

Acute Kidney Injury Recognition in Low- and Middle-Income Countries



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Acute kidney injury (AKI) is increasingly common around the world. Because of the low availability of effective therapies and resource limitations, early preventive and therapeutic measures are essential to decrease morbidity, mortality, and cost. Timely recognition and diagnosis of AKI requires a heightened degree of suspicion in the appropriate clinical and environmental context. In low- and middle-income countries (LMICs), early detection is impaired by limited resources and low awareness. In this article, we report the consensus recommendations of the 18th Acute Dialysis Quality Initiative meeting in Hyderabad, India, on how to improve recognition of AKI. We expect these recommendations will lead to an earlier and more accurate diagnosis of AKI, and improved research to promote a better understanding of the epidemiology, etiology, and histopathology of AKI in LMICs.

Kidney Int Rep (2017) 2, 530–543; <http://dx.doi.org/10.1016/j.ekir.2017.04.009>

KEYWORDS: acute kidney injury; biomarkers; detection; developing countries; diagnosis; recognition; resources
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The incidence of acute kidney injury (AKI) is increasing around the world.^{1–4} The ongoing search for supporting procedures and interventions has produced improved guidelines and recommendations.^{5,6} Demonstration of increasing AKI incidence has led to an emphasis on prevention or early intervention,⁵ but unfortunately, analytical methods that predict AKI, or preventive and therapeutic approaches to accelerate recovery or prevent progression to chronic kidney disease (CKD), are only beginning to be understood.^{7–9}

Early recognition of AKI is essential to ensure prompt and appropriate management, and to avoid progression to deadlier stages of the disease^{10,11} (Figure 1). In the appropriate context, early detection requires a high degree of suspicion that AKI is

occurring. Diagnosis requires a combination of a clinical history, a thorough physical examination, an accurate assessment of kidney function, appropriate imaging, and when indicated, a kidney biopsy.

In low- and middle-income countries (LMICs), early detection is impaired by limited resources and poor understanding of the condition.^{1,2,9,12–15} Such limited understanding—to a large extent determined by inadequate reporting and education—limits awareness and early recognition, and delays the implementation of measures that permit early and adequate management.¹⁶

To address this goal, the steering committee of the 18th Acute Dialysis Quality Initiative (ADQI) conference dedicated a work group with the task to identify what elements affect the recognition of AKI within the limited resource constraints prevalent in LMICs. Using a modified Delphi process, this group reached consensus regarding strategies to recognize and diagnose AKI focusing on low resource countries. The group addressed the following 3 questions that served as the basis for accompanying consensus statements:

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Received 28 February 2017; revised 17 April 2017; accepted 19 April 2017; published online 25 April 2017

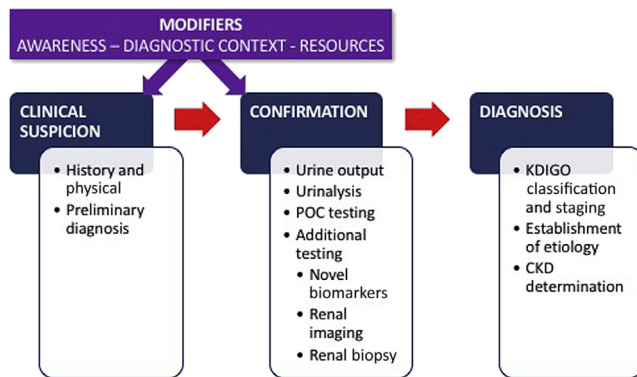


Figure 1. Acute kidney injury (AKI) recognition: the process and its modifiers. In addition to the usual AKI trajectory from clinical suspicion to confirmation to diagnosis, other factors modify the process. The degree of AKI awareness, the context in which the patient is encountered, and the available diagnostic resources may facilitate, delay, or impede the achievement of early AKI diagnosis. CKD, chronic kidney disease; KDIGO, Kidney Disease: Improving Global Outcomes; POC, point of care.

1. When should AKI be suspected?
2. What tests are needed when AKI is suspected?
3. How do we confirm the diagnosis of AKI in patients with an initially elevated serum creatinine (Scr) level?

