Harmonizing acute and chronic kidney disease definition and classification: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference

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Kidney disease is an important public health problem. Both acute kidney injury (AKI) and chronic kidney disease have been well defined and classified, leading to improved research efforts and subsequent management strategies and recommendations. For those patients with abnormalities in kidney function and/or structure who meet neither the definition of AKI nor chronic kidney disease, there remains a gap in research, care, and guidance. The term acute kidney diseases and disorders, abbreviated to acute kidney disease (AKD), has been introduced as an important construct to address this. To expand and harmonize existing definitions and to ultimately better inform research and clinical care, Kidney Disease: Improving Global Outcomes (KDIGO) organized a consensus workshop. Multiple invitees from around the globe, representing both acute and chronic kidney disease researchers and experts, met virtually to examine existing data, and discuss key concepts related to AKD. Despite some remaining unresolved questions, conference attendees reached general consensus on the definition and classification of AKD, management strategies, and research priorities. AKD is defined by abnormalities of kidney function and/or structure with implications for health and with a duration of ≤3 months. AKD may include AKI, but, more importantly, also includes abnormalities in kidney function that are not as severe as AKI or that develop over a period of >7 days. The cause(s) of AKD should be sought, and classification includes functional and structural parameters. Management of AKD is currently based on empirical considerations. A robust research agenda to enable refinement and validation of definitions and classification systems, and thus testing of interventions and strategies, is proposed.

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In August 2020, Kidney Disease: Improving Global Outcomes (KDIGO) convened a Consensus Conference to address the need to harmonize existing acute kidney disease (AKD) and chronic kidney disease (CKD) definitions, in recognition that the concept of acute kidney diseases and disorders, abbreviated as AKD, as different from acute kidney injury (AKI), is not well acknowledged or understood. Conference participants met virtually in a series of plenary, discussion, and closing sessions. Data were presented, and interpretations debated, with discussion groups focused on 3 related goals of the conference:

(i) to revisit and refine definitions and classifications of AKD to improve understanding and to describe the relationships between AKD, AKI, and CKD;
(ii) to delineate and propose management strategies for AKD; and
(iii) to identify key areas of research in AKD to address improved understanding and improvements in clinical practice and public health.

Herein, we describe the background, rationale, and outputs of those deliberations.

Background

In the last 2 decades, we have defined and classified CKD and AKI, and established standard definitions and staging systems for both. This has enabled robust estimates of their incidence

and prevalence, allowed standardization of their management, and stimulated research and funding in the field of human kidney disease (KD).[1–3]

KDIGO guidelines define KD as functional and/or structural abnormalities of the kidneys with implications for health, and classify KD according to cause, severity of structural and functional abnormalities, and duration of those abnormalities. The key phrase delineating those with KD from those with no kidney disease (NKD) is "with implications for health" (e.g., a simple renal cyst would not have implications for health). AKI has been defined and staged according to serum creatinine (SCr) and/or urine output (UO) criteria; however, this is without mention of duration of AKI, criteria for recovery, or markers of kidney damage (e.g., urinalysis, albuminuria, more recent biomarkers, and imaging abnormalities). CKD is defined by markers of kidney damage or decreased glomerular filtration rate (GFR) persisting for >3 months and is classified according to cause, GFR, and albuminuria criteria (CGA classification). More importantly, patients may have significant abnormalities of function and structure with implications for health and with a duration of ≤3 months that do not fulfill the definitions of AKI or CKD.[2,3] The term AKD should be used to define that time and state (Figure 1). AKI is included specifically within AKD, thus capturing all patients who have functional and/or structural abnormalities with implications for health and for ≤3 months.

Defining and staging AKD enables better description of its incidence, prevalence, morbidity, and mortality, thus allowing development of care models linked to severity, and research on interventions targeted at specific stages of AKD. This requires clear standardized descriptions of methodologies to assess functional and structural abnormalities, methodologies for establishing baseline kidney function from which any change is measured, and approaches to assessing changes in the absence of previous values. Assessment of alterations in kidney function following AKD should also encompass loss or reduction of functional reserve,[4] in addition to kidney function per se (Figure 2). Descriptions need to encompass both adult and pediatric KD and be applicable across all jurisdictions.

AKD may occur either in a setting of no known prior KD or in association with CKD. Recent data suggest that AKD not associated with AKI is common, nearly 3 times more prevalent than AKI, and that like AKI, is associated with increased risk of death and development or progression of CKD.[5] Conceptually AKD, AKI, and CKD are interlinked by their relationship with one another and by their criteria, complications, and outcomes (Figure 3).[1,6,7] The terms AKI, AKD, and CKD describe abnormalities in kidney function and/or structure, and do not constitute a "diagnosis." It is important to determine the cause of each, recognizing that in some circumstances AKI, AKD, and CKD may be caused by the same conditions. It is apparent that there will be a wide heterogeneity of causes of AKD, ranging from those directly affecting function, such as decreased perfusion following volume depletion or heart failure, parenchymal disease affecting both structure and function, such as glomerulonephritis or interstitial nephritis, to obstructive causes. All of these occur without or before sufficient decline in function to meet AKI criteria, or sufficient duration to meet CKD criteria.

