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The definition of acute kidney injury and its use in practice

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Acute kidney injury (AKI) is a common syndrome that is independently associated with increased mortality. A standardized definition is important to facilitate clinical care and research. The definition of AKI has evolved rapidly since 2004, with the introduction of the Risk, Injury, Failure, Loss, and End-stage renal disease (RIFLE), AKI Network (AKIN), and Kidney Disease Improving Global Outcomes (KDIGO) classifications. RIFLE was modified for pediatric use (pRIFLE). They were developed using both evidence and consensus. Small rises in serum creatinine are independently associated with increased mortality, and hence are incorporated into the current definition of AKI. The recent definition from the international KDIGO guideline merged RIFLE and AKIN. Systematic review has found that these definitions do not differ significantly in their performance. Health-care staff caring for children or adults should use standard criteria for AKI, such as the pRIFLE or KDIGO definitions, respectively.

These efforts to standardize AKI definition are a substantial advance, although areas of uncertainty remain. The new definitions have enabled the use of electronic alerts to warn clinicians of possible AKI. Novel biomarkers may further refine the definition of AKI, but their use will need to produce tangible improvements in outcomes and cost effectiveness. Further developments in AKI definitions should be informed by research into their practical application across health-care providers. This review will discuss the definition of AKI and its use in practice for clinicians and laboratory scientists.

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Why have a definition of acute kidney injury?

Acute kidney injury (AKI) is a frequent and sometimes devastating syndrome, with high costs to patients and health-care systems.[1,2] It has multiple risk factors or causes.[2,3] A uniform definition of AKI is needed that can be applied in both clinical practice and research, to enable recognition and treatment consistently across health-care systems. An ideal definition might have these characteristics:

1. Limited complexity—allowing a certain memorability. For instance, the New York Heart Association's classification of functional status in heart failure remains well used,[4] perhaps because of its simplicity.
2. Correlation should exist between stages and outcome.
3. High sensitivity and specificity to detect a disease such as AKI with a high diagnostic accuracy.
4. Low to moderate cost to operate the definition in real time.

Such an ideal definition of AKI currently does not exist, perhaps to be expected for a syndrome of many causes, which has only limited markers. In the course of developing AKI guidance for the UK's National Institute for Health and Care Excellence (NICE), we considered many of the issues discussed in this review.

Development of current definitions of AKI

Currently, most studies of AKI detection are based on serum creatinine levels, with or without urine output measurement. Historically, this area was plagued by multiple and conflicting criteria for AKI. To address this, in 2004, the Acute Dialysis Quality Initiative group[5] published their landmark consensus definition of AKI in adults, the **R**isk, **I**njury, **F**ailure, **L**oss, and **E**nd-stage renal disease (RIFLE) classification. This gave five stages of AKI. AKI was defined as a rise in creatinine of $\geqslant$50% from its baseline value and/or a fall in the glomerular filtration rate (GFR) by $\geqslant$25%, and/or a decrease in urine output below 0.5 ml/kg/h for 6 h or more. The 'acute' element of the definition of AKI requires that creatinine is observed to rise within a specified time frame.

Table 1 | The initial diagnosis (detection) and staging of acute kidney injury in adults according to KDIGO[3]

Stage	Creatinine	Urine output
1	Rise of $\geqslant$26 μmol/l[a] or 0.3 mg/dl within 48 h	$<$0.5 ml/kg/h for more than 6 h
	Or 50–99% Cr rise from baseline within 7 days[b] (1.50–1.99$\times$baseline)	—
2	100–199% Cr rise from baseline within 7 days[b] (2.00–2.99$\times$baseline)	$<$0.5 ml/kg/h for more than 12 h
3	$\geqslant$200% Cr rise from baseline within 7 days[b] ($\geqslant$3.00$\times$baseline)	$<$0.3 ml/kg/h for 24 h or anuria for 12 h
	Or (current) Cr $\geqslant$354 μmol/l, with either: rise of $\geqslant$26 μmol/l[a] or 0.3 mg/dl within 48 h or $\geqslant$50% Cr rise from baseline within 7 days[b]	—
	Or any requirement for renal replacement therapy	—

Abbreviations: Cr, creatinine; KDIGO, Kidney Disease Improving Global Outcomes.
The initial diagnosis or detection of acute kidney injury is based on a patient meeting any of the criteria for stage 1. Staging is carried out retrospectively when the episode is complete. Patients are classified according to the highest possible stage where the criterion is met, either by creatinine rise or by urine output.
[a]SI units rounded down to the nearest integer.
[b]Where the rise is known (based on a prior blood test) or presumed (based on the patient history) to have occurred within 7 days.

RIFLE required that the $\geqslant$50% rise was known or presumed to have developed over $\leqslant$7 days.

Large studies have shown that small rises in creatinine are independently associated with increased mortality.[6–12] Chertow *et al.*[7] studied 9210 inpatients admitted to one academic medical centre. Multivariate analysis showed that a rise in creatinine of $\geqslant$0.3 mg/dl, ($\geqslant$26 μmol/l), was independently associated with an approximately fourfold increase in hospital mortality. Although causality is not fully established, this and other studies[13,14] indicate that patients do not just die from their comorbidities 'with AKI' but die 'from AKI'. In 2007, the AKI Network (AKIN)[15] published their AKI classification for adults, an evolution of the RIFLE criteria. The Risk, Injury, and Failure stages became stage 1, 2. and 3, and a $\geqslant$0.3 mg/dl rise in creatinine within 48 h was included in stage 1. GFR criteria were removed as markers of adult AKI. The Loss and End-stage categories of RIFLE were dropped as they were felt to be outcomes, not stages.