Methods

The ADQI process has been described previously.^{17,18} Complete ADQI methodology description is available at www.adqi.org and in the editorial accompanying the ADQI 18 conference papers.¹⁹ The broad objective of ADQI is to provide expert-based statements and interpretation of current knowledge for use by clinicians according to professional judgment, and to identify clinical research priorities to address these gaps. The 18th ADQI Consensus Conference Chairs convened a diverse panel that represented relevant disciplines (i.e., adult and pediatric nephrology, critical care, and renal pathology) from several continents (e.g., Africa, Asia, North America, Latin America, and Europe) around the theme of “Management of Acute Kidney Injury in the Developing World” for a 2-1/2-day consensus conference in Hyderabad, India on September 27 to 30, 2016.

The preconference activities involved a search of the literature for evidence on the epidemiology, recognition, and management of AKI in developing countries and their differences with developed countries. A literature search was conducted using the following terms: recognition; awareness; diagnosis; point of care; and low income countries or developing countries, together with either acute kidney injury and acute renal failure in PubMed. This work group

was also tasked to summarize the scope, implementation, and evaluative strategies for AKI recognition and diagnosis based on the location, resource availability, and a critical evaluation of the relevant literature. A series of phone conferences and emails that involved work group members before the meeting identified current knowledge to enable the formulation of main questions from which discussion and consensus would be developed. A formal systematic review was not conducted. During the conference, the work group developed consensus positions, and plenary sessions that involved all ADQI contributors were used to present, debate, and refine these positions. Following the meeting, this summary report was generated, revised, and approved by all members of the ADQI participants. All the participants interacted throughout the meeting in the general session, and all group deliberations were subjected to review and consensus agreement in the final versions. In addition, all participants discussed and approved the contents of this paper. The participants did not represent specific societies, but were invited because they had domain knowledge expertise. Their affiliations are provided in the Supplementary Appendix.

For the purposes of all work group discussions, we used the current Kidney Disease Improving Global Outcomes (KDIGO) definitions for AKI and stages of AKI, which defines AKI as an episode that occurred within a 7-day timeframe.⁵ Community-acquired AKI was defined as an episode of AKI when the initial event occurred outside of the hospital setting and where the patient was admitted to the hospital with AKI; hospital-acquired AKI was defined as an episode of AKI due to a kidney insult that occurred to hospitalized patients who developed de novo AKI during their hospital stay.¹⁵

Q1: When Should AKI Be Suspected? Consensus Statement

1. In the appropriate clinical context, AKI should be suspected in patients who present with the signs and symptoms listed in [Table 1](#).

During the initial interaction of a patient with the health care system, the diagnosis of AKI is influenced by the clinical presentation and the context of the encounter^{11,20} ([Figure 2](#)). Improved awareness that the presenting symptoms and signs might correspond to AKI is the first step toward timely recognition. Unfortunately, AKI is frequently not recognized or is recognized too late, at a more severe stage.²¹ Failure to recognize early AKI is frequently associated with disease progression that requires more aggressive therapies and support when recovery is less likely and mortality is heightened.²²

Table 1. Signs and symptoms leading to suspicion of acute kidney injury in low- to middle-income countries

In the community setting
History of kidney disease
Oliguria
Total body swelling
Hypotension
Dehydration
GI loss of volume and electrolytes
Dark, concentrated urine
Sepsis syndrome
Fever in the context of prevalent endemic disease
Exposure to potential nephrotoxins
Pregnancy-related complications
Plus, in the hospital setting,
Multiple organ failure
Nephrotoxic medication exposure

GI, gastrointestinal.