Data have been published that support these concepts. James *et al.*,[5] using a large administrative population database, divided their cohort into those without KD (NKD) or with either CKD and AKD, CKD and AKI, CKD, AKI, and AKD (where AKD referred to AKD without AKI). AKD in combination with CKD conferred the highest risk of progression of CKD and kidney failure, and CKD in combination with AKI conferred the highest risk of death. In a retrospective cohort study of 36,118 hospitalized adult patients followed up for a median of 2.6 years (interquartile range, 0.8–4.4 years), See *et al.* examined outcomes in patients with AKD without AKI and patients with AKD post-AKI. The primary outcome was the composite outcome of incident CKD, kidney failure,

	AKI	AKD	CKD	NKD
Duration	Within 7 days	≤3 months	>3 months	
Functional criteria	Increase in SCr by 50% within 7 days *Or* Increase in SCr by 0.3 mg/dl (26.5 μmol/l) within 2 days *Or* Oliguria for ≥6 hours	AKI *Or* GFR < 60 ml/min/1.73 m^2 *Or* Decrease in GFR by ≥35% *Or* Increase in SCr by >50%	GFR < 60 ml/min/1.73 m^2	GFR > 60 ml/min/1.73 m^2
And/or		And/or	And/or	And
Structural criteria	Not defined	Marker of kidney damage (albuminuria, hematuria, or pyuria are most common)	Marker of kidney damage (albuminuria is most common)	No kidney damage

Figure 1 | Functional and structural criteria for kidney diseases and disorders. AKD, acute kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease; GFR, glomerular filtration rate; NKD, no kidney disease; SCr, serum creatinine.

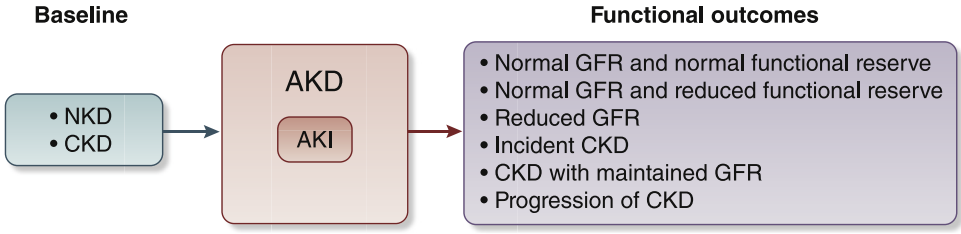

Figure 2| Acute kidney disease (AKD), acute kidney injury (AKI), and kidney disease outcomes. CKD, chronic kidney disease; GFR, glomerular filtration rate; NKD, no kidney disease.

or death. Compared with no AKD, those with AKD post-AKI had an adjusted hazard ratio (HR) of 2.51 (95% confidence interval, 2.16–2.91) for the primary outcome and those with AKD without AKI had an adjusted HR of 2.26 (95% confidence interval, 1.89–2.7).[8]

Other published data to date chiefly concentrate on AKD with AKI in clinically enriched populations mainly related to cardiovascular disease but also including all hospitalized patients and patients from various clinical areas (critical care, postsurgical, liver disease, etc.) (Table 1).[9–19] Studies were perforce retrospective with reported outcomes mainly confined to mortality and incident CKD, and periods of follow-up ranging from 90 days to 10 years. What these studies confirm are increased risks of both mortality and incident CKD associated with AKD.

Both AKI and AKD may occur in hospital or community settings. There is growing literature describing community-acquired AKI,[20–22] some of which may be AKD without AKI. Community-acquired AKD likely often goes undetected and has long-term implications for health.

Definition and staging for AKD

Defining AKD. We propose a broader term of "kidney diseases and disorders" (KD) to describe abnormalities of kidney function and/or structure, with implications for health. Thus, AKD and CKD can be distinguished based on duration, and harmonized under the one term KD. The term "acute" defines a condition of recent or sudden onset that is short-lived and reversible; in contrast, "chronic" refers to long-term and persisting conditions. AKI is a subset of AKD, such that AKD can occur with or without AKI, consistent with the 2012 AKI guideline.[2] The definition of AKI includes criteria for the functional abnormality according to the rate and severity of increase in SCr or decline in UO, during

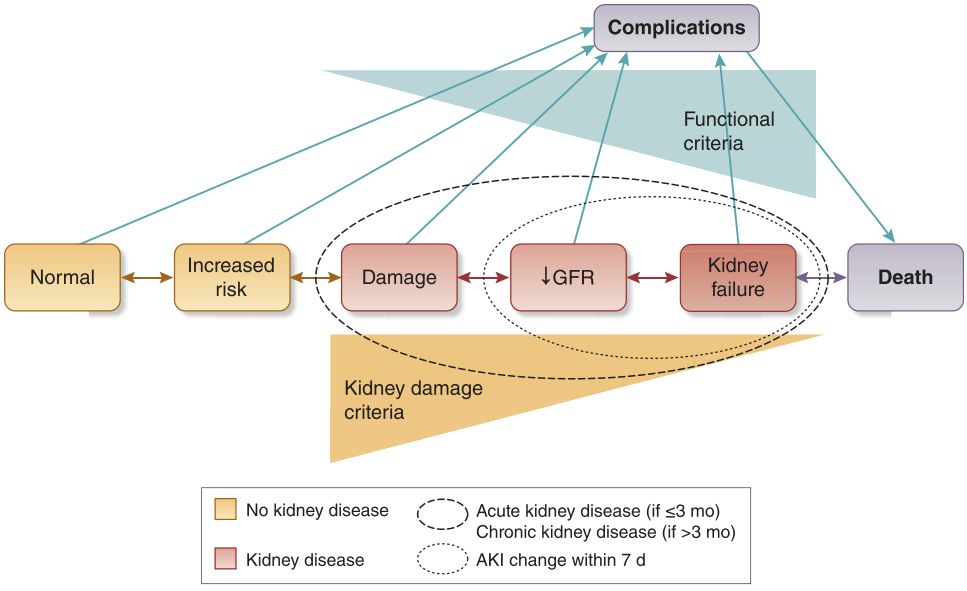

Figure 3| Conceptual model of the continuum of kidney disease. Modified with permission from National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39(suppl 1):S1–S266.[1] © 2002 National Kidney Foundation, Inc. Note that kidney damage and/or reduction in glomerular filtration rate (GFR) can be present in both acute kidney disease (AKD) and chronic kidney disease (CKD). AKI, acute kidney injury.