The recent International Kidney Disease Improving Global Outcomes (KDIGOs) guideline[3] merged RIFLE and AKIN (Table 1). Although AKIN stipulated that adequate fluid resuscitation should have been undertaken and urinary obstruction excluded before applying the criteria, this was not specified by KDIGO. KDIGO also modified the criteria for stage 3 AKI, including any rise in creatinine to $\geqslant$4.0 mg/dl ($\geqslant$354 μmol/l), when the rise is $\geqslant$0.3 mg/dl ($\geqslant$26 μmol/l) or $\geqslant$50% within the time frames noted above. This has the effect that such rises in creatinine in a chronic kidney disease (CKD) patient are classified as stage 3, whereas such a rise in a patient without CKD is classified as stage 1. There has been some controversy regarding the KDIGO guideline,[16–18] which has been acknowledged by the KDIGO group.[19] The term 'acute kidney disease' (AKD) was proposed when kidney damage is present for $<$3 months (unlike CKD). Within this, AKI is a subset in which the disease process is known or inferred to have occurred within 7 days. A biopsy study found that 35% of cases with acute diffuse parenchymal pathology did not meet the KDIGO criteria for AKI, mainly because of a slow rise in creatinine.[20] Non-AKI cases of AKD had similar outcomes to AKI, so the division between AKI and AKD may be arbitrary. The introduction of a further term may risk confusing clinicians, particularly the nonspecialist.[16] The criterion for acute-on-chronic kidney disease (ACKD) proved controversial because of biological variability (see below).[16,17] There remain unresolved issues with the definition of AKI and ACKD, in particular correlation with baseline renal function, renal parenchymal measurements by imaging, biopsy data, and renal recovery.

Initial detection of AKI is based on the early change in a marker of AKI and needs to be carried out in real time (Figure 1). Staging differs in that it determines the maximum severity of AKI—for example, as indicated by the peak creatinine value—and can only be done retrospectively at the end of the episode. The rapid development of these definitions represents a major advance. Further development needs to include testing of use by nonspecialists, use in CKD patients, and incorporation of baseline function. In the longer term, evidence-based definitions should allow more accurate data collection for research, registries, and audits. The emphasis of the NICE AKI guideline was that clinicians should use a definition, such as KDIGO for adults and pediatric RIFLE (pRIFLE) for children, in routine clinical practice.[2] The above controversies do not detract from that advice.

Comparison of RIFLE, AKIN, pRIFLE, and KDIGO

The recent NICE systematic review[2,23] investigated the ability of the AKIN, RIFLE, pRIFLE, and KDIGO definitions to, first, diagnose and stage AKI and, second, to predict future adverse outcomes. Agreement between classifications was reported only in four studies.[24–27] One study in children and young people was included comparing pRIFLE to AKIN.[28] Broadly similar percentages of adult patients were diagnosed by RIFLE or AKIN as stage R, I, or F or stages 1, 2, and 3 (respectively), with similar findings for pRIFLE and AKIN in children.[23] In adults, there was generally good agreement between RIFLE and AKIN, with each definition performing similarly in different settings. Only one study included KDIGO, finding the incidence of AKI to be identical to that using AKIN.[25]

For prognostic outcomes, we included cohort studies with a multivariate analysis, including confounding factors, to assess whether AKIN, KDIGO, or RIFLE stages were independent prognostic factors. Fourteen studies in adults

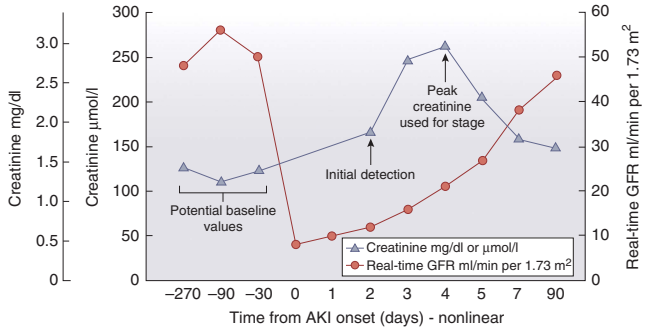

Figure 1 | A hypothetical example of real-time glomerular filtration rate (GFR) and creatinine values before and during an episode of acute kidney injury (AKI). There is a single insult to the kidneys with an abrupt drop in GFR (a 'ramp decrement'[21,22]). This shows creatinine values in the months before the episode, from which a baseline value will be selected (see text). Often creatinine values at the onset of illness are not available. Creatinine peaks on day 4 with a rise of about 115% (stage 2 AKI). Note the lag between the changes in GFR, compared with the later creatinine rise and recovery.

were included: five in which AKIN and RIFLE were directly compared within the same population,[24,26,29–31] one study using AKIN alone,[32] and eight using only the RIFLE criteria.[13,33–39] Eight studies did not include urine output data to define AKI.[13,26,31,33–35,38–39] The association between stage and mortality for the same classification varied substantially across studies.[23] Very low to moderate quality evidence[40] showed an increase in mortality with stage of RIFLE. For AKIN, low to moderate quality evidence showed a slight decrease in the median odds ratio for mortality between AKIN 1 and 2; however, mortality was higher with AKIN 3. Three studies of RIFLE[33–35] assessed longer-term mortality (1–14 years), showing a trend for RIFLE stage having diminished the power to predict longer-term mortality. For the studies comparing AKIN and RIFLE within the same cohort, it was possible to analyze this as a ratio of odds ratios to gain a more direct comparison of AKIN versus RIFLE. Figure 2 shows that overall AKIN and RIFLE were comparable in predicting mortality. Studies of patients needing renal replacement therapy did not consider covariates, and therefore interpretation of the results was limited. Only one small single center study, in intensive care, examined the prognostic use of creatinine change and urine output.[30] Overall, there was no evidence that the combination of creatinine and urine output improved prediction of mortality, compared with monitoring creatinine alone. For pediatrics, two single center studies were included in the prognostic review: one directly compared the AKIN and pRIFLE classifications within the same population,[28] whereas another used the pRIFLE criteria alone.[41] In both, pRIFLE and AKIN showed a similar and graded relationship to mortality across the stages. The limited data did not show any superiority of either classification.