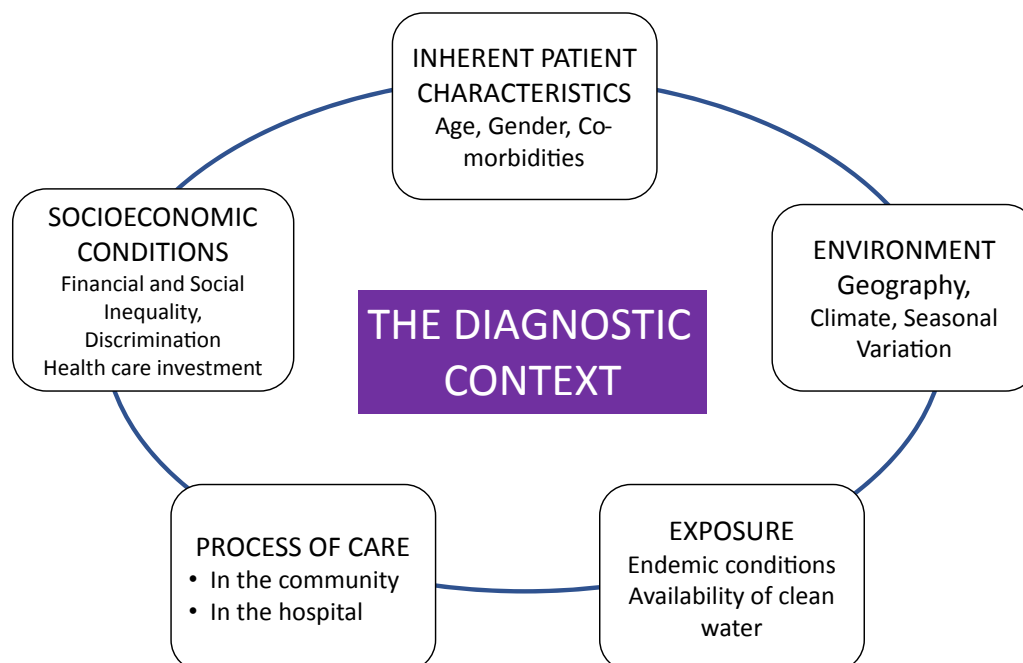
In LMICs, because of the common absence of access to specialized nephrology care, increased awareness of the clinical situations associated with AKI, and the implications of failing to detect it, AKI must be more understood at all levels of the health care system.²³ A practical and easily accessible educational strategy focused on providers at the forefront of health care delivery is indispensable to achieve this goal. Providers must be trained to consider AKI in patients who present with certain signs and symptoms (Table 1)²⁴ in the right clinical context. For example, in areas where infectious diseases (e.g., severe malaria, leptospirosis, or dengue) are endemic and associated with high rates

of AKI,^{20,25–27} a febrile patient should elicit concern for renal injury.^{28–48} Similarly, in patients with severe volume depletion due to gastrointestinal loss, volume resuscitation is central to care and to prevent renal injury—preferably before the onset of persistent oliguria.¹⁵ Management must be appropriate to the clinical condition.^{49,50}

The development of AKI as a maternal and neonatal complication deserves special consideration in the LMIC environment,^{51–62} because failure to recognize renal injury frequently leads to significant consequences for both the mother and child.

Successful efforts to improve early recognition have clearly demonstrated benefit, especially by reducing some of the more dreaded consequences such as cortical necrosis.^{63,64} In some areas of the world, exposure to snake venom represents a frequent cause of AKI.^{65,66} Administration of herbs by traditional healers has been associated with nephrotoxicity, and must be considered when confronted with AKI of unclear etiology.^{12,21,67} Increased availability and use of over-the-counter allopathic medications (e.g., nonsteroidal anti-inflammatory drugs) significantly contribute to a rising incidence of AKI.

In LMIC, recognition of AKI in the hospital faces challenges that are akin to those seen in the developed world; hospitalized patients demonstrate a high incidence of AKI related to exposure to nephrotoxic medications, antibiotics, intravascular administration of iodinated radiocontrast, and surgical procedures.^{68,69}

**Figure 2.** Main components of the acute kidney injury diagnostic context.

Consensus Statement

2. Evaluation for AKI should be incorporated into the diagnosis and management of specific endemic conditions associated with a high AKI risk (e.g., severe malaria, leptospirosis, dengue, and HIV).

Endemic infections contribute significantly to the burden of AKI in LMICs. Much remains to be learned about the prevalence of AKI, the clinical characteristics that predispose to the onset of AKI, and the impact of AKI on the management of patients with those infections. Thus, the HIV epidemic in Sub-Saharan Africa has contributed to the rising burden of AKI, either as a direct result of the viral infection or as an unintended consequence of antiretroviral therapy.^{16,26,70–73} Other infectious diseases in LMICs have not received the same level of attention, and much remains to be understood about the nature of AKI associated with these conditions.^{48,49,74,75}

Research Recommendation

- In LMICs, efforts must be directed to a better understanding of the epidemiology and management of infection-related AKI.

Q2. What Tests Are Needed When AKI Is Suspected?

Consensus Statement

1. We recommend that patients suspected to have AKI should have an estimation of urinary output, a measurement of SCr levels, and a thorough urinalysis.
2. Whenever possible, the performance of urine microscopy and urine biochemistry is essential to elucidate the underlying etiology and to assess severity.
3. We recommend that point-of-care testing (POCT) technologies should be made available for the diagnosis of AKI in low resource settings.
4. In hospitalized patients, we recommend additional testing, including renal imaging and renal biopsy, as indicated. The use of newer biomarkers of structural injury in economically constrained environments should await demonstration of efficacy.