Table 1 | AKD and outcomes in clinically enriched populations

Study	Clinical area	N	Follow-up	AKD phenotype	Mortality	Incident CKD
Xiao *et al.*, 2020[9]	Hospitalized patients	2556	90 d	AKD after AKI	HR, 1.98 (95% CI, 1.43–2.75)	
Nagata *et al.*, 2021[10]	Hospitalized patients	7582	3600 d	AKD after AKI		HR, 6.69 (95% CI, 5.0–8.94)
Hsu *et al.*, 2020[11]	ECMO	168	Up to 10 yr	AKD after AKI	HR, 2.58 (95% CI, 1.27–5.23)	
Mizuguchi *et al.*, 2018[12]	Bypass surgery	10,234	Up to 8 yr	AKD vs. no AKD AKD on CKD vs. CKD	15.9% vs. 2.9% 47.0% vs. 19.3%	
Cho *et al.*, 2021[13]	Valvular surgery	1190	1 yr	AKD vs. no AKD		OR, 16.8 (95% CI, 8.2–34.2)
Matsuura *et al.*, 2020[14]	Cardiac surgery	3605	90 d	AKD	HR, 63.0 (95% CI, 27.9–180.6)	
Chen *et al.*, 2020[15]	Coronary care	269	5 yr	AKD after AKI vs. no AKD	22.7% vs. 14.2%; $P = 0.083$	
Kofman *et al*, 2019[16]	STEMI	225	90 d	AKD after AKI	HR, 2.42 (95% CI, 1.52–3.92)	
Long *et al.*, 2019[17]	Postsurgical	2520	Median, 3.4 yr (IQR, 1.2–7.1 yr)	AKD after AKI	OR, 2.4 (95% CI, 1.85–3.12)	OR, 1.5 (95% CI, 1.29–1.75)
Tonon *et al.*, 2021[18]	Liver disease	272	5 yr	AKD vs. no AKD	65.2% vs. 11.2%	13.8% vs. 2.1%; $P < 0.001$
Mima *et al.*, 2019[19]	Stem cell transplant	108	100 d	AKD	29.4% vs. 20.2%; $P = 0.409$	

AKD, acute kidney disease, AKI, acute kidney injury; CKD, chronic kidney disease; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; HR, hazard ratio; IQR, interquartile range; OR, odds ratio; STEMI, ST-segment–elevation myocardial infarction.
All HRs and ORs are adjusted for covariates.

intervals from 6 hours to 7 days. The AKI definition does not specifically include markers of kidney damage, such as abnormalities of urine sediment or proteinuria, nor cases in which increase in SCr or decline in UO is less severe or develops less rapidly than AKI, nor cases where markers of kidney damage exist without functional abnormalities. To address these gaps and harmonize definitions across time, the defining criteria for AKD have incorporated some AKI criteria and dovetail into those for CKD (Figure 1). The rationale for these criteria was based on modeling the relationship between decrease in GFR and increase in SCr, which is described in detail in the appendices of the KDIGO AKI guideline.

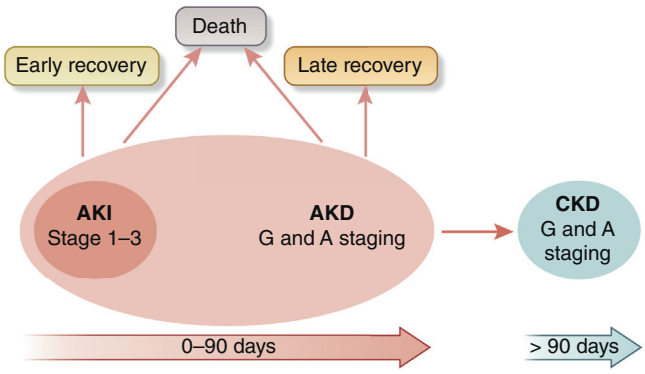

Figure 4 | Proposed conceptual model for the continuum of acute kidney disease (AKD) and chronic kidney disease (CKD) and acute kidney injury (AKI). The relationship between AKI, AKD, and CKD is depicted. Note that multiple AKI events may occur and that AKD too may resolve and/or recur. For simplicity, the well-known associations of CKD with complications and mortality, as shown in Figure 3, are not repeated above.

Figure 4 describes a conceptual model for the continuum of AKI, AKD, and CKD. Various examples of GFR trajectories (functional criteria) in AKD are depicted in Figure 5. Similar trajectories may exist for various markers of kidney damage.