Review of these studies revealed important issues, which may have implications when interpreting the data. The majority of studies were based on critical care databases, and their conclusions may not apply to other patient populations. Studies differed in how the definitions were applied (whether serum creatinine, urine output, or both were used to define AKI, and in how baseline renal function and missing baseline results were handled).[2] To show a difference in diagnostic accuracy or prediction of mortality for related definitions is challenging, and requires large studies with longer-term follow-up.

Measurement of kidney function in adults with AKI

At the onset of AKI, assuming a simple single insult to the kidneys, such as a defined period of ischemia, the true GFR will drop rapidly to a nadir. Serum creatinine will then rise over hours to days,[21] before a new steady state is reached (Figure 1). Some AKI patients sustain multiple renal insults over a prolonged period,[21] further complicating the assessment of renal function. Estimated GFR (eGFR) will take days before it reflects the true GFR.

The Modification of Diet in Renal Disease (MDRD) equations were developed in patients with stable CKD[42] and are inappropriate for use in AKI in adults.[43] Also, all creatinine-based definitions of AKI can be misleading in patients whose creatinine kinetics and volume of distribution are extreme or variable (Figure 3). The lack of a gold standard[44] in the diagnosis of AKI means that there are no data on the sensitivity and specificity of a creatinine-based diagnosis of the condition.

The creatinine rise used to detect AKI may be measured as a percentage or an absolute rise. The former might be thought to take more account of muscle mass, but there is increasing evidence that the latter may be useful in the detection of AKI.[7–12,45–46] The use of an absolute creatinine rise may identify AKI earlier,[12,46] but data on community-acquired AKI are lacking.

There will be a proportion of patients in whom creatinine or urine output readings will produce a false-positive or a false-negative diagnosis. Creatinine may uncommonly rise acutely for reasons other than AKI (Figure 3). Numerous factors can interfere with laboratory measurement of creatinine, more commonly with Jaffe-based assays (Figure 3). Enzymatic assays are more expensive, deterring their widespread routine use. The measurement of renal function in CKD is discussed elsewhere.[47,48] Creatinine assays should be specific and zero-biased compared with isotope-dilution mass spectrometry reference methods, with calibration traceable to a standardized reference material.[49]

Oliguria as an indicator of AKI

Oliguria is traditionally defined as a urine output of <400 ml/day,[59] equivalent to 0.24 ml/kg/h in a 70-kg patient. It is a complex process with various causes, not only hemodynamic changes or 'tubular necrosis'.[60] Real-time monitoring of GFR showed that oliguria and GFR usually, but not always, show parallel changes in AKI.[61] Oliguria is a frequent occurrence in intensive care,[62] but is infrequently followed by AKI, as defined by a later creatinine rise. Interestingly, oliguria without a rise in

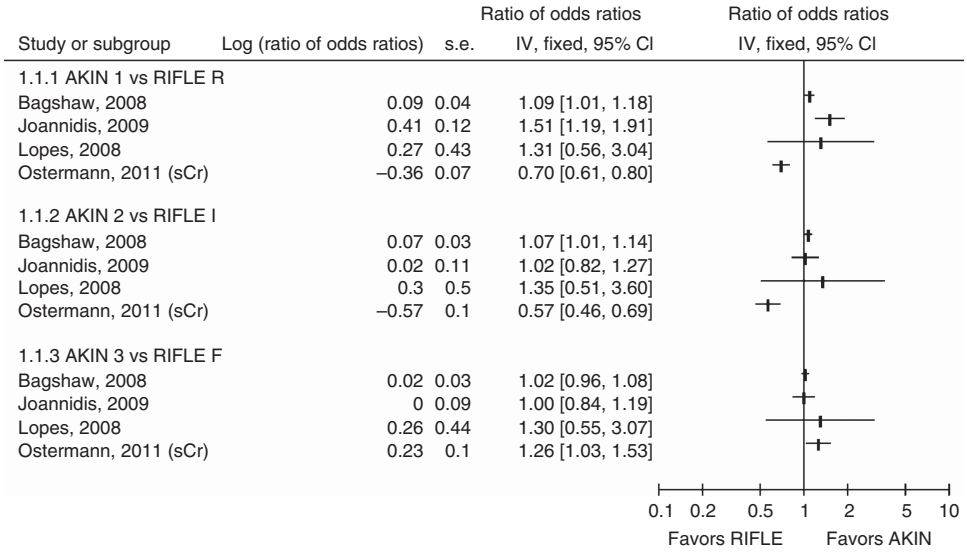

Figure 2 | Mortality (AKIN versus RIFLE). The figure shows the ratio of odds ratios (RORs) for each stage of AKI within RIFLE and AKIN. A ROR >1 indicates that AKIN is a better predictor compared with RIFLE. For example, Lopes[30] had odds ratios for mortality of 2.01 for RIFLE I and 2.71 for AKIN 2. This results in a ROR of 1.35 in favor of AKIN, as shown with 95% confidence intervals. Reproduced by permission of the National Institute of Health and Care Excellence.[23] AKI, acute kidney injury; AKIN, AKI Network; CI, confidence interval; RIFLE, Risk, Injury, Failure, Loss, and End-stage renal disease; sCr, serum creatinine.