Confirmation of AKI

The diagnosis and staging of AKI using current KDIGO definitions rests upon changes in serum creatinine and/or urinary output.⁵ Additional testing and urinary microscopy are necessary to identify the underlying etiology.

Urinary Output

In patients with developing AKI, urine output is a sensitive functional marker of kidney dysfunction.^{76–80}

Unfortunately, oliguria may be easily confounded in its significance⁷⁹ and can be difficult to record accurately, thereby limiting its reliability as a marker of AKI. In the community setting, diuresis is often unknown or inaccurately recorded, which limits its usefulness.⁵ In LMICs, oliguria is usually an accurate marker of AKI severity in children and neonates, and is associated with patient outcomes.^{39,81–83}

Urinalysis

When available, use of urine dipsticks and measurement of urinary indices such as urinary sodium,^{84,85} fractional excretion of sodium,^{86–88} fractional excretion of urea,^{84–86,89–91} urine plasma creatinine ratio,⁸⁴ urine concentration (osmolality or specific gravity),^{84,85,92} and protein are useful for the initial evaluation of AKI.

The performance of basic urine microscopy,^{85,91,93–96} which focuses on the presence of erythrocytes, leukocytes, eosinophils, and casts in the sediment,^{60,97,98} is invaluable to assess the initial presentation of the patient with AKI (Table 2).

We recommend that training in microscopic urine examination and availability of basic examination equipment for such testing should be promoted as a key, low-resource test for detection of AKI in LMICs.

Although the usefulness of urinary indices (Table 3) in the critically ill patient with sepsis has been questioned,^{86,99} and may be confused by the use of diuretics, the combination of these tests with a thorough patient history, physical examination, and urinalysis will increase the sensitivity and specificity of AKI prediction and severity.¹⁰⁰

Serum Creatinine

Despite limitations in the use of serum creatinine as a marker of renal function, changes in SCr and/or urine output form the basis of all AKI diagnostic criteria. SCr is a frequently inaccurate biomarker due to the need for a baseline and/or historical value to provide context^{101–104} and the limitations of a delayed diagnosis.^{105–108} Serum creatinine concentrations are affected by age, sex, and muscle mass¹⁰⁹; they can change in response to certain drugs and are unreliable in patients with liver dysfunction or fluid overload. Serum levels take 24 to 36 hours to rise after a definite insult.^{110–113} In addition, although changes in creatinine concentration remain central to the diagnosis of AKI, differences in individual body composition that result in differences in creatinine production and volume of distribution across populations, as well as variations in dietary composition, have largely been ignored,¹⁰² and may be different from current estimates originated in the developed world.

Table 2. Urine microscopy

Reference	Test	Patients (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Comments
Bagshaw ⁹⁶	UMS ≥ 3	83	0.67 (0.39–0.86)	0.95 (0.84–0.99)	0.80 (0.49–0.94)	0.91 (0.78–0.96)	The UMS was compared between septic and nonseptic AKI and correlated with NGAL, worsening AKI, RRT, and hospital mortality. UMS correlates with uNGAL, but not with pNGAL; a UMS score ≥ 3 was associated with increased odds of worsening AKI (AOR: 8.0; 95% CI: 1.03–62.5; $P = 0.046$).
Perazella ⁹³	USS ≥ 2	267	0.76	0.86	100	44	Using the final diagnosis as the gold standard, the ability of the urine microscopy diagnosis to distinguish ATN from prerenal AKI was fair (sensitivity 0.76; specificity 0.86; positive LR 5.75). However, the scoring system was highly predictive of the final diagnosis of ATN
Chawla ⁹⁶	CSI	30					Gold standard was patients with AKI consistent with the syndrome of acute tubular necrosis. The patients with nonrenal recovery had a higher CSI compared to those patients who did recover renal function (2.55 ± 0.93 vs. 1.57 ± 0.79 ; $P = 0.04$). Limitations: small sample, lack of control for urine osmolality and pH, the number of reviewers and the variation in the reviewer's training was relatively limited.
Carvounis ⁹⁹	Scr ≥ 1.1 mg/dl Renal epithelial cells or epithelial/ granular casts NGAL (ng/ml) ≥ 42.71	363	84.2 (74.4–90.7) 22.4 (14.5–32.9)	77.7 (72.5–82.1) 91.3 (87.5–94.0)	50.0 40.5	94.9 81.6	
			64.5 (53.3–74.3)	64.5 (58.8–69.8)	32.5	87.3	

AKI, acute kidney injury; AOR, adjusted odds ratio; ATN, acute tubular necrosis; CI, confidence interval; CSI, Cast score index; LR, likelihood ratio; NGAL, neutrophil gelatinase-associated lipocalin; NPV, negative predictive value; PPV, positive predictive value; RRT, renal replacement therapy; UMS, urine microscopy score; USS, urinary scoring system.

