Definition and epidemiology of acute kidney injury

Venuste Nsengiyumva*, Grace Igiraneza*, Norbert Lameire**

*Department of Internal Medicine, University Teaching Hospital Of Kigali
**University Hospital, Gent, Belgium

ABSTRACT

This first paper in a continuous medicine education series on acute kidney injury (AKI) provides recent information on definition, staging and epidemiology of AKI, focusing on resource-limited sub-Saharan countries, including Rwanda.

A first part of the paper discusses the several causes of the AKI syndrome, classified according to their traditional major pathophysiological mechanisms in "prerenal, post renal and intrarenal, intrinsic AKI". Some differential diagnostic approaches are provided, emphasizing that all AKI is not acute tubular necrosis.

The history of the modern definitions and classification systems of AKI, starting with RIFLE, AKIN and finally KDIGO is described and the differentiation of acute versus chronic kidney disease is discussed, in particular when a baseline serum creatinine is not available.

Finally, the global epidemiology, and some data, be it incomplete, on epidemiology of AKI in sub- Saharan Africa countries and Rwanda are provided.

Key words (MeSH)
Acute kidney injury; definition and classification; epidemiology; Africa ; Rwanda

INTRODUCTION

This initial paper reviews the definitions, staging systems and epidemiology of acute kidney injury (AKI) with a focus on AKI in a low-income country such as Rwanda.

The basic diagnostic, clinical, laboratory investigations, short and long-term prognosis, selected non-dialytic and dialytic therapeutic aspects of AKI, and short and long-term prognosis of the patients with AKI will be discussed in future reviews.

Because of limited access to specialized nephrology care, increased awareness of the clinical situations associated with AKI, and the implications of failing to detect it must be further understood at all levels of the health care system, especially in low and middle income countries (LMICs), like Rwanda [1, 2]. A practical and easily accessible education strategy focused on providers at the forefront of health care delivery is indispensable in achieving this goal. We hope that these papers will contribute to a wider knowledge of AKI in the resource-limited setting.

General definition and major causes of AKI

Acute kidney injury, previously termed acute renal failure (ARF), is a syndrome characterized by an abrupt deterioration in kidney function, defined by an acute fall in glomerular filtration rate (GFR) that disrupts metabolic, electrolyte and fluid homeostasis over a period of hours to days. The spectrum of AKI extends from less severe forms of injury characterized by a minimal rise in serum creatinine (SCr) to more advanced injury where a patient may require renal replacement therapy (RRT) [3].

The causes of AKI, based on their underlying pathophysiology, are decreased kidney perfusion, (hemodynamic AKI), obstruction of the urinary tract (post renal AKI), parenchymal kidney diseases other than acute tubular necrosis (ATN) (also named intrinsic or intrarenal AKI), and ATN. In ATN, the fall in GFR is the consequence of renal damage caused by ischemia-reperfusion; for example postcardiac surgery, exposure to extrinsic or intrinsic nephrotoxins or by a combination of both ischemia and nephrotoxicity in sepsis-associated AKI.

It is important to identify causes of intrinsic or parenchymal AKI other than ATN because specific treatment of them can reverse the decline in GFR whereas treatment for ATN is only supportive.

The most important diseases causing intrinsic, but non-ATN parenchymal AKI include aggressive glomerular diseases, vasculitis, acute interstitial nephritis, severe pyelonephritis, thrombotic microangiopathies, cast nephropathy, renal infarction and intrarenal emboli.

Most of these diseases have either a more or less typical clinical presentation or are part of a systemic disease, including many infectious diseases. They often present with proteinuria, macro-or microhematuria, or pyuria. Confirmation of acute parenchymal diseases causing the syndrome of AKI often requires specific immunological testing or renal histological examination by kidney biopsy. Although a discussion of these non-ATN forms of AKI is beyond the scope of this paper, the clinician confronted with a patient with AKI should include all these diseases in the differential diagnosis.

This paper focuses on AKI caused by hemodynamic (pre-renal) AKI and ATN in adults.

Acute versus chronic renal failure

In the absence of pre-existing medical records, a major problem particularly in resource-limited settings is to solve the question of whether the renal failure is acute or chronic. Both AKI and chronic kidney disease (CKD) are risk factors for each other. In other words, CKD is a significant risk factor for AKI and many recent cohort studies suggest that episodes of AKI, even with only small transient decreases in kidney function are associated with the subsequent development of CKD (for excellent reviews see [4-6]).

