and during their practical application some concerns and limitations have been observed [18, 19].

The incidence and outcome of AKI have varied according to health care settings (hospital ward, ICU, and population based), parameters used for the criteria (SCr alone or both SCr and urine output), baseline or estimated creatinine, and timing of study endpoint (hospital mortality, post-discharge follow up) [20].

Comparison between RIFLE and AKIN does not demonstrate clear superiority of one to another, they have quite similar rate of incidence detection, although AKIN has the advantage of including more patient with minor SCr change (stage 1) [21]. In critically ill patient KDIGO criteria was reported to be more sensitive in the detection of AKI than RIFLE and AKIN [22], with better prediction of in-hospital mortality than RIFLE but similar to AKIN [23]. The recognized imprecision in determining change in GFR led to removal of GFR from AKIN classification so that an absolute or percentage increase in creatinine alone or in combination with oliguria has become the new consensus definition of AKI. AKIN criteria also does not need baseline SCr but requires at least two SCr determinations within 48 hours, moreover, AKIN emphasized the need for exclusion of hypovolemia and urinary

Exposure	Susceptibility
Sepsis	Dehydration or volume depletion
Critical illness	Advanced age
Circulatory shock	Female gender
Burns	Black race
Trauma	Chronic kidney disease
Cardiac surgery (especially with cardiopulmonary bypass)	Chronic diseases (heart, lung, liver)
Major non-cardiac surgery	Diabetes mellitus
Nephrotoxic drugs	Cancer
Radiocontrast agents	Anemia
Poisonous plants and animals	

Table 2: Causes of AKI: exposures and susceptibilities for nonspecific acute kidney injury.

obstruction before AKI is diagnosed [13].

The KDIGO criteria eliminate GFR and adding a time frame according to absolute level of (≥ 0.3 mg with 48 hours) or relative increase SCr (≥ 1.5 times baseline value within 7days). A new class to include patients with acute kidney damage super imposed chronic kidney disease (CKD) has been added [14]. In a recent retrospective study of hospitalized children, comparison between pRIFLE, AKIN and KDIGO revealed differences in AKI incidence and disparity in staging, while demonstrated excellent interstage discrimination and high correlation with respect to outcomes [24]. Variation between different criteria in diagnostic accuracy and outcome predictability makes none of the current criteria optimal, therefore AKI definition and classification considered to be a work in progress [25].

It is recognized that GFR can be difficult to measure directly, and biochemical surrogate are used, currently SCr elevation above baseline is used for the diagnosis of AKI, which indicate the importance of knowing the reference serum creatinine. However, AKI often begins before patients are admitted to hospital and for many patients there is no record of baseline kidney function. Therefore, if baseline SCr value is not available the Modification of Diet in Renal Disease (MDRD) formula is used with creatinine clearance (CCL) of 75ml/min/1.73m² to “back-calculate” SCr level [10]. Although convenient, MDRD estimation is based on the assumption that the patients have near normal pre-morbid renal function i.e. the endogenous generation of creatinine from muscle is in balance with renal clearance, which is not the case in individuals with chronic kidney disease (CKD) [26]. This estimation could be more reliable in children than adults due to the reduce prevalence of CKD [27].

The major problems of AKI classifications are that they aim to be diagnostic as well as prognostic, despite the fact that they include subjective criteria like initiation of RRT and the serial SCr measurements [28]. Several limitations in relation to the use of SCr as renal function indicator include a wide variation with repeated measurements has been observed even in healthy individuals, and tubular secretion accounted for approximately 10–40% of SCr elimination a mechanism which is augmented when GFR decline. Other factors could influence SCr level such as age, gender, race, body weight, drugs, diet, volume of distribution, muscle mass and muscle metabolism [18]. SCr alteration does not accurately reflect the GFR in a patient who is not in steady state, it increases slowly relative to the amount of lost filtration function, accordingly creatinine is not a real-time marker of GFR during rapidly changing kidney function and this may delays diagnosis of AKI for about 48-72 hours post injury, a critical time for intervention and prevention of further damage [29-31].

Urine output is easy and inexpensive to determine but can be

significantly change by the use of diuretics, fluid therapy and by hemodynamic status [26, 32]. To be measured accurately it needs bladder catheterization which is difficult in routine clinical practice outside the ICU settings.

The European Renal Best Practice (ERBP) work group in a position statement on KDIGO guidelines recommends using a uniform AKI definition based on both SCr and urine output and stresses on the need to use the first available (admission) serum creatinine in that episode as baseline creatinine rather than historical or estimated creatinine based on eGFR and to use 6- to 8-hour observation blocks of urinary output calculated on ideal weight (age, length, gender norms, edema free weight) rather than the true weight with no receiving diuretics [33]. However admission value of SCr is most probably elevated and baseline creatinine is better to be the most recent test before the current illness, or among several measurements is that one judge to represent patient’s premorbid renal function [19].

The recent development of AKI novel biomarkers, such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), liver-type fatty acid binding protein-1(L-FABP), IL-18, Cystatin-C, tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) might allowed the development of better approach for early detection of kidney dysfunction, localization of injury, stage-specific treatment, monitoring of therapeutic intervention and help in initiation of effective prevention within the appropriate time [30,34]. The incorporation of new biomarkers into current consensus of AKI definitions could represent an important and very useful improvement in diagnosis, severity assessment and patient prognosis [32]. Although e-alert and automated detection algorithm might be adjunctive in clinical decision, clinical judgment in diagnosis, grading, selection of type and time of therapeutic intervention remains crucial [35].

Conclusion

The introduction of RIFLE, pRIFLE, AKIN and more recently KDIGO bring more uniformity in diagnosis and staging of AKI and facilitate comparisons between results. These classifications have been tested in numerous studies and currently become acceptable criteria for patient diagnosis and stratification indicating their recognition by medical community. Despite of the mentioned limitations which do not detract the values of these criteria, they will be continue in use until a more robust method with high specificity and sensitivity become available. Particular interest is relay on the development of new AKI biomarkers which appear to hold promise to replace or complement conventional markers, although still not widely available and require more study to validate their clinical utilities and standardize their measurements.

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