Until recently, the most common assay for measurement creatinine was the alkaline picrate (Jaffé) assay. However, chromogens other than creatinine interfere with the assay, giving rise to errors in up to 20% in subjects with a normal glomerular filtration rate (GFR). Modern assays do not detect noncreatinine chromogens and yield lower levels of creatinine. The lack of standardization to adjust for this interference affects the ability to estimate kidney function based on SCr concentration by different laboratories, especially at higher levels of estimated GFR. Standardization will reduce but not completely eliminate this error.¹¹⁴

Blood and Saliva Urea Nitrogen

Serum urea and blood urea nitrogen (BUN) levels must be carefully interpreted as markers of kidney function in view of the numerous non-GFR factors that influence their blood concentrations. Levels of urea and/or BUN depend on protein intake, endogenous urea production, and tubular reabsorption. Reduced kidney perfusion in the setting of volume depletion enhances reabsorption of urea, which may lead to an elevation of BUN disproportionate to the concomitant decrease in GFR. Conversely, decreased protein intake

or underlying liver disease can prevent the expected rise in BUN, whereas increased urea production (gastrointestinal bleeding, hypercatabolic status) or impaired protein anabolism (corticosteroid administration) can increase BUN in the absence of increased urea reabsorption.^{84,115} Because of multiple confounding, the use of BUN as an isolated marker of kidney injury may be unreliable. Additional POCT tools such as saliva urea nitrogen have been recently proposed and may be effective to screen patients with elevated urea nitrogen levels when blood tests may be unavailable or unaffordable.¹¹⁶

Serum Cystatin C

Currently, cystatin C is not being widely used. The absence of a relationship with body composition makes this marker an interesting alternative, but its value is limited by changes in concentration in response to inflammation, lung disease, and cigarette smoking.¹¹⁷

Point-of-Care Testing

POCT for creatinine measurements occurs close to the patient instead of in a central laboratory (Table 4).

Table 3. Urine biochemistry

Reference	Test	Patients (n)	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Comments
Carvounis ⁸⁹	FeU vs. FENa	102 PR = 50 Prdiu = 27 ATN = 25		90	96	99	75	Gold standard clinical grounds; more sensitive and specific index than FENa in differentiating between ARF due to prerenal azotemia and that due to ATN, especially if diuretics have been administered; in osmotic diuresis, the proximal tubular absorption of salt and water is impaired; thus, increased FEUN is expected despite renal hypoperfusion. A similar picture emerges in patients given a high protein diet or having excessive catabolism.
Pepin ⁹⁰	FeNa vs. FEur in transient AKI (prerenal)	99 FENa FENA + dir FEur FEur + diur	0.83 ± 0.07 0.75 ± 0.06 0.56 ± 0.11 0.57 ± 0.08	78 68 48 79	75 81 75 33	86 86 79 71	64 49 43 44	Gold standard clinical context and whether serum creatinine level returned to baseline within 7 days. In patients without diuretic use, FENa is better able to distinguish transient from persistent AKI. In patients administered diuretics, this distinction cannot be made accurately by means of FENa. FEur cannot be used as an alternative tool because it lacks specificity.
Bagshaw ⁸⁶	FeU ≤35% FeNa <1%	n = 28 n = 47	0.54 (0.42–0.67) 0.54 (0.42–0.67)	40 50	59 58			Gold standard: uNGAL. In sepsis, FeNa and FEUN are not reliable markers of renal hypoperfusion. Urine biochemical profiles and microscopy do not discriminate septic and non-septic AKI. UNa, FeNa, and FeU do not reliably predict biomarker release, worsening AKI, RRT or mortality. These data imply limited utility for these measures in clinical practice in critically ill patients

AKI, acute kidney injury; ARF, acute renal failure; ATN, acute tubular necrosis; AUC, area under the curve; diur, diuretics; FENa, fractional excretion of sodium; FeU, fractional excretion of urea; FEUN, fractional excretion of urea nitrogen; NPV, negative predictive value; PPV, positive predictive value; RRT, renal replacement therapy; UNa, urine sodium; uNGAL, urine neutrophil gelatinase-associated lipocalin.