The duration of AKD and AKI, progression to CKD, and markers of kidney damage. By definition, AKD lasts for ≤3 months. If resolution of AKD occurs, it must occur before 3 months. After 3 months, most patients without resolution of AKD will meet the criteria for CKD and be described as having CKD and a history of AKD. Data describe that they are at increased risk for worsening of CKD. Patients not meeting criteria for CKD after the period of AKD will be described as having a history of AKD and are at increased risk for new onset of CKD.[5,11,13,14,16,22]

Figure 5 describes numerous possible trajectories, based on data from patients in various settings.[23] Previously, clinicians have viewed AKI as a discrete event that either resolves or reaches a new steady state before 3 months. Current AKI management recommendations concentrate on the initial period of AKI, not the period after the AKI event, even if kidney function has not recovered. Multiple episodes of AKI may occur over the course of an illness (or in association with multiple different illnesses), within one individual.[23] After AKI resolves, patients may still have abnormalities in kidney function and/or structure that fulfill the criteria for AKD. The workgroup believed that an arbitrary time-based definition for the duration of AKI of 7 days, as proposed by the Acute Disease Quality Initiative (ADQI),[24] warrants additional consideration, and deferred the development of specific

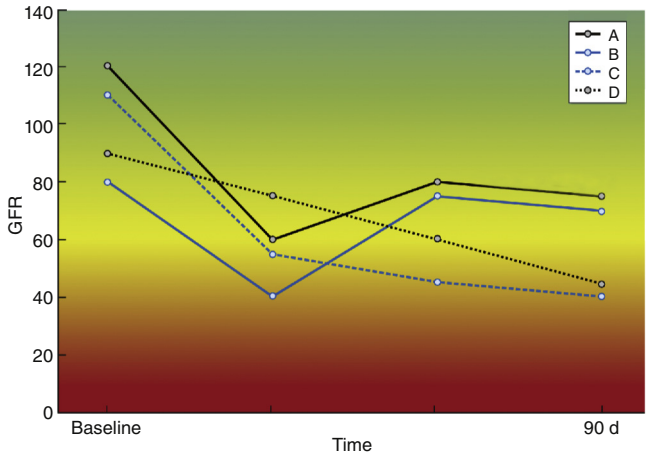

Figure 5 | Clinical examples of glomerular filtration rate (GFR) trajectories in acute kidney disease (AKD). Hypothetical GFR trajectories for patients with AKD. If we assume that patients A and B both develop acute kidney injury (AKI) and recover to similar GFRs, we can appreciate that patient A has residual decreased GFR relative to baseline, whereas patient B does not. Patient C does not recover and has further decline in GFR after AKI. Patient D has AKD without AKI.

criteria for duration and resolution of AKI to the next AKI guideline updating group. Until then, some ambiguity will remain about the appropriate nomenclature for patients following an episode of AKI. Figure 6 describes the current proposed AKD, AKI, and CKD framework.

Markers of kidney damage may precede functional abnormalities in both AKD and AKI, as well as in CKD. The magnitude of damage should also have "implications for health." Using the term kidney damage allows harmonization of definitions of CKD, AKD, and AKI. Recently, ADQI proposed a schema for AKI staging[25] that included markers of kidney damage. Research is underway to qualify specific markers for this purpose. Possibly, some markers used in either AKI (e.g., neutrophil gelatinase-associated lipocalin [NGAL] and kidney injury molecule-1 [KIM-1]) or CKD

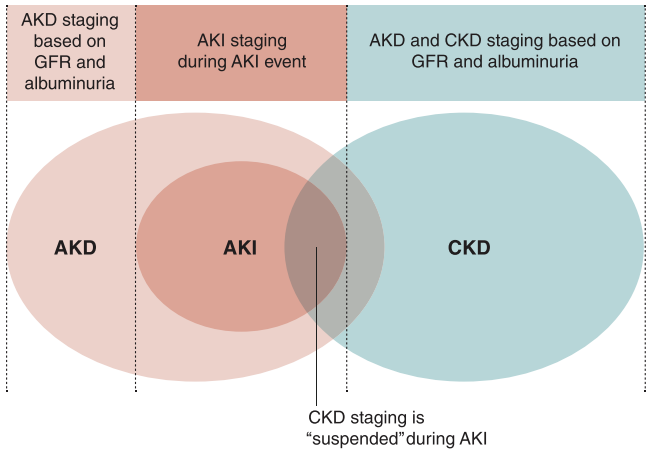

Figure 6 | Kidney disease severity staging across the continuum of acute kidney injury (AKI), acute kidney disease (AKD), and chronic kidney disease (CKD). GFR, glomerular filtration rate.

Table 2 | AKI and AKD considerations for management

KDIGO AKI guideline recommendation[2]	Relevance to AKD with or without AKI
Discontinue all nephrotoxic agents when possible	Moderate; damage from nephrotoxic agents usually occurs quickly; although there may be unusual situations where injury is subacute
Ensure volume status and perfusion pressure	Moderate (e.g., cardiorenal syndrome)
Consider functional hemodynamic monitoring	Very low
Monitor serum creatinine and urine output	Mixed; creatinine monitoring is relevant, urine output is not
Avoid hyperglycemia	Low
Consider alternatives to radiocontrast	Moderate
Noninvasive diagnostic workup	Low; however, it could be relevant if the etiology is still unclear
Consider invasive diagnostic workup	Moderate; unresolving AKI/AKD might prompt kidney biopsy
Check for change in drug dosing	High
Consider kidney replacement therapy	Low; initiation of KRT for AKI is usually in the early period (if at all) or once the patient develops CKD
Consider ICU admission	Very low
Avoid subclavian catheters if possible	Moderate

AKD, acute kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease; ICU, intensive care unit; KDIGO, Kidney Disease: Improving Global Outcomes; KRT, kidney replacement therapy.

(e.g., albuminuria, hematuria, red blood cell casts of glomerular origin, and imaging abnormalities) will be useful in further categorizing AKD, depending on the underlying cause.

