5. Classification of chronic kidney disease based on evaluation of kidney function

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GUIDELINES

No recommendations possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV sources)

- **The diagnosis of kidney disease should be based on a glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 and/or the presence of kidney damage (manifested by persistent microalbuminuria, persistent proteinuria, persistent haematuria after exclusion of urological causes, or structural abnormalities on kidney imaging tests), irrespective of the underlying diagnosis. (Opinion)**
- **A diagnosis of chronic kidney disease (CKD) requires the presence of kidney damage and/or GFR < 60 mL/min/1.73 m^2 for a period of at least 3 months. (Opinion)**
- **Staging of CKD should be based on the measured or estimated GFR, irrespective of the underlying diagnosis. (Opinion)**
- **The suffix 'P' should be applied to the corresponding CKD stage for all patients with at least moderate proteinuria (≥ 1 g/day) because of the increased risks of cardiovascular disease and CKD progression in this group. (Opinion)**
- **The suffix 'T' should be applied to the corresponding CKD stage for all kidney transplant recipients at any level of GFR because of the increased risks of cardiovascular disease and CKD progression in this group. (Opinion)**
- **The suffix 'D' should be applied to CKD stage 5 to denote patients receiving dialysis. (Opinion)**

Background

Chronic kidney disease is a major public health problem in Australia and throughout the world. Based on data from the Ausdiab study (Chadban et al 2003), it is estimated that over 1.7 million Australian adults have at least moderately severe kidney failure, defined as an estimated GFR less than 60 mL/min/1.73 m^2. This pernicious condition is often not associated with significant symptoms or urinary abnormalities and is unrecognised in 80%–90% of cases (Chadban et al 2003, McClellan et al 1997, John et al 2004). Chronic kidney disease progresses at a rate that requires approximately 1900 individuals each year in Australia to commence either dialysis or kidney transplantation (McDonald & Russ 2005). Furthermore, the presence of CKD is one of the most potent known risk factors for cardiovascular disease, such that individuals with CKD have a 10- to 20-fold greater risk of cardiac death than age- and sex-matched controls without CKD (Foley et al 1998, Weiner et al 2004). Developing an operational definition and classification of the stages of CKD is therefore critically important for guiding research to provide estimates of CKD prevalence by stage, for developing a 'clinical action plan' for evaluating and managing each stage of CKD, and for defining individuals at increased risk of developing progressive CKD and cardiovascular disease.

The objective of this guideline is to develop a classification of CKD stages that can be readily linked to management strategies, such as cardiovascular and CKD risk modification, nephrologist referral, and preparation for commencement of kidney replacement therapy.

Search strategy

Databases searched: Text words for chronic kidney disease were combined with MeSH terms and text words for classification or staging. The search was carried out in Medline (1966 – 18 April 2005). No language restrictions were placed on the search. The conference proceedings of the American Society of Nephrology from 1994–2004 were also searched for trials.

Date of searches: 18 April 2005.

What is the evidence?

No randomised controlled trials (RCTs) are available which address this issue.

There are no RCTs or cohort studies of outcomes following the application of a CKD staging system to the population in a primary or institutional health care setting.

In principle, CKD should be classified according to severity, diagnosis, treatment and prognosis, and should be readily linked to 'clinical action plans' to facilitate management (particularly in the primary care setting).

Although the aetiology of CKD may have important implications for management under certain circumstances, this is not the case for the majority of CKD encountered by clinicians. Moreover, adding the disease aetiology to a CKD classification system builds in additional complexity that mostly is unwarranted and unnecessary.

GFR should form an important part of any CKD classification system since it strongly predicts CKD and cardiovascular risks (Fox et al 2004, Vanholder et al 2005, Go et al 2004). There is reasonable justification for the GFR cut-off points in CKD staging to be 60, 30 and 15 mL/min/1.73 m^2:

- the limitations of eGFR at normal or near-normal renal function suggest that a GFR of 60 mL/min/1.73 m^2 is a reasonable cut-off point in a CKD classification system (see guideline titled 'Use of estimated GFR to assess level of kidney function'),
- the CARI guidelines recommend referral of CKD patients to a nephrologist when the GFR falls below 30 mL/min/1.73 m^2,
- nearly all CKD patients who commence dialysis in Australia do so at a GFR level below 15 mL/min/1.73 m^2, and
- it could be argued that an additional cut-point of 45 mL/min/1.73 m^2 should be considered, since large cohort studies have identified a gradation of cardiovascular risk between patients with GFR 30–44 mL/min/1.73 m^2 compared with 45–59 mL/min/1.73 m^2 (Go et al 2004).