It can be performed by nonlaboratory trained individuals, thus eliminating delays in testing and reporting of results.¹¹⁸ Although POCT is a particularly attractive option in remote and low resource environments, it requires the implementation of a quality assurance program that ensures accurate and reliable results. Several POCTs for Scr are available in the market across the world^{116,118–124} and can be classified into blood gas analyzers and nonblood gas analyzers. They also vary with respect to the types of samples that can be processed—whole blood, plasma, or serum. Other specific requirements include a power source, availability of deionized water, specific consumables (which sometimes require refrigeration), space, and requirements for calibration and disposal as a biohazard waste. As a result, most POCTs for Scr are not yet cost-effective and must be further tested for their usefulness in the detection of AKI.¹¹⁹ The failure of most of POCT creatinine devices to be in full alignment with isotope dilution mass spectrometry equivalent standards is another limitation.^{118,125} Definitive studies to determine the best practices to incorporate POCTs in low-resource health care settings are needed.

Novel Biomarkers

As discussed, Scr as the current gold standard remains a flawed marker of renal dysfunction. Newer biomarkers are being developed, but even in high-income countries their use is yet to become a standard of care; their application in the developing world is even more challenging.¹²⁶

Table 4. Issues that must be considered when selecting a point-of-care test

Ease of use
Accuracy
Low error rate (imprecision + bias)
Consumable need: strips, cassettes, cartridges, rotor system, etc.
Portability (handheld vs. bench top); different models may be appropriate for field vs. hospital settings
Power source (battery vs. mains)
Scalability
Processing time
Sample source and volume
Connectivity (e.g., Bluetooth integration)
Ability for integration into electronic decision support systems
Possibility to do >1 test
Cost of the device and consumables

Because of their simplicity of use and limited requirement for technological support, dipsticks are one of the most widely used tools to assess renal injury. Although traditional dipsticks allow the assessment of renal injury by primarily testing glomerular integrity (albuminuria and/or proteinuria), newer devices have more recently been modified as markers of renal dysfunction by estimating elevated BUN using saliva, or novel blood or urine markers of tubular injury such as kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin.^{123,127} Recently, newer biomarkers in dipstick format have been made commercially available.¹¹²

AKI etiologies in low-resource rural areas, where volume depletion, infection, and nephrotoxic agents are leading causes of AKI,^{12,26} are usually different from those seen in the developed world.¹² Such differences pose a challenge in our understanding of how potential novel biomarkers can be deployed. The ideal biomarker would facilitate the distinction between AKI due to volume depletion and AKI due to intrinsic kidney injury, and must be able to distinguish transient elevations in SCr from persistent changes consistent with injury. Such markers should allow early detection of the most likely cause of AKI, facilitate a diagnosis in the absence of historical information on baseline renal function, and support early therapeutic intervention.^{12,127} Unfortunately, novel AKI biomarkers remain poorly studied in clinical conditions commonly associated with AKI in LMICs; such limitations raise questions about their potential usefulness and practical implementation in those areas.¹²⁸

Newer AKI Definitions, Staging Criteria, and Recent Uncertainties

Although newer AKI definitions and staging criteria such as KDIGO; acute kidney injury network (AKIN); and risk, injury, failure, loss, and end-stage kidney disease (RIFLE)^{5,129–131} are appropriate to define AKI epidemiology and to design clinical trials, questions have been raised on their clinical application to the individual patient.^{111,112} The classification of AKI and its various stages has been validated in multiple hospitalized populations by demonstrating a strong association with short- and long-term outcomes,^{13,132} but significant problems in the usefulness of this classification persist.¹¹⁰ Because they rely on renal function changes, current AKI definitions only permit a relatively late diagnosis hours or days after the risk of injury or when the actual lesion began. As discussed previously, efforts to achieve an earlier diagnosis have led to the development of biomarkers of injury and are currently in progress.¹³³ It is expected that newer

biomarkers may detect kidney damage before the SCr and GFR become abnormal, but it is unclear how accurately those biomarkers will measure kidney damage instead of the severity of disease.^{134–139}

Because of current uncertainties on the correlation among AKI definitions, biomarker data, and histopathology,¹⁴⁰ better availability of histopathologic data in LMICs provides a unique opportunity to probe such correlation, and begins to close the gap between our understanding of actual human histopathology, the pathogenesis of AKI, and our current, strictly functional KDIGO, AKIN, and RIFLE definitions.^{5,129–131}