Classification and severity staging. Current classifications of both AKI and CKD are based on cause of disease in addition to severity of functional abnormalities or structural abnormalities. Identification of cause(s) allows implementation of cause-specific therapy. The AKI guideline recommends a cause-specific classification when possible but recognizes that AKI is often multifactorial. The CKD guideline also recommends a cause-specific classification, in combination with staging of severity by GFR and albuminuria levels (cause, GFR, and albuminuria criteria, CGA classification). We propose that the causes of AKD may include many of the causes of AKI and CKD, but we do not further specify a classification system at this time.

Thus, we propose a classification system that differentiates AKD without AKI and AKD with AKI (either before or after AKI). Like AKI, AKD without AKI and AKD with AKI can occur in association with CKD. It is necessary to acknowledge the different entities because management considerations may differ (Table 2).[2] Severity staging for AKI and CKD, irrespective of cause, drives prognostic and management recommendations. More severe stages portend worse outcomes.

Staging systems are important for circumstances such as defining clinical trial end points. Current AKI and CKD staging systems are based on different principles (relative change in SCr or UO for AKI vs. level of GFR and albuminuria in CKD)[2,3]; therefore, combining them for the staging of AKD is problematic. The transition from AKI-based management to CKD-based management should occur before 90 days, and AKI-based staging may not be appropriate for AKD in the absence of AKI. Thus, the conference participants considered 3 key questions regarding severity staging of AKD:

- Can we use AKD staging to harmonize AKI-based and CKD-based staging?
- Is GFR staging appropriate for AKD without AKI? When does it become appropriate following AKI?
- Should both GFR and albuminuria staging criteria be included in AKD staging? If so, when?

The ADQI 16 Workgroup proposed an AKI-based staging system for AKD post-AKI episode, with a limit of 7 days, and an AKD period of 7 to 90 days after a known AKI episode.[24] For patients with community-acquired AKI and those in whom baseline kidney function is neither known nor measured, it would be difficult to determine the timeline of the initial AKI event. In the absence of specifics on the duration of AKI, an approach based on GFR, once stability is achieved, is more appropriate, because attribution of stage is not possible when GFR is changing rapidly. As GFR becomes more stable after the AKI episode, adopting stages based on GFR categories would be practical. Similarly, in the absence of AKI, AKD could be staged based on GFR categories. After discussion, consensus was reached that staging of AKD based on GFR and albuminuria categories could be used in AKD without AKI or AKD following AKI. However, while staging and classifying AKD is highly desirable, further evidence is required before the approach is standardized.

It is important to emphasize that GFR thresholds to define and stage AKD and CKD are expressed as GFR and may refer to estimated GFR (eGFR) or measured GFR (mGFR). The KDIGO CKD guideline for GFR evaluation recommends initial testing with eGFR and confirmatory testing with mGFR where clinical circumstances dictate.[3] When GFR is changing rapidly, one should consider using mGFR, rather than eGFR. In patients with very low muscle mass (a common problem during and after hospitalization), consider using cystatin C rather than creatinine to estimate GFR or actually measure GFR.[26]

The group suggested adding albuminuria categories to GFR categories for AKD severity staging to be consistent with CKD severity staging. CKD staging using albuminuria is based on substantial evidence showing the magnitude of albuminuria to be an independent prognostic factor for CKD outcomes. Because AKD may be caused by many of the same diseases that cause CKD, the pathophysiology of albuminuria is similar in AKD and CKD, and treatment strategies for albuminuria are similar in AKD and CKD (particularly for severe and nephrotic-range albuminuria); the authors considered that adding albuminuria categories in AKD staging is justifiable. The association of the magnitude of albuminuria with severity outcome in AKD is not yet proven, and further research is needed.

Unresolved questions and future directions in defining and classifying AKD. Defining AKD by SCr criteria requires knowledge of baseline SCr. Several approaches have been used in studies of AKI when the baseline SCr value is missing: use of admission SCr, use of the lowest inpatient SCr, or imputation of a value back calculated from an assumed eGFR of 75 ml/min per 1.73 m^2. These approaches have a bidirectional impact on the incidence of AKI and also affect reported outcomes, as elegantly reviewed by Siew and Matheney.[27] The magnitude of the variation in the incidence of AKI was up to 15% using 4 different approaches in a *post hoc* analysis of data from the Simple Intensive Care Studies II (SICS-II) study.[28] Such variation will be greater in studies of AKD without AKI, particularly in community studies, dictating the need for a standardized approach for comparability wherever possible. A clear description of the methodology applied and description of the potential bias and likely direction should be mandatory for all reports.

Some patients who satisfy AKI/AKD criteria may be left with kidney function that is reduced relative to baseline but at 3 months may not meet CKD criteria. These patients will be categorized as having a history of AKI/AKD (Figure 4) and have been shown to have the highest risk for sustained 40% decline in GFR or kidney failure.[29] Further research is required to determine the specific health implications for patients who either start from different levels of GFR and maintain GFR >60 ml/min per 1.73 m^2 or arrive at a similar GFR with similar markers of kidney damage via different trajectories[30] (e.g., Figure 5).

AKD (like AKI) may be informed by better markers of function and not only by damage markers. Creatinine has numerous limitations that might be overcome by alternative functional markers (e.g., cystatin C and proenkephalin).[31–33] GFR alone may not be as important as an assessment of GFR reserve (stimulated GFR minus basal GFR), which has been used to help better describe kidney function.[34] One study has shown that individuals who develop postcardiac surgery AKI, with normal GFR and GFR reserve prior to the event, have variable outcomes: recovery of both GFR and GFR reserve, recovery of GFR with impaired GFR reserve, or impaired GFR and reduced reserve.[35] Further study is needed to understand the implications of these findings.