Where the presence of oliguria supports a diagnosis of acute kidney failure, laboratory values do not clearly discriminate between acute versus chronic kidney diseases. Clues to a chronic kidney disease are older age, the presence of pre-existing chronic illness such as hypertension, diabetes, and vascular disease, and the presence of "uremic" symptoms- pruritus, fatigue, nausea, anorexia, altered taste sensation, and/or hiccup. An important clue for chronicity is an ultrasound finding of small kidneys (< 9 cm), often with poor cortico-medullary differentiation.

Definition and staging of AKI

Over many decades the definition of AKI has proven to be controversial with more than 35 different definitions found across the medical literature. This ambiguity has resulted in notable differences in reported incidence (1-30%) and patient outcomes with mortality rates between 28-82% [7].

Several staging systems of AKI have been proposed, but all are based on reports stating that even small increases in SCr are linked to worsening short-term and long-term prognosis [8, 9]. Because of the difficulty to compare findings across epidemiological studies, the lack of standardization has led to a series of attempts to formulate a consensus definition.

In 2004, the Acute Dialysis Quality Initiative (ADQI) Group proposed the first international and interdisciplinary consensus definition of AKI [10]. The ADQI work group proposed a classification scheme with three strata based on the magnitude of the increase in serum creatinine level and/or the duration of oliguria. These three strata were combined with two outcome stages defined by the need for and duration of renal replacement (RRT) therapy, which resulted in the five-tiered RIFLE classification:

- **R**isk of renal dysfunction
- **I**njury to the kidney
- **F**ailure of kidney function
- **L**oss of kidney function
- **E**nd-stage kidney disease.

AKI was defined as a rise in SCr of ≥50% from its baseline value and/or a fall in the GFR by ≥25%, and/or a decrease in urine output (UO) below 0.5 ml/kg/h for 6 h or more. RIFLE also required that the ≥50% rise was known or presumed to have developed over ≤ 7 days.

In 2007 the Acute Kidney Injury Network (AKIN) proposed some small modifications of the RIFLE classification that includes the 3 stages of RIFLE with the addition of a 0.3 mg/dL or higher absolute increase in the SCr above baseline developing in ≤48 hours [11], even if this does not reach the 50% threshold. In addition, AKIN categorized patients as 'failure' if they are treated with renal replacement therapy (RRT) regardless of what their SCr or urine output is at the point of initiation. AKIN also proposed that stages 1, 2 and 3 be used instead of R, I and F. The Loss and End-stage categories of RIFLE were dropped as they are outcomes, and not stages.

In an attempt to simplify further the definitions developed by RIFLE and AKIN, the most recently developed Kidney Disease Improving Global Outcomes (KDIGO) guidelines, published in 2012 merged both earlier definitions and also modified the criteria for stage 3 AKI, including any rise in SCr to ≥ 4.0 mg/dl, when the rise is ≥ 0.3 mg/dl or ≥ 50% within the time frames as noted above. The urine output criteria as in RIFLE and AKIN were maintained in KDIGO [12]. It should be noted that both SCr and UO criteria are important predictors of AKI and the use of the KDIGO definition without assessment of UO underestimates the incidence and grade of AKI and can delay diagnosis [13]. In all three proposed definitions of AKI, determination of baseline SCr is very important in AKI diagnosis and classification. Inaccurate determination of baseline SCr can misclassify AKI and subsequently affect the prognostication of AKI-related outcomes [14, 15].

When preadmission baseline SCr values are not available, as is frequently the situation in resource-limited countries, the Acute Dialysis Quality Initiative recommends that an estimated baseline SCr could be calculated using the Modification of Diet in Renal Disease (MDRD) formula [16]. However, back-calculating baseline SCr with the MDRD formula can misclassify AKI and overestimate the incidence of AKI in both CKD [17] and ICU patients [18].

Studies have shown that outpatient SCr is a more robust assessment of baseline renal function than inpatient SCr, because it represents a steady state and is not altered by a preadmission ongoing acute illness [19]. However, there is currently no consensus on how to optimally determine baseline SCr when multiple preadmission SCr measurements are available, leading to heterogeneity across research studies [20, 21]. Thongprayoon et al [22] found that using the minimum value and not the average preadmission SCr as a baseline kidney function was more performant not only to detect more AKI cases, but it provided also a better predictive ability for 60 day mortality. Since the definition of AKI covers only the first 7 days of AKI, the KDIGO AKI guidelines also introduced the term of acute kidney disease (AKD). AKD refers to a condition in which the renal pathophysiological processes are still ongoing and AKI stage 1 or greater [as defined by the KDIGO criteria] is present for longer than 7 days after an AKI initiating event [12, 23]. AKD that persists beyond 90 days is considered to be CKD.