Histopathology in AKI

A better understanding of the histopathology and pathogenesis of AKI is indispensable to continue to unveil the process of kidney injury,¹⁴¹ and by developing bench-to-bedside processes, to foster a better understanding on how to avoid and how to treat kidney injury.¹⁴²

During the evaluation of patients with renal injury, a diagnosis based on histopathology remains important because it not only provides insight into the injury pattern, but often guides patient management. Multiple causes of AKI require histopathological diagnosis, but unfortunately, the number of biopsies and publications on the histopathology of AKI is declining.^{110,143} Concerns about procedural complications, including the risk of bleeding and the perception that AKI is commonly the result of acute tubular necrosis, appear to contribute to the reluctance to perform biopsies in the acute setting, despite evidence to the contrary.^{144–148}

Kidney biopsies are indicated when: (i) The clinical presentation suggests that biopsy findings will likely lead to important therapeutic changes, an improved probability of recovery, and avoidance of further injury; (ii) when the magnitude of benefit is assessed to be greater than the risk of the procedure; and (iii) when the temporal course of the disease and delayed recovery dictates the need for further ascertainment of histopathologic diagnosis and prognosis. Multiple old and new studies have reviewed the indications and attested to the safety and usefulness of percutaneous kidney biopsies in the management of kidney disease.^{149–161}

Currently, kidney biopsies in patients with AKI are more common in LMICs than in high-income countries; thus, there is a greater appreciation of the relative incidence of multiple etiologies and the value of a renal biopsy to guide management.^{1,15,20,21,162} Although results from biopsy series are likely confounded by indication bias, those studies suggest that the role of a renal biopsy must be reconsidered in the diagnosis and management of AKI of unclear etiology, such as:

unexplained AKI; acute interstitial nephritis^{60,163,164}; acute or chronic glomerulonephritis, or rapidly progressive glomerulonephritis¹⁶⁵; interstitial or tubular injury due to drug toxicity, or exposure to traditional herbal remedies^{21,166–170}; thrombotic microangiopathies¹⁷¹; or leptospirosis.^{172–176}

Because of current uncertainties on the relationship among AKI definitions, biomarker data and renal histopathology, and their effects on treatment and prognosis,¹⁴⁰ we strongly recommend that kidney biopsies be considered in patients with AKI, whenever appropriate and feasible.

We further recommend that in LMIC settings, basic training be provided to local pathologists on renal histopathology, understanding that even the limited information provided by light microscopy may provide invaluable guidance in patient management. Training of members of the health care team in simple imaging, including ultrasonography, when feasible, is also desirable.

Research Recommendation

- We recommend the development, validation, and standardization of POCT to facilitate the diagnosis of AKI in the community.

Q3: How Do We Confirm the diagnosis of AKI in Patients With an Initially Elevated SCr Level?

Consensus Statement

1. We recommend that patients with an isolated (single) elevated creatinine or oliguria be considered to have AKI until proven otherwise, to ensure rapid implementation of effective treatment measures.

Concerns that the initially elevated SCr may be due to CKD may unnecessarily delay the initiation of urgent therapeutic measures. We strongly recommend that patients with apparently acute, severe dysfunction be emergently treated as if they had AKI, until proven otherwise (see the following).

Consensus Statements

2. We recommend that the presence of CKD be evaluated using clinical history, urinalysis, renal imaging, and biopsy when indicated.

Table 5. Factors that can cause worsening renal function in a patient with preexisting kidney disease

Systemic infection
Infection of the urinary tract
Volume deficit
Urinary tract obstruction
Uncontrolled hypertension
Unrecognized renovascular disease
Drug-induced (hemodynamic, interstitial nephritis)

3. We recommend that the diagnosis of AKI should be confirmed by repeat assessment of renal function at no later than 7 days.
 - a. We recommend that the frequency of repeat assessment of renal function be guided by the clinical context and response to intervention.

Differentiation Between AKI and CKD

When a patient without historical information presents in the community center with clinical features and/or an elevated creatinine consistent with a diagnosis of kidney injury, distinguishing isolated AKI from AKI superimposed on CKD or baseline CKD can be challenging. We believe this distinction should not be immediately relevant to the initial management, which should focus on the amelioration of the urgent metabolic and/or volume imbalances and on the correction of all known precipitating factors (Table 5).