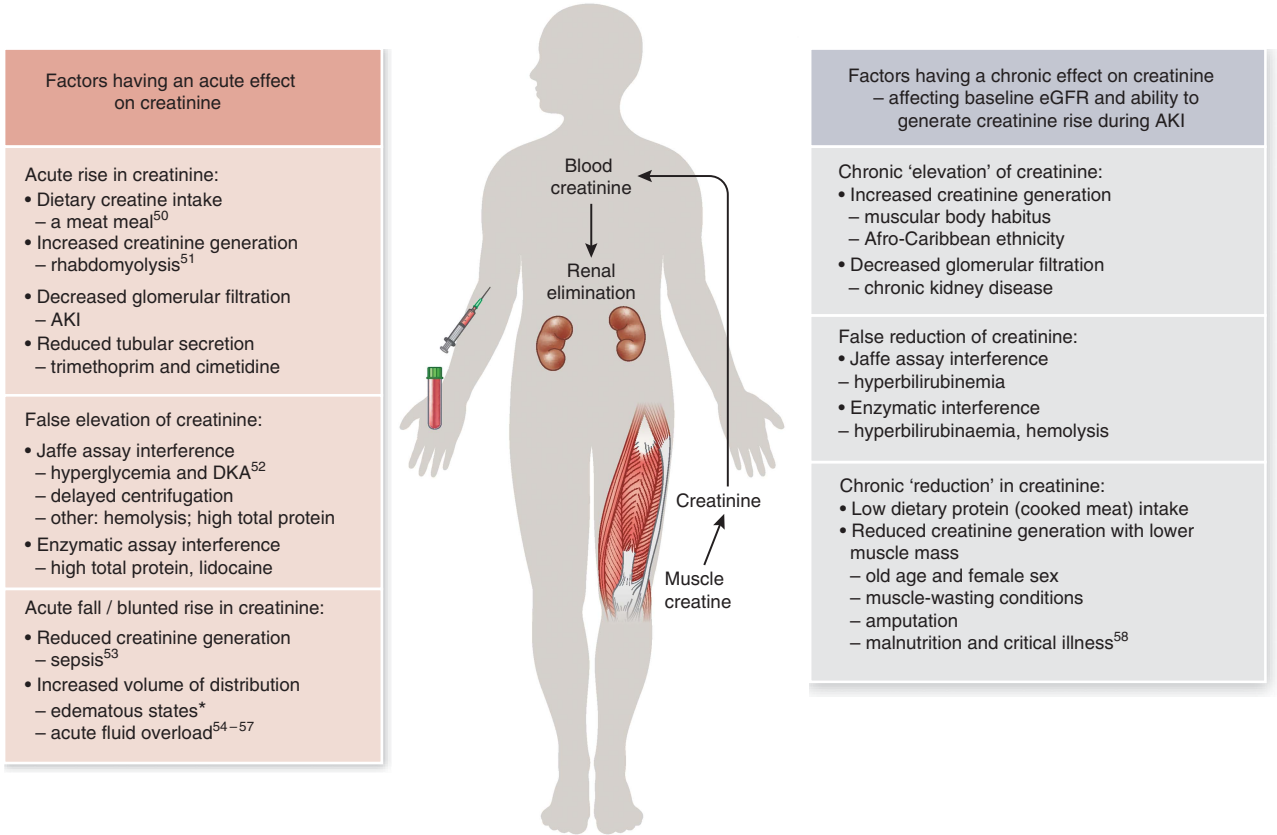

Figure 3 | Factors affecting serum creatinine interpretation in possible acute kidney injury (AKI). Many factors can cause an acute increase (left panel) or decrease in creatinine, often making the confident diagnosis of AKI difficult. The estimation of GFR to determine baseline status is also affected by many factors (right panel). Creatinine generation is reduced with lower muscle mass, which will blunt any rise in creatinine with AKI. Assay interferences are more pronounced at normal than at elevated levels of creatinine. Good laboratory practices should routinely detect hemolysis, icterus, and delayed separation, preventing the release of erroneous results. Note blood creatinine is eliminated by glomerular filtration but also by tubular secretion.[57] *Edematous states: cirrhosis, the nephrotic syndrome, and heart failure. DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate.

creatinine shows higher mortality than in patients with no evidence of AKI.[63] Oliguria independently predicts a higher risk of mortality.[64–67]

Short durations (<4 h) of oliguria show reduced sensitivity and specificity for predicting later AKI, defined by creatinine criteria.[62] A strict interpretation of the definition of oliguria[5,15] is a urine output <0.5 ml/kg/h in each of the 6 consecutive hours. However, total urine output of <3 ml/kg over a fixed 6 h block showed the best predictive ability.[63,68] In a larger prospective study, a threshold of <0.3 ml/kg/h for 6 h was most predictive of death and/or dialysis, suggesting that the current criterion is too liberal.[69] The optimum threshold for oliguria varies with its duration—thus urine output averaging <0.5 ml/kg/h over 12 h may be equivalent in seriousness to <0.3 ml/kg/h for 6 h. The existing urine output criteria appear to diagnose more patients with AKI than using the creatinine criteria alone,[63,68] however, that may not translate into improved mortality prediction (see above). Thus, the same stage of AKI, defined either by creatinine rise or oliguria, may have different prognostic implications.