The proposed criteria for AKD encompass the definition for AKI, but may also be defined by a glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 for <3 months, a decrease in GFR by ≥ 35% for <3 months, or an increase in SCr by >50% for <3 months.

Table 1 summarizes the KDIGO definitions and a comparison between the staging criteria between KDIGO and the RIFLE criteria adapted to children with AKI, i.e. the pRIFLE staging system.

In individuals younger than 18 years, stage 3 in the KDIGO staging system includes an acute decrease in estimated glomerular filtration rate (eGFR) to <35 mL/min per 1.73 m² [12].

The pRIFLE staging system [24] uses the original Schwartz equation [25] to calculate estimated creatinine clearance. The Schwartz formula accounts for the expected normal changes in SCr that accompany somatic growth and is still the most popular formula for the estimation of GFR in children (for review [26]). The pRIFLE modification quantitates the change in estimated creatinine clearance rather than absolute changes in SCr as used in the adult version of RIFLE.

The introduction of the RIFLE, AKIN and KDIGO staging criteria have brought uniformity to the diagnostic process of AKI. This uniformity allows comparison between studies and populations [27].

Global epidemiology of AKI

Compelling evidence indicates that in both pediatric [28, 29] and adult populations [2, 30, 31] the global burden of AKI is enormous. In the first meta-analysis conducted to estimate the world incidence of AKI, it was found that approximately 1 in 5 adults (21.6%) and 1 in 3 children (33.7%) experienced AKI as defined by KDIGO during a period of hospital care [31]. The AKI associated mortality rate in this meta-analysis was 23.9% in adults and 13.8% in children. This figure was found to be inversely correlated to country Gross Domestic Product (GDP) percentage spent on total health expenditure. This meta-analysis mainly included studies from high income countries (Europe, North America, Japan, Australia and New Zealand). Only a small amount of studies came from Africa and Asia because it is difficult to find accurate data on the incidence of AKI in resource-limited countries. This is due to few data registries, scarcity of nephrologists, and few nephrology care units and dialysis centers. Although the burden of AKI in resource-limited countries is difficult to estimate the ISN Global Snapshot, [32], an international cohort study asking physicians from around the world to record AKI on a single day obtained information on >4000 pediatric and adult patients from 72 countries on 6 continents. The snapshot data reveal significant similarities in the risk factors and causes of AKI worldwide, suggesting that the burden of AKI is equally important in resource-limited countries.

Major heterogeneity also exists in the epidemiology of AKI in critically ill patients admitted to an Intensive Care Unit (ICU) where significant differences in risk factors, etiology, management and outcomes based on available resources are reported. Bouchard et al [33] have shown that patients in emerging countries were more likely to have glomerulonephritis (GN) and acute interstitial nephritis, while those in developed countries had higher reported rates of prerenal AKI, sepsis, and acute tubular necrosis. Residence in an emerging country was associated with more than a two-fold increase in hospital mortality and a threefold lower rate of renal recovery in survivors. Hoste et al [34] describing the epidemiology of AKI in critically ill patients, found similar results with a significant relationship to the underlying gross national income. Based on the accumulated evidence so far, it is evident that AKI continues to be major worldwide problem [30].

In industrialized nations, AKI is seldom a community-acquired disease, i.e. AKI develops outside the hospital and the patient is admitted to the hospital with AKI. The condition develops primarily in patients hospitalized for another disease. In these regions, the incidence of hospital-acquired AKI exceeds that of community- acquired AKI by five- to ten-fold, with AKI being reported in 7-18% of hospital inpatients yearly [2, 8]. In less developed nations, AKI commonly occurs in the community [35]. Because community-acquired AKI originates in the communities in which patients live or work, environmental and lifestyle differences will affect the incidence and patterns of community-acquired AKI [1, 2].

In 2013, to improve the diagnosis and treatment of AKI worldwide, the International Society of Nephrology (ISN) launched the "0by25" global target, that is, zero avoidable deaths of patients with untreated AKI by 2025 [36]. More information on AKI in resource-limited countries has recently been summarized in a series on AKI in resource-limited countries [37-40].

Epidemiology of AKI in sub-Saharan Africa

Overall, the true epidemiology of AKI in sub- Saharan Africa is not well understood. Late presentation of patients to mostly tertiary centers, under-reporting, and a reduced capacity to provide intensive care, including renal replacement therapy (RRT) to severely ill and /or late stage AKI patients, are contributors to the lack of understanding. An important weakness of all epidemiological reports in Africa is the high selection bias in the described populations. The publications are all coming from university hospitals where a nephrological service is present. Virtually no data on the incidence of community-acquired AKI in the vast rural areas in Africa are available [38, 41].