The degree of proteinuria is also a significant risk factor for CKD progression (Iseki et al 2003) and cardiovascular disease (Iseki et al 2003, Klausen et al 2004, Hillege et al 2002, Yuyun et al 2004a, Yuyun et al 2004b, Yuyun et al 2004c, Yuyun et al 2004d, Brown et al 2000). Consideration should therefore be given as to whether the extent of proteinuria should be incorporated into the CKD classification system. For example, the CARI guidelines recommend earlier referral to a nephrologist if the degree of proteinuria exceeds 1 g/day, even at GFR levels > 30 mL/min/1.73 m^2.

Summary of the evidence

There are no RCTs on this topic.

There are no RCTs or cohort studies of outcomes following the application of a CKD staging system to the population in a primary or institutional health care setting. In principle, CKD should be classified according to severity, diagnosis, treatment and prognosis, and should be readily linked to 'clinical

action plans' to facilitate management (particularly in the primary care setting). Since GFR and level of proteinuria are strongly linked to the risks of CKD progression and cardiovascular disease, these variables should form a part of any CKD classisification.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: Adverse outcomes of chronic kidney disease can often be prevented or delayed through early detection and treatment. Earlier stages of chronic kidney disease can be detected through routine laboratory measurements.

- The presence of chronic kidney disease should be established, based on presence of kidney damage and level of kidney function (glomerular filtration rate [GFR]), irrespective of diagnosis.

- Among patients with chronic kidney disease, the stage of disease should be assigned based on the level of kidney function, irrespective of diagnosis, according to the K/DOQI CKD classification (Table 10).

Table 10. Stages of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mild ↓ GFR	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	Kidney failure	<15 (or dialysis)

Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m^2 for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

Source: National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. Am J Kidney Dis 39: S46, 2002 (suppl 1).

Chronic kidney disease has been defined according to the criteria listed in Table 11.

Table 11. Definition of Chronic Kidney Disease

Criteria
1. Kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by *either*: • Pathological abnormalities; or • Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests
2. GFR <60 mL/min/1.73 m^2 for ≥3 months, with or without kidney damage

Methods to estimate GFR are discussed in Guideline 4. Markers of kidney damage are discussed in Guidelines 5–6.

Source: National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. Am J Kidney Dis 39: S47, 2002 (suppl 1).

British Renal Association: We recommend adoption of the classification of CKD proposed by the US K-DOQI group.
This classification is based on estimated GFR, and recognises five stages of kidney disease, as follows:
Stage 1: Normal GFR; GFR > 90 mL/min with other evidence of chronic kidney damage*
Stage 2: Mild impairment; GFR 60–89 mL/min with other evidence of chronic kidney damage*
Stage 3: Moderate impairment; GFR 30–59 mL/min
Stage 4: Severe impairment: GFR 15–29 mL/min
Stage 5: Established renal failure (ERF): GFR < 15 mL/min or on dialysis.

For CKD Stage 5, we have adopted the term established renal failure instead of end-stage renal disease or end-stage renal failure, as this is the term used in the National Service Framework for Renal Services.

* The “other evidence of chronic kidney damage” may be one of the following:

• Persistent microalbuminuria

• Persistent proteinuria

• Persistent haematuria (after exclusion of other causes, e.g. urological disease)

• Structural abnormalities of the kidneys demonstrated on ultrasound scanning or other radiological tests, e.g. polycystic kidney disease, reflux nephropathy

• Biopsy-proven chronic glomerulonephritis (most of these patients will have microalbumuria or proteinuria, and/or haematuria).