Other methods of measuring kidney function in AKI

As yet there are no readily available methods for continuous monitoring of the GFR.[70] Rabito *et al.*[61] demonstrated that such monitoring is feasible. It is likely to be introduced in the future once practical obstacles have been overcome.[70] Short 2 (ref. 71) to 4 (ref. 72) hour urine collections with a blood sample for creatinine clearance determination are a useful method of relatively rapid kidney function assessment. This is the case in spite of oliguria or irregular urine output in unstable AKI patients. The 4-h creatinine clearance has been shown to detect AKI earlier than a plasma creatinine rise.[72]

Variability of creatinine measurement and relevance to AKI

The factors that influence variability in creatinine are better understood by laboratory scientists.[73–76] It is possible to calculate the change in creatinine that represents a change in the status of the patient, over and above normal variability in health, with a specified probability. This is the reference change value (RCV—Table 2) and reflects a change above that which might be expected because of normal pre-analytical, analytical, and biological variation. The RCV for a rise in creatinine has been estimated at 14% (ref. 74) to 17%, (ref. 76) and its use has been suggested for incorporation into laboratory reporting and AKI definitions.[75–77] These estimates of RCV were derived from healthy subjects or stable CKD patients under highly standardized conditions, in the absence of factors that interfere with assay specificity. They may underestimate the true RCV in the acutely unwell and those with AKI (as conditions cannot be standardized), and the RCV is likely to exceed that of a healthy population.[75,76] The relatively small rises of creatinine now incorporated into the definition have to be seen in this context, particularly in CKD (Table 2). So creatinine increments at the lower end of the spectrum may not exceed expected variability attributable to factors other than renal function, and clinicians need to take this into account in their decision making. This may explain why small absolute rises in creatinine are associated with lower mortality risk in CKD.[10,78] Nevertheless, such rises should be taken as a possible warning of serious illness.

Table 2 | Biological variability and its effect on AKI

Baseline mg/dl	Creatinine µmol/l	Absolute mg/dl	Rise µmol/l[a]	% Rise	*Z*-score	Probability or *P*-value
1.0	88	0.3	26	30.0	2.91	<0.002
2.0	177	0.3	26	15.0	1.46	0.07
3.0	265	0.3	26	10.0	0.97	0.17
4.0	354	0.3	26	7.5	0.73	0.23
5.0	442	0.3	26	6.0	0.58	0.28

Abbreviation: AKI, acute kidney injury.

Creatinine in a stable, well person varies in a relatively narrow range around a homeostatic 'set point.'[73,75] Interpretation of a change in creatinine is affected by biological and analytical (laboratory) variability. The reference change value (RCV) indicates the value by which two serial results must differ to be considered statistically significant:

$RCV = 2^{½} * Z * (CV_A^2 + CV_I^2)^{½}$

where: CV_A, analytical variability; CV_I, biological or within-individual variability; Z, the standard normal deviate value determined by the required degree of significance (for example, 95% probability).

$RCV = 2^{½} * Z * (CV_A^2 + CV_I^2)^{½} = 2^{½} * 1.65 * ((0.05)^2 + (0.053)^2)^{½} = 0.17$

CV_A, 5% for creatinine;[76] CV_I, 5.3% for creatinine in healthy individuals;[76] Z, 1.65 for a power of 95% to detect a rise in creatinine (the one-tailed *t*-test).

In addition, the equation can be rearranged to determine the *z* value for any given rise in creatinine, and hence find the probability that the rise is a random fluctuation:[79]

$$Z = \frac{\text{Change}}{2^{1/2} * (CV_A^2 + CV_I^2)^{1/2}} = \frac{\%\,\text{Change}}{10.3} \quad \text{for the above } CV_A \text{ and } CV_I$$

Small absolute creatinine rises on a background of chronic kidney disease are progressively smaller percentage increases as baseline creatinine rises (above). Thus, in chronic kidney disease, the probability that small absolute rises are random variation is considerable.

[a]Rounded down to the nearest integer.

Baseline kidney function

The baseline creatinine value is a measure of the patient's premorbid kidney function and is compared with the current value in the detection and staging of AKI (Figure 1). Methods of 'looking back' to obtain a baseline value for the initial detection of AKI (Table 3) have been studied and can be incorporated into routine laboratory reporting.[80] Broadly, these methods are as follows:

a Using a short time frame—requiring a measured creatinine within 7 days from the current value
b Using a longer time frame—finding a measured creatinine between 7 and 365 days before the current value from all results within the time window (Figure 1).
c By 'imputation'—when creatinine results are missing.

KDIGO suggested the use of the lowest creatinine during hospitalization as the baseline value,[3] although this was before the publication of important data.[81] KDIGO does allow the use of the longer time frame method, in an otherwise stable patient, with no recent creatinine and without (progressive) CKD.[3] The longer time frame will detect more patients with less severe AKI, who may have a

Table 3 | Methods for determining baseline kidney function in AKI

Methods of baseline determination	Comments
Use of creatinine results within last 7 days	• May need high rate of imputation—in one study, 29% of patients had a creatinine within 7 days of admission[81] • Risk of creatinine elevated by prodrome being used as 'baseline'—hence, extent of AKI underestimated[81]
Admission creatinine	• Higher than outpatient creatinine; reduced detection of AKI—likely reflects community-acquired AKI[83]
Minimum inpatient value during first 7 days of admission as baseline	• KDIGO suggested the use of lowest creatinine during hospitalization[3] • Lower than outpatient creatinine • Overestimates prevalence of AKI[83]
Imputation or back-calculation by reversing MDRD equation using age, sex, and an assumed normal GFR of 75 ml/min per 1.73 m^2	• Baseline creatinine will often be underestimated, and GFR overestimated, notably in CKD[84] • Prone to error[83,85,86]
Mean outpatient value as baseline (− 7 to − 365 days look-back[a])	• Highest correlation 0.91[b] with adjudicated baseline value—availability 81% of patients in the study[81]
Most recent outpatient value as baseline (− 7 to − 365 days look-back[a])	• Moderately lower correlation 0.84[b] with adjudicated baseline value[81]
Lowest or nadir outpatient value as baseline (− 7 to − 365 days look-back[a])	• Moderately lower correlation 0.83[b] with adjudicated baseline value[81]
Most recent inpatient or outpatient value as baseline (− 7 to − 365 days look-back[a])	• Allows inclusion of last creatinine from previous inpatient stay if ⩾7 days away • May allow simpler programming • Correlation 0.88[b] with adjudicated baseline value—availability 93% of patients in study[81]
Extended baseline look-back (− 7 to − 730 days)	• Improved availability of baseline creatinines but some drop in correlation with adjudicated baseline[81]
Multiple imputation	• Recently assessed as a research technique[87]

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease Improving Global Outcomes; MDRD, Modification of Diet in Renal Disease.
[a]7–365 days before admission.
[b]Intra-class correlation coefficient.

lower mortality.[78] All methods are a working compromise: trying to use a measured creatinine, avoiding creatinine values influenced by the illness prodrome, and going back only as far as needed to earlier creatinine values. The older the creatinine result, the higher the chance that it will not reflect the true baseline function shortly before the onset of AKI.