However, recent considerable efforts to collect epidemiological data on AKI in sub-Saharan Africa have yielded a very interesting report, be it still with fragmentary data [29]. The major conclusions of this report indicate that AKI in sub-Saharan Africa is severe, with 1042 (66%) of 1572 children and 178 (70%) 253 of adults needing

dialysis in studies reporting dialysis need. Only 666 (64%) of 1042 children (across 11 studies) and 58 (33%) of 178 adults (across four studies) received dialysis when needed. Overall mortality was 34% in children and 32% in adults, but rose to 73% in children and 86% in adults when dialysis was needed but not received. The Olowu study defined out-of-pocket costs, erratic hospital resources, late presentation, and female gender as major barriers to access to care.

The interested reader can also be referred to an in depth analysis and review of AKI in sub-Saharan countries, published by the senior author of this paper [28].

In developed countries, major risk factors for AKI include sepsis, cardiac surgery, heart failure and other chronic diseases, such as diabetes mellitus and pre-existing chronic kidney disease. On the other hand, infections, toxins, environmental and occupational exposures, pregnancy- related complications and hypovolemia are the main etiologies of AKI in resource-limited countries [38, 41]. Furthermore, patients frequently consult traditional healers and ingest nephrotoxic herbal products, which have been reported to contribute to AKI in Africa [29, 38].

The human immunodeficiency virus (HIV) epidemic in sub-Saharan Africa has contributed significantly to the burden of kidney disease in the region as well. AKI is one of the many manifestations of renal diseases that may occur in HIV-infected individuals (for recent reviews see [42-45]. HIV associated AKI may result from the infection itself or as a complication of treatment [46]. Some risk factors for AKI among HIV-positive patients are similar to risk factors for AKI in the general population, but some risk factors are specific to HIV, including a diagnosis of AIDS, low CD4 count, high viral load, and co-infection with hepatitis C virus [47-49]. In the era before the introduction of the highly effective combination antiretroviral therapy (cART) volume depletion, sepsis and nephrotoxicity were the leading causes, with 38% of AKI cases being hemodynamically mediated or prerenal AKI [50].

Since the introduction of the potent antiretroviral therapy, the incidence of AKI has decreased but remains substantial, and there is evidence that in more recent years an increased incidence of more severe AKI occurs [45]. In general, AKI in HIV-infected individuals is more frequently related to severe opportunistic infections than to direct cART toxicity [48, 51]

Nephrotoxic medications that are frequently used to treat HIV-related infections have been associated with AKI, such as aminoglycosides, pentamidine, amphotericin and trimethoprim/ sulfamethoxazole, and antivirals such as acyclovir and foscarnet, among others, may account for up to 30% of AKI [52]. Patients with HIV infection are particularly at risk for nephrotoxic side-effects of the combination antiretroviral therapy. This nephrotoxicity may clinically present as AKI, CKD often in combination with acid-base and electrolyte disturbances. A detailed

discussion of this important topic is beyond the scope of this paper but the reader can be referred to excellent reviews on this subject [53, 54]. Successful public health programs targeting treatment and prevention of endemic diseases like malaria or dengue have also contributed to the decrease of AKI incidence in the tropics.

Epidemiology of AKI in Rwanda

A prospective, observational and multi-center cohort study was recently conducted on incidence and short term outcome of AKI in Rwandan tertiary teaching hospitals using the KDIGO criteria [55]. This study evaluated adult patients diagnosed with AKI who were admitted to tertiary care teaching hospitals in Rwanda - Kigali University Teaching Hospital (KUTH), Butare University Teaching Hospital (BUTH), Rwanda Military Hospital (RMH) and King Faisal Hospital (KFH). All patients were screened for AKI and the diagnosed patients were followed from time of diagnosis to either discharge from hospital or in-hospital death. A SCr value available within one year prior to enrolment in the study was considered as patient's baseline SCr. For patients who reversed AKI during the hospital stay, the lowest SCr level was considered as their baseline. When a documented baseline SCr was not available, and in those where SCr did not decrease back to normal and when no history or clinical features suggestive of CKD were present, a back calculation of an estimated baseline SCr was performed using the modification of the MDRD formula, as outlined above. Patients with clinical signs of ESRD and with sonographically small (< 9 cm) echogenic kidneys consistent with CKD and without known SCr were excluded from the study.