Patients found to have a GFR of 60–89 mL/min without one of these markers should not be considered to have CKD.

Canadian Society of Nephrology: Recommend using the K/DOQI classification.

European Best Practice Guidelines: No recommendation.

International Guidelines:

Kidney Disease Improving Global Outcomes: (Levey et al 2005)

I.A Definition of CKD

The K/DOQI definition of chronic kidney disease (Table 3) was accepted, with the following clarifications:

I.A.1. Retain the term "disease" to convey importance. It is important that the definition use terms that reflect an appropriate balance between emphasizing need for diagnosis and treatment as opposed to that of labelling a risk condition as a disease. The K/DOQI definition of chronic kidney disease as a "disease" is consistent with current usage of this term. The Oxford English Dictionary (compact) defines a disease as "A disorder of structure or function in a human, animal, or plant, especially one that produces specific symptoms." Evidence in support of a disease include clinical-pathological correlations (as defined by case series), associations with symptoms or findings (as defined by cross-sectional analyses), and associations with outcomes (as defined by longitudinal analyses). The use of the term "disease" in CKD is consistent with: (1) the need for action to improve outcomes through prevention, detection, evaluation and treatment; (2) providing a message for public, physician and patient education programs; (3) common usage; and (4) its use in other conditions defined by findings and laboratory tests, such as hypertension, diabetes, hyperlipidemia.

I.A.2. Infer chronicity from documentation or presumption of kidney disease for ≥ 3 months. This clarification allows clinical judgment about chronicity in the absence of past data on levels of GFR or markers of kidney damage. In the future, it will be important to link the definition of chronicity with definition of acute kidney disease.

I.A.3. Retain reduced GFR as a criterion for kidney disease. GFR is widely accepted as the best index of kidney function. The rationale for a threshold level of GFR < 60 mL/min/1.73 m^2 is as follows:

- It is substantially above the level associated with kidney failure
- It is less than half the adult level of GFR
- Lower levels are very infrequent in young men or women (< 40 years)
- Lower levels are associated with complications of CKD
- Lower levels are associated with adverse outcomes, including cardiovascular disease morbidity and mortality in individuals with and without diabetes
- Lower levels can be detected with current estimating equations for GFR based on serum creatinine, but not by serum creatinine alone.

I.A.4. Retain albuminuria as a marker for kidney damage. Threshold values for spot urine albumin to creatinine ratio are discussed subsequently. The rationale for the recommended threshold (> 30 mg/g) is as follows:

- Threshold level is 2–3 times greater than the normal value
- Higher levels are infrequent in general population (< 40 years)
- Higher levels are the earliest marker of kidney damage due to diabetes, glomerular diseases, and hypertension
- Higher levels are associated with adverse outcomes, including progression of kidney disease and cardiovascular disease in individuals with and without diabetes mellitus
- Therapies that reduce albuminuria are associated with slowing the progression of diabetic and nondiabetic kidney disease.

I.A.5. Allow clinical judgment regarding the relevance of other markers of kidney damage. Other markers of kidney damage include abnormalities in the urine sediment (casts, tubular epithelial cells); abnormalities in imaging studies (polycystic kidneys, hydronephrosis, small 'echogenic' kidneys); and abnormalities in the composition of the blood and urine that define 'tubular syndromes' (renal tubular acidosis, nephrogenic diabetes insipidus, Fanconi syndrome, etc). The K/DOQI guidelines address the clinical relevance of these abnormalities based on whether they "can lead to decreased kidney function." This language is included in the definition of CKD (Table 3).

I.A.6. Consider all kidney transplant recipients to have chronic kidney disease, irrespective of GFR level or presence or absence of markers of kidney damage. The rationale for this is based on damage to native kidneys, presumed damage to the kidney transplant based on studies of "protocol biopsies", and need for life-long care caused by complications of prior CKD.

I.A.7. Do not include cause of kidney disease in definition of CKD. Identification of the cause of kidney disease is one of the goals of evaluation of CKD, and may lead to changes in management of CKD. However, CKD can be detected without knowledge of its cause, ascertainment of the cause may require specialized knowledge and procedures not available