So what is the best method to find the baseline creatinine (Table 3)? Siew *et al.*[81] studied various ways of picking a baseline value for hospitalized patients, compared with a 'gold standard' value adjudicated by a panel of nephrologists. The mean outpatient creatinine during 7–365 days before admission correlated most closely with the adjudicated value. This is likely the best method, if automatic selection of a value can distinguish between outpatient and inpatient results.

In the absence of such values, the controversial use of 'imputed' baseline creatinine values has been advised. The GFR equation from the MDRD study is reversed using a normal GFR of 75 ml/min per 1.73 m^2, to then back-calculate a presumed baseline creatinine for that patient. The use of imputation requires that the relevant IT system has a table of imputed values,[3,5] adjusted for the local isotope-dilution mass spectrometry traceable version of the MDRD equation.[47] The overestimation of kidney function may be reduced if age- and sex-matched creatinine or GFR values are used. There will still be some false-positive detection of AKI, but realistically this is necessary. As an example, one university hospital runs a fully automated AKI electronic alert (e-alert), using RIFLE or AKIN criteria.[82] Creatinine on admission is compared with the lowest creatinine from 7 to 365 days before admission. Using this time frame, ~80% of patients have a measured baseline creatinine available, reducing imputation.

Using a definition in practice to warn of possible AKI

Health-care IT systems have developed the ability to 'alert' the clinician to a potential problem with patient care. Alert use has been successful in changing clinician behavior and outcome, with reductions in nephrotoxic medication use in AKI,[88,89] and prevention of contrast-induced AKI (CI-AKI).[90] The use of alerts in critical care has been reported to increase interventions in AKI.[91] The options for warnings include the following:

(a) a passive alert, such as a warning statement with AKI stage as an addendum to the creatinine result, which might contain a hyperlink to the local AKI clinical guideline or
(b) an interruptive alert, where the clinician has to acknowledge the alert, or
(c) an active alert, where a direct response is triggered, such as an outreach team visit.

Some alert studies have failed to change clinician behavior.[92] Furthermore, clinicians may override or defer a response to alerts.[89,93,94] In one study of nephrotoxic medication use in AKI patients, interruptive alert warnings were deferred a median of four times before a definitive response.[89] Alert fatigue remains a concern for clinicians assailed by a barrage of alerts for various conditions within IT systems.

A basic form of AKI e-alert utilizes a 'delta check' to identify a percentage[95] or an absolute[76] increase in creatinine compared with the immediate previous creatinine, whenever that was measured. Such an alert is simple to operate and can detect large numbers of AKI patients.[95] A delta check looking for any absolute rise of $>26\,\mu mol/l$ (0.3 mg/dl) within 30 days is effective.[76] Recent e-alert studies have employed definitions based on RIFLE, AKIN, or, more recently, KDIGO criteria.[96] A recent national audit across England found that acute hospitals with various alert algorithms quite consistently detected AKI stage 3 in 1–2% of emergency admissions (Dr James Medcalf, personal communication).

Algorithms can operate in the laboratory information management system or within other hospital information systems. More sophisticated alert algorithms interface with the Patient Administration System, to identify dialysis patients, and prevent false-positive alerts.[82] A UK consensus conference encouraged the use of electronic alerts for AKI.[97] A standardized algorithm for automated KDIGO-like staging is currently undergoing mandatory implementation in the United Kingdom.[80] Manufacturers of laboratory information management system are incorporating AKI e-alerts within their systems.

Specific situations

Acute-on-CKD. AKI poses particular risks to CKD patients.[14,98–101] The handling of CKD patients who develop AKI (or ACKD) is difficult within an AKI definition. Percentage rises in creatinine are curtailed in CKD and do not readily detect ACKD.[46] It is known that progressively larger absolute rises in creatinine are required to show an independent association with mortality as the baseline GFR falls.[10] Current AKI staging may have lower prognostic value in CKD when based on absolute increases in creatinine at the lower end of the spectrum. However, clinicians need to recognize the serious risks for the patient facing ACKD, and placing it in stage 3 does, in our opinion, convey an appropriate message.

Transient AKI. Transient AKI is a rapidly reversible form of AKI, closely related to 'pre-renal azotemia.'[102–105] However, it is not benign. Recent evidence suggests that it does involve modest structural injury to the kidney and is best viewed as part of a spectrum of injury.[106] Patients who developed a transient $\geqslant 26\,\mu mol/l$ rise in creatinine within 48 h (while in hospital) had significant mortality (13–14%), compared with patients without AKI (3%).[102] Another larger study found that transient AKI, defined as recovery within 3 days of diagnosis, represented one-third of all AKI. Hospital mortality was 4, 15, and 29% for no AKI, transient AKI, and persistent AKI, respectively.[103] Transient AKI is not separately recognized by current definitions.