Based on these criteria an overall AKI incidence of 2.8% of the hospitalized population was found while the AKI mortality rate was around 32%. It was difficult to establish a direct causal relationship between AKI and the numerous co-morbidities many patients presented.

Table 2 summarizes the comorbidities in the Rwandese AKI patients. It is noted that 69% of the comorbidities were of infectious origin, followed by cardiovascular diseases, and exposure to nephrotoxins. More general health parameters like anemia, hypertension and obstetric complications were also prominent, although it is difficult to know if these were all causally related to AKI. Other co-existing comorbidities include trauma, cancers, cirrhosis, and obstructive uropathies.

Table 3 provides a more detailed analysis of the specific infectious diseases associated with AKI in this population. HIV infections, followed by Hepatitis B and C, sepsis, pneumonia, malaria and tuberculosis were the most prevalent infections.

Remarkably enough, the Rwandese study pointed to a quite common practice of prescribing diuretics (furosemide) in non-fluid overloaded patients with oliguria/anuria before referral in an effort to force diuresis. This practice is one of the largest modifiable risk factors used to reduce the rates and severity of pre-renal AKI in Rwanda.

The KDIGO clinical practice guidelines recommend the use of diuretics only in fluid overloaded patients. Hypovolemic and anuric patients should receive optimum fluids to establish euvolemia instead of diuretics.

Table 1. The definition of AKI according to the KDIGO guidelines for AKI

A. The **definition** of AKI determined by either an increase in sCr or an episode of oliguria

- Increase of sCr > 0.3 mg/dl (> 26.6 µmol/L) within 48 hours, or
- Increase of sCr by > 1.5- fold above baseline, known or assumed to have occurred within 7 days, or
- Urine volume < 0.5 ml/kg/hour for 6 hours

B. **Comparison between the KDIGO and pRIFLE staging criteria**. The **severity** of AKI is staged by the worst of either sCr changes or oliguria

pRIFLE classification			KDIGO classification		
Category	Estimated Cr clearance *	Urine output	Stage	SCr	Urine output
Risk (R)	Decrease by 25%	<0.5ml/kg/hr for 8h	1	Rise of 0.3 mg/dl or 26.5 µmol/L within 48 h OR 50-99% rise from baseline within 7 days**	< 0.5 ml/kg/h for 6 -12h
Injury (I)	Decrease by 50%	<0.5ml/kg/hr for 16h	2	100-190% increase in SCr level from baseline within 7 days** (2-2.99xbaseline)	< 0.5 ml/kg/h for > 12 h
Failure (F)	Decrease by 75% or < 35 ml/min per 1.73 m²	<0.3 ml/kg/h for 24 h or anuric for 12h	3	≥200% increase in SCr level from baseline within 7 days** (3.00 x baseline) OR Need for RRT OR In patients < 18 years decrease in eGFR to ≤35 ml/min per 1.73m²	< 0.3 ml/kg/h for ≥ 24 h OR anuria for ≥12h

* Where the rise is known (based on a prior blood test) or presumed (based on the patient history) to have occurred within 7 days. Baseline sCr is defined as the sCr occurring before the episode of AKI. When baseline is unknown and the patient has no history of CKD, the earlier RIFLE classification suggested the use of a so-called MDRD derived baseline sCr. This is based upon the assumption that the baseline GFR > 75 ml/min.1.73m². It has been proven that this renders a less reliable estimate.

** Calculated with Schwartz equation: Length (cm) x K (constant)/ SCr (see references [25, 26]).

Table 2. Co-morbidities associated with AKI in Rwanda (taken from ref [55])

Diagnosis	Frequency (n= 427)	Percent
Infections	294	68.9
Pregnancy related	53	12.4
Cancer	34	8.0
Trauma	16	3.8
Chronic kidney disease	42	9.8
Cardiovascular disease	46	10.8
Hypertension	106	24.8
Diabetes	49	11.5
Stroke and CNS tumors	22	5.1
Cirrhosis	34	8.0
Tubuloglomerular diseases	5	1.2
Obstructive uropathy/nephrolithiasis	10	2.3
Anemia	224	52.5
Others*	20	4.6

Table 3. Infectious co-morbidities associated with AKI in Rwanda (taken from ref 27).

Diagnosis	Frequency (n=427)	Percent (n= 427)
Pneumonia	32	7.5
Malaria	29	6.8
HIV	70	16.4
Tuberculosis	24	5.6
Urinary tract infections	20	4.7
Abscesses	5	1.2
Peritonitis/ intestinal obstruction	42	9.8
Hepatitis B	11	2.6
Hepatitis C	52	12.2

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