Finally, although we tend to assume reduction in GFR when discussing loss of functional reserve, we should also consider loss of tubular and endocrine function. There is a definite need for sensitive and prognostic markers of all forms of renal functional loss, especially when they are still clinically silent.

Evaluation and management of ambulatory AKD patients

Conference attendees recognized the paucity of data to guide evaluation and management of AKD. Consensus was reached about approaches to the evaluation and management of

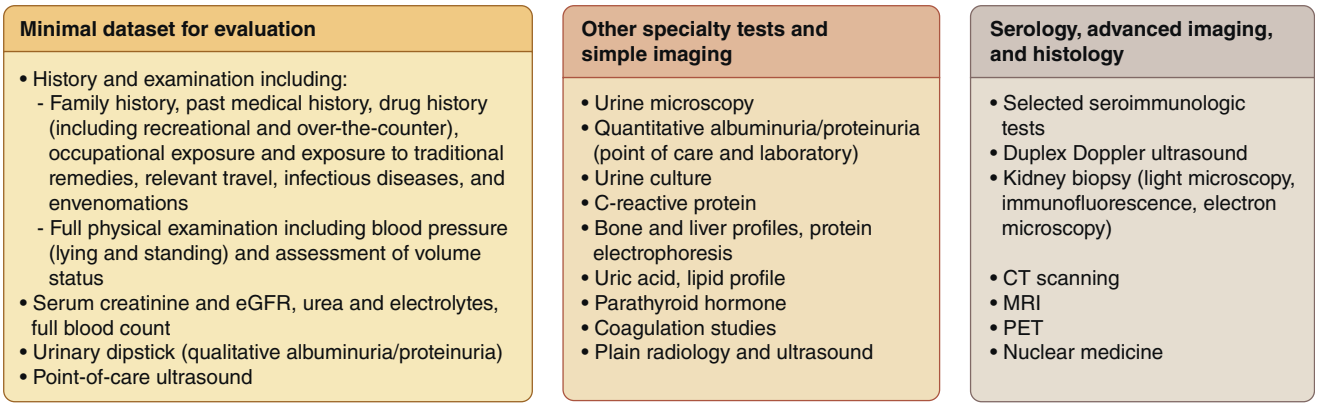

Figure 7 | Suggested clinical evaluation of a patient with acute kidney disease. CT, computed tomography; eGFR, estimated glomerular filtration rate; MRI, magnetic resonance imaging; PET, positron emission tomography.

patients with AKD, drawing on ancillary evidence, clinical experience, and data about prognosis.

Consequently, and taking the global mission of KDIGO into account, Figure 7 summarizes a 3-tier diagnostic dataset for evaluation of patients with AKD, reflecting worldwide differences in availability of resources and local health care systems.

AKD without AKI frequently occurs in community or primary care settings: data to inform clinicians and researchers to better understand this are needed. However, in some cases, the trend of slowly increasing SCr may also be recognized on hospital admission. The evaluation and management of AKD depends on clinical context, local resources, and local health care systems. AKD without AKI may be appropriately treated as AKI driven by the clinical correlate. Patients with AKD may have signs directly referable to the kidney (such as abnormal urinary sediment) or have associated nonkidney manifestations (e.g., edema or hypertension). Others may have an incidental elevated SCr, abnormal urine test result, or abnormal imaging of the kidneys as part of routine monitoring, or following investigation of a concurrent illness.

Recent hypovolemia occurring during an episode of concurrent illness (e.g., upper or lower respiratory tract infection, urinary tract infection, or gastrointestinal illness and/or exposure to potentially nephrotoxic substances in the recent past) may suggest that the present AKD is most likely following an episode of "undiagnosed" AKI.

Figure 7 provides a guide to evaluation depending on available resources, health care settings, and etiologies common to the geographic region. For example, endemic tropical diseases and envenomation may be common in some areas of the world. Medication histories should include prescribed drugs, over-the-counter, herbal, or complementary medicines, and use of "recreational" substances. Identification of medications that may contribute to prolongation of AKI or AKD is important in managing these patients. Drugs may reduce GFR via hemodynamic, nephrotoxic, or other mechanisms; and also included are medications that impair creatinine secretion, which reduce creatinine-based eGFR, but do not affect cystatin C–based eGFR or mGFR. Note that a history of recent exposure to iodinated contrast agents, wherein decrements in GFR are associated with that exposure, can be better explained by changes in kidney hemodynamics rather than by intrinsic tubular injury and are less likely to be clinically relevant.[36] Physical examination should include appropriate volume assessment, and urinary tract obstruction should be actively excluded using available resources.

Evaluation of the urine in AKD. Dipstick results for blood, protein, leukocytes, and glucose are often sensitive but not necessarily specific, and AKD can occur with a normal dipstick urinalysis. Availability of tests will be resource driven. Both dipstick analysis and careful knowledgeable examination of the urine sediment may aid in establishing the cause of AKD and direct further diagnostic tests; these are thus essential elements in patient evaluation.[37]

Additional diagnostic procedures. Figure 7 suggests several complementary diagnostic procedures (classified in the second and third tiers) for use where available. Immunologic tests can help in diagnosing several parenchymal KDs either before a kidney biopsy is available or when it is not possible to obtain renal tissue. Several glomerular/vascular KDs account for approximately 10% of AKD (and even AKI) in both adults and children, which may require urgent care.[38] Where AKD is diagnosed in the absence of a specific illness or precipitant, consider less common causes, such as myeloma or systemic vasculitis. The presence of hemoptysis, hemolysis, hypercalcemia, rash, recent vascular intervention, or increased creatine kinase all indicate less common causes of AKD; presence of any of these with AKD should prompt referral to secondary care.[39]

The historical context and finding small kidneys relative to the patient's habitus on ultrasound may be suggestive of chronicity and point to the possibility of AKD superimposed on preexisting CKD. Kidney ultrasound, preferably after correction of hypovolemia if present, may also exclude urinary tract obstruction as cause of AKD.