Contrast-induced AKI. The development of CI-AKI is shown by a rise in creatinine, typically peaking at 24–72 h after iodinated contrast administration.[107] It is defined among radiology organizations as an absolute rise of $\geqslant 44\,\mu mol/l$ ($\geqslant 0.5$ mg/dl) or a relative rise of $\geqslant 25\%$ from the baseline value (without an alternative explanation).[108,109] The detection of CI-AKI depends on the time point(s) at which creatinine is measured—for example, at 24 or 48 h or both.[110,111] The absolute rise identifies fewer cases than a relative rise[112] and is associated with considerably higher mortality.[113,114] The relative rise of $\geqslant 25\%$ has been found to occur in over one half of inpatients who are not exposed to contrast.[115] We and others have suggested that the definition of CI-AKI should be changed to the KDIGO AKI definition to allow further standardization and data collection on outcomes.[116]

AKI in the intensive care unit. AKI is particularly common in intensive care unit patients. AKI definitions based on creatinine have limitations when applied to critically ill patients in the intensive care unit for prognostic purposes (Figure 3).[53–55] Creatinine levels can rise more slowly, contributing to a delay in the diagnosis of AKI. The AKIN and KDIGO classification recommend that patients who receive acute renal replacement therapy should automatically be classified as having AKI stage 3. However, clinical practice is very variable. In addition, renal replacement therapy may be initiated for reasons other than clearance, for instance, to maintain a euvolemic fluid balance. Hence, AKI staging depends directly on the decision-making process rather than renal function.[31] Finally, the timing of change is particularly important in the critically ill with AKI. The prognosis of patients admitted with AKI stage 3 is significantly better than that of patients with the same degree of renal impairment, which occurred later while in hospital.[31] Current AKI definitions do not take this into account.

Pediatric AKI

Measurement of kidney function in children with AKI. After 2 years of age, renal growth results in a GFR equivalent to that of adults, when adjusted for body surface area.[117,118] The older Schwartz equation[119,120] for estimating GFR in children is no longer valid.[121] Schwartz *et al.*[118,122] developed an updated version of their eGFR equation for children with CKD (aged 1–16 years), using an isotope-dilution mass spectrometry traceable creatinine assay. This 'Bedside Schwartz equation' has been validated in a non-CKD population.[123] An example of its use is given in Table 4. Different methodologies for measurement of creatinine require method-specific age-standardized reference ranges in children. The lack of specificity of Jaffe-based methods is particularly marked at the low creatinine values encountered in children. For these reasons, many laboratories use enzymatic assays for neonatal and pediatric populations. Using isotope-dilution mass spectrometry-calibrated enzymatic creatinine assays for all pediatric patients should enable the use of harmonized age-standardized reference ranges in children.[124] We call on Clinical Chemistry societies and laboratories to work with their pediatricians to introduce these ranges. This will facilitate the introduction of AKI alerts for children. The use of eGFR estimated by the revised Schwartz formula to detect AKI in children needs further

Table 4 | An example of pediatric AKI in a 7-year-old child with length (height) of 120 cm

Premorbid (baseline)			AKI		Change
Height	120 cm		Height	120 cm	
Cr	50 μmol/l (0.57 mg/dl)	→	Cr	67 μmol/l (0.76 mg/dl)	33% Rise
eGFR*	88 ml/min per 1.73 m^2		eGFR	65 ml/min per 1.73 m^2	25% Fall

Abbreviations: AKI, acute kidney injury; Cr, creatinine; eGFR, estimated glomerular filtration rate.
eGFR is calculated using the revised or Bedside Schwartz equation,[118,122,123] which adjusts the estimated GFR to a standard (adult) body size of 1.73 m^2. Note, the reduction in eGFR with AKI is 25%—that is, pRIFLE stage R, while the increase in creatinine (Cr) is 133%—that is, less than the required increase in Cr to be classified as pRIFLE stage R. Thus, the change in kidney function in one child may be classified differently, if either GFR or creatinine alone is used.[125] This is inherent with the use of both creatinine and GFR changes within the same definition (that is, within RIFLE or pRIFLE).
The original Schwartz equation[119,120] (using a modified Jaffe reaction to measure creatinine):

$$\text{GFR (ml/min per 1.73 m}^2) = \frac{0.55\times(\text{length or height})(\text{cm})}{\text{Creatinine (mg/dl)}} \quad \text{or}$$

$$\frac{48.6\times(\text{length or height})(\text{cm})}{\text{Creatinine }(\mu\text{mol/l})}$$

The revised or 'Bedside' Schwartz equation[118,121–123] (using an enzymatic assay of creatinine—traceable to an isotope-dilution mass spectrometry reference):

$$\text{GFR (ml/min per 1.73 m}^2) = \frac{0.413\times(\text{length or height})(\text{cm})}{\text{Creatinine (mg/dl)}} \quad \text{or}$$

$$\frac{36.5\times(\text{length or height})(\text{cm})}{\text{Creatinine }(\mu\text{mol/l})}$$

To convert creatinine in mg/dl to μmol/l, multiply by 88.4.

study. The studies of GFR estimation in children do not include neonates.

The pRIFLE definition of AKI in children. Pediatric AKI is mainly an issue for children in critical care. A pediatric modification of the RIFLE definition (pRIFLE) was developed[126] using the original Schwartz equation[119] to calculate 'estimated creatinine clearance' or eGFR. The KDIGO guidelines[3] refer to pRIFLE for the definition of AKI in children, and the latter remains the one in use for children aged over 1 month. Further work is needed before pRIFLE can be recommended for neonates.

The pRIFLE definition was subsequently confirmed to be of value.[127] It stages AKI by the fall in eGFR, rise in creatinine, or decrease in urine output (Table 5). Zapitelli *et al.*[128] found that the use of change in eGFR, with the original Schwartz formula, resulted in a higher prevalence of AKI diagnosis, compared with that using change in creatinine in pediatric inpatients. A change in eGFR may result in different staging compared with the increase in creatinine in the same patient (Table 4). This definition requires a comparison with eGFR measured in the previous 3 months.[126] If no creatinine result is available in that time period, imputation is permitted assuming a previously normal GFR of 100 ml/min per 1.73 m^2 and using the patient's height. The likelihood of a child who develops AKI having undiagnosed CKD is very low (unlike adults), justifying the assumption of a previously normal eGFR.