We suggest that all patients without a known history of renal disease who present with a first episode of kidney injury must be presumed to have potentially reversible AKI, until proven otherwise. Moreover, even when the presence of CKD is demonstrated, modifiable factors that could have led to potentially reversible acute deterioration of renal function should be identified and corrected. This distinction becomes very relevant in certain regions of the world, where decisions are made on resource allocation in countries where public health care systems only offer support for the dialytic management of potentially reversible AKI, but frequently deny dialysis if renal failure is irreversible.

In patients presenting with kidney failure, all attempts should be made to explore whether previous measures of kidney function are available. This information can be part of previous encounters in the health care system, such as during pregnancy; presurgical screening; evaluation during an unrelated illness; or as part of medical screening before employment, insurance, or during school, corporate, or community health

Table 6. Features that indicate the presence of preexisting kidney disease in a patient presenting with kidney injury

History of long-standing nocturia
History of edema, hematuria or renal stones
History of long-term intake of painkillers, herbal medicines, over-the-counter drugs
History of recurrent dehydration
Family history of kidney disease
Urinalysis showing broad casts
Musculoskeletal manifestations: growth retardation, rickets, or proximal myopathy
Anemia out of proportion to the duration of symptoms in the absence of another cause
Elevated phosphate and/or PTH levels
Characteristic imaging abnormalities (e.g., renal cysts or obstruction)
Small and/or highly echogenic kidneys on ultrasound

PTH, parathyroid hormone.

checks. In the fragmented LMIC health care systems, records are often unavailable, so when consulting, patients should be encouraged to bring all records of previous encounters with the health care system, which is a common practice in LMICs.

Certain symptoms, signs, and laboratory or imaging findings (Table 6) can increase the suspicion of preexisting kidney disease, but should not be used to exclude the presence of coexisting AKI.

In high-income countries, the first 48 hours of the SCr trajectory of patients hospitalized with initially elevated SCr has been used to evaluate the rate of AKI development and to assess whether kidney injury is transient or persistent.¹⁷⁷ In this approach, the attainment of peak SCr after the initial creatinine elevation is considered an indication of persistent AKI. In LMICs, when community patients reach hospitals with established AKI such time-course information is usually not available. In those situations, excluding the possibility of the preexisting presence of CKD on a clinical basis may not be possible. Diagnosis may require either a kidney biopsy or be made retrospectively, when kidney function fails to improve despite appropriate supportive therapy.

Limitations

The recommendations in this paper should not be limited to LMICs, but extended to all areas where nephrology resources are not widely available due to a variety of reasons, including cultural, geographic, or religious limitations. The World Bank country economic classification does not necessarily reflect either the health care structure or health care investment of each country. Many countries included in the LMIC category offer universal health care coverage, whereas some subpopulations in high-income countries may not have access to primary care, such as refugees, minorities, aboriginal peoples, or persons without health care coverage. Efforts should be directed toward a more granular analysis of the impact of health care investment and delivery on the recognition and management of AKI. Current limitations in the understanding of the epidemiology of AKI in LMICs are only beginning to be understood; continuously improving information will be necessary to enable the development of more accurate recommendations.

Conclusions

Measures to increase AKI awareness and recognition are essential to improve the treatment and prognosis of AKI in all regions of the world. To ensure a prompt to potentially reversible AKI, once a preliminary diagnosis is obtained by the demonstration of an elevated SCr, patients must be managed as if they had AKI until

proven otherwise. Whenever possible, we recommend the pursuit of a diagnostic strategy geared toward the identification of the etiology of AKI to guide therapeutic options. This is particularly important in LMICs, where various endemic infections and toxicities often underlie renal damage. AKI is potentially treatable and reversible, and treatment is often specific to the underlying condition.

To enhance AKI recognition, it is necessary to promote a better understanding of this epidemiological association of AKI with highly prevalent conditions, including endemic diseases, and to promote widespread education on AKI at all levels and to all members of the health care system.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENT

Supported through the UAB-UCSD O'Brien Center NIH-NIDDK Grant DK079337.

AUTHOR CONTRIBUTIONS

JC, SM, GG, VJ, SS, SG, RC, and RM all participated in the consensus-building process and drafting of this paper. RM, RC, and AB provided a critical review of this paper.

SUPPLEMENTARY MATERIAL

Appendix S1. ADQI participants' names and affiliations. Supplementary material is linked to the online version of the paper at www.kireports.org.

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