Role of kidney biopsy in exploring the histopathology of AKD. A limited number of studies have explored the role of

Table 3 | Key elements of an appropriate post-AKD care bundle

- Documentation of the AKD episode in the medical record
- Education of caregivers at primary and secondary care level about AKD and its consequences, including nutritional aspects
- Instruction on the nonkidney complications of AKD (e.g., cardiovascular disease, hypertension, infections, diabetes control, and malnutrition)
- Instruct patients on blood pressure control and blood pressure targets
- Follow-up of eGFR and albuminuria at least 3 mo after hospital discharge
- If CKD, consider referral to nephrology
- Medication reconciliation: discuss risk benefits of ACEIs, ARBs, low-dose aspirin, statins, and immunosuppressants
- Adapt the dose of renally eliminated drugs, if needed
- Instruct on over-the-counter drugs, herbal medicine, and NSAIDs
- Discuss fluid status, salt intake, and role of diuretics
- Ask prompt medical advice during intercurrent diseases

ACEI, angiotensin-converting enzyme inhibitor; AKD, acute kidney disease; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; NSAID, nonsteroidal anti-inflammatory drug.

Table 4 | Key research questions in AKD

Defining the problem: identifying causes and risk factors

Improve identification and risk stratification

- Can we consistently identify patients at risk for AKD where AKD is defined with different parameters, different severity, and timing/duration than AKI?
- Can we identify patients who are more likely to have AKI vs. AKD despite similar exposures?
- Do CKD albuminuria categories convey the same impact in AKD?
- Do we know how much albuminuria might change during AKD?

Patient and health care provider understanding of AKD

- What is the value proposition for patients and health care providers to identify AKD?

Optimizing diagnosis and evaluation, and follow-up

- Can we improve the precision of the diagnosis and workup for AKD, across all communities and health care systems?
  - What is a minimum diagnostic workup for those with AKD?
  - Is there value in a kidney biopsy in AKD? (in all vs. specific situations)
- Can we develop more sophisticated tools to assess clinical state, and the degree of kidney functional reserve that may help further classify individuals at risk for AKI or AKD, and to further characterize AKD?

Develop and test interventions

- What is the appropriate follow-up for patients who have experienced an episode of AKD?
  - Depending on severity, duration, context, and resources
  - Minimum clinical surveillance
- When is the optimal time to reintroduce withheld medications after AKD has been identified?
- Are there interventions that mitigate, prevent, or delay consequences of AKD?
- Do we know that treatment strategies for albuminuria are similar in AKD and CKD?
- Are there novel study designs (e.g., stepped wedge, platform trials, etc.) that would improve our ability to answer specific questions?

Improving mechanistic understanding of AKD

- Can we improve our understanding of the disease state from a mechanistic standpoint using animal and human studies?
- Is there a molecular signature evidence on biopsy that may inform therapeutic strategies?

AKD, acute kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease.

kidney biopsies in understanding AKD, and have described a wide spectrum of primary histopathologic diagnoses.[40–42] Those studies suggested that the histologic diagnoses described did not have a major therapeutic impact in most patients presenting with AKD without AKI. Nonetheless, obtaining histology may improve understanding of diagnosis and prognosis in the future. Given the potential risks of kidney biopsy, one should consider specific risks and benefits of kidney biopsy in cases of AKD. Note that in those with AKD and significant urinary abnormalities, nonresolving AKI, rapidly progressive AKD, and AKD superimposed on CKD, the value of a histopathologic diagnosis and prognosis from kidney biopsy should be appreciated.[43]

Management of the AKD post-AKI patient after hospital discharge

Hospitalized patients in whom AKI does not completely and rapidly reverse require a reevaluation of the initial cause of AKI and exclusion of any additional causes.

Data suggest early risks after hospital discharge for these patients, including death or rapid rehospitalization from the underlying nonkidney illness, recurrent AKI, or worsening of AKD after AKI. Those who were seriously ill may have ongoing illness and remain vulnerable to recurrent insults due to modifiable risk factors that might be missed.[44] A retrospective study of 20,260 patients with AKI requiring dialysis who became dialysis independent found that only 7550 (37%) were followed up by a nephrologist during the AKD period. During a mean 4.04 ± 3.56 years of follow-up, those followed up by nephrology had a lower mortality (HR, 0.87; $P < 0.001$), and were less likely to have major adverse cardiovascular events (HR, 0.85; $P < 0.001$) or sepsis (HR, 0.88; $P = 0.008$).[45]

Long-term risks for patients with AKD after hospital discharge, depending on severity and duration of AKD, are development of *de novo* CKD or progression of preexisting CKD, eventually leading to kidney failure.[46,47] The degree of risk driven by GFR decrement and level of albuminuria should prompt reassessment at 3 months, or less, after hospital discharge, depending on the individual patient. Table 3 summarizes the key elements of an appropriate post-AKD care bundle.[44]

Research and future directions in AKD

Little is known about the epidemiology, causes, pathophysiological subtypes, prevention, and treatment of AKD without AKI. It is likely that these are not merely extensions of what is known about AKD after AKI. The continuum from AKI and AKD to CKD is an area of growing research intensity that will benefit from an organized approach.

There is a need for precision and clarity to inform future work, identify patients consistently (for clinical practice and research purposes), and design studies to test appropriate interventions. There remain significant gaps in the evidence to support clinical decision making and care; thus, it behooves the medical and public health communities to enable research in this area and address methodological issues that complicate the study of this entity. Table 4 summarizes the key questions to be addressed by the community.

Research on AKD should include large clinical datasets, augmented by administrative data (e.g., diagnostic codes). Large clinical datasets are available in most high-resource settings but they are virtually absent in low-resource areas. Nevertheless, it has been demonstrated that with support of the international nephrology community, prospective epidemiologic data on AKD and CKD can also be obtained in low-income countries.[48] However, even in high-resource settings, there is often poor integration across transitions of care or between various service providers (i.e., insufficient communication from primary care to specialist and vice versa). Because AKD occurs in various settings (community and hospital), we will need to have integrated datasets that can inform the following: (i) population incidence and prevalence; (ii) prognosis across the entire spectrum of disease, not just of the select subset who are most visible; and (iii) extent of variation that exists. To achieve this, prospective studies are also required, particularly in countries without well-developed electronic medical record systems.

To move beyond basic prognosis questions, we must better understand specific time windows and reasons as to why health deteriorates; thus, we need detailed clinical data collection across serial data capture points, performed irrespective of clinical status, to avoid the inherent bias created by examining treated patients (confounding by indication) that occurs when data capture is reliant on clinical reasons. Without serial surveillance, we will not be able to determine if individuals experience adverse consequences, deterioration in kidney or cardiovascular function (or other events), gradually or suddenly in the community.

Critical questions to guide clinical practice will include the following:

(i) better description of the timing to resolution or change in various parameters (urine sediment, protein, and biomarkers), and the impact of those on prognosis; this will help to refine the proposed staging and classification system;
(ii) role of diagnostic biopsies to guide prognosis and intervention, and identify new targets for treatment;
(iii) role of GFR reserve in both health and AKD for prognosis and treatment strategies; the development of simple robust measures of renal reserve to be administered in clinical practice; and
(iv) execution of well-designed interventional studies of specific therapies and strategies for patients with AKD of similar cause, and stage to determine best practices.

There are 3 main sources of datasets that should be considered by the research community.

Existing clinical trials of AKI interventions: an opportunity for evaluation of AKD and outcomes. Several clinical trials of candidate interventions for AKI prevention and treatment have been conducted in recent decades. Many of these datasets followed up patients beyond 90 days after the AKI diagnosis and yet few of these studies formally reported AKD data; but now with a clear definition, these data may be easy to obtain and summarize.

Existing administrative and clinical datasets collected for other reasons. Increasing availability of the electronic medical record has been accompanied by the development of large, often multicenter, databases of patient information collected as part of the routine delivery of care. Some of these contain administrative (billing) data only, but others are rich repositories of administrative, clinical (physiological), imaging, laboratory, and outcome data. These databases provide excellent sources of epidemiologic information, particularly those that include granular records of laboratory (i.e., SCr) data organized longitudinally and with accurate time stamps. Data relating to medication use (before and after AKD diagnosis) and outcomes following AKD are especially valuable in this context. Situations where the cause or timing of the insult leading to AKD is less well characterized may be informed from these datasets because of the number of patients available. Large sample sizes reduce uncertainty around associations between exposures and observed outcomes but may amplify the effects of various biases.

New databases and clinical trials. Any new trials of interventions for AKI (prevention and treatment) ought to include data relating to AKD, and the definitions reported in this conference might be used to permit subsequent summation and meta-analysis. Identifying a "minimum dataset for AKD research" will be of value. This would permit an organized assessment of patient-level data across clinical trials and would make any meta-analysis conducted in the future more meaningful. This approach would benefit studies in the area of KDs, and further clarify the incidence and prevalence of both AKI and AKD.

In summary, the concept of AKD is receiving increased attention in the literature and has been substantiated as an "entity." To improve outcomes of patients, we need to firmly validate and socialize the definition of AKD and design studies to properly capture outcomes and test interventions. Without a commitment to both developing and executing a robust research agenda, within a global context, we will undoubtedly fail to improve outcomes and evidence to inform guidelines.

APPENDIX

List of other Conference Participants

Fergus J. Caskey, UK; Chris K.T. Farmer, UK; Alejandro Ferreiro Fuentes, Uruguay; Masafumi Fukagawa, Japan; Stuart L. Goldstein, USA; Grace Igiraneza, Rwanda; Andreas Kribben, Germany; Edgar V. Lerma, USA; Andrew S. Levey, USA; Kathleen D. Liu, USA; Jolanta Małyszko, Poland; Marlies Ostermann, UK; Neesh Pannu, Canada; Claudio Ronco, Italy; Simon Sawhney, UK; Andrew D. Shaw, Canada; and Nattachai Srisawat, Thailand.

DISCLOSURE

JAK declared receiving consultant fees from Astute, Baxter, bioMérieux, Dialco, Fresenius Medical Care, and Quanta; and is currently chief medical officer for Spectral Medical. MJ declared receiving consultant fees from Astellas, AstraZeneca, Boehringer Ingelheim, Fresenius Medical Care Asia Pacific, Mundipharma, and Vifor Fresenius Medical Care; speakers bureaus from Astellas, AstraZeneca, Mundipharma, and Vifor Fresenius Medical Care; research support from Amgen; and future research support from AstraZeneca. WCW declared receiving consultant fees from Akebia/Otsuka, AstraZeneca, Bayer, Janssen, Merck, Reata, and Relypsa; future consultant fees from

Boehringer Ingelheim; and research support from the National Institutes of Health. All the other authors declared no competing interests.

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