Schneider *et al.*[41] used the RIFLE classification based on serum creatinine alone and found it to be valid in their pediatric intensive care unit population. The use of serum creatinine, and not eGFR, has one advantage: accurate measurement of height is necessary to calculate eGFR using the Schwartz formula, and this can be difficult in sick, ventilated patients. There are few published studies using pRIFLE, and there is variation in both the reported incidence of AKI[129] and the exact methodology for defining AKI.[128] Nevertheless, the studies do show a correlation between adverse outcomes and increasingly severe AKI (above). A study of an automated electronic intervention to reduce exposure to nephrotoxins, combined with pRIFLE detection of AKI, suggests that AKI can be reduced in non-critically ill children.[130]

Biomarkers—where are we in practice?

The issue of novel biomarkers was not within the scope of the recent NICE guideline.[2] AKI biomarkers are broadly divided into functional or structural (indicating injury or damage) biomarkers.[131–134] There is much expectation that they will be incorporated into definitions of AKI as well as routine clinical practice. However, some degree of caution is warranted.[135] Various obstacles exist to the widespread routine application of biomarkers,[44,136–138] including

- poorer performance when the timing of renal insult(s) is unknown[137]
- reduced performance in the presence of common confounding comorbidities, especially CKD and sepsis[139–143]
- inability to reliably detect AKI at the level of the individual, especially in the presence of heterogeneous causes, CKD, and comorbidities[139,141,142,144]
- inability of biomarkers to determine the specific etiology of AKI.[134]

It has been suggested that AKI should be designated a 'Kidney attack',[145] analogous to heart attack, and that a 'renal troponin' may be used to detect AKI earlier in its course, similar to the use of cardiac troponin in the detection of myocardial infarction. Unfortunately, the analogy between the two conditions breaks down when interventions are considered. Myocardial infarction has specific treatments. Even if a biomarker reliably shows early AKI, there are currently no specific therapies for ischemic or septic tubular injury. There have been conflicting results regarding the ability of biomarkers to improve on the predictive value of clinical factors.[136,146–149] A large study of biomarkers after the timed insult of cardiac surgery found a modest increase in the predictive power for outcomes with their use.[147] A study of two urine biomarkers of cell cycle arrest showed moderate improvement in the prediction of the development of stage 2 or 3 AKI.[149] Another recent study found limited ability to distinguish between AKI cases and controls in intensive care.[150] Demonstrating the cost effectiveness of biomarker

Table 5 | The initial diagnosis (detection) and staging of acute kidney injury in children—comparing pRIFLE, AKIN, AND KDIGO

Stage	pRIFLE criteria[126]	AKIN[15]/KDIGO[3,16] criteria	Urine output
Risk or stage 1	—	Rise of ⩾26 μmol/l[a] or 0.3 mg/dl within 48 h	<0.5 ml/kg/h for more than 8 h[b]
	eGFR decrease by ⩾25% or 50–99% Cr rise from baseline within 7 days[c] (1.50–1.99×baseline)	Or 50–99% Cr rise from baseline within 7 days[c] (1.50–1.99×baseline)	—
Injury or stage 2	eGFR decrease by ⩾50% or 100–199% Cr rise from baseline within 7 days[c] (2.00–2.99×baseline)	100–199% Cr rise from baseline within 7 days[c] (2.00–2.99×baseline)	<0.5 ml/kg/h for more than 16 h[b]
Failure or stage 3	eGFR decrease by 75% or eGFR <35 ml/min per 1.73 m^2 or ⩾200% Cr rise from baseline within 7 days[c] (⩾3.00×baseline)	⩾200% Cr rise from baseline within 7 days[c] (⩾3.00×baseline)	<0.3 ml/kg/h for 24 h or anuria for 12 h
	(In pRIFLE, RRT does not automatically equate to stage Failure or stage 3)[126]	Or any requirement for renal replacement therapy	—

Abbreviations: AKIN, the AKI Network; Cr, creatinine; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease Improving Global Outcomes; RRT, renal replacement therapy.
[a]Equivalent to 0.3 mg/dl, with the SI units rounded down to the nearest integer.
[b]Note that the duration of oliguria in the Risk and Injury stages differs from that for the same stage in adults and is quoted for the pRIFLE classification.
[c]Where the rise is known (based on a prior blood test) or presumed (based on the patient history) to have occurred within 7 days.

use in addition to creatinine and urine output monitoring presents a challenge. The patient's general management would be optimized as part of any study. New biomarkers will need to demonstrate 'added value', over and above optimal patient care and use of traditional AKI markers. In future, the earlier detection of AKI with biomarker(s) may allow a targeted approach to the use of novel therapies.

CONCLUSIONS

A universal definition of AKI is crucial for its identification and management. It is vital for translation of preventative and therapeutic research into practice for this condition, which is common in aging societies. The new definitions of AKI have already revolutionized both research and routine clinical practice. We recommend that future modifications are based on thorough evaluation. Research should now extend to evaluation of their practical implementation in diverse clinical settings and their operational performance in prospective studies on AKI clinical interventions. Definitions should now evolve on the basis of evidence, rather than opinion or consensus.[2] The high cost of AKI to an individual's health and to health-care systems means that this field should be a priority for health-care research.

DISCLOSURE

The views expressed in this publication are those of the authors and not necessarily those of the Institute. Dr Ostermann has received speaker honoraria from Fresenius, Gilead, and Alere and has taken part in educational meetings sponsored by Fresenius. All the other authors declared no competing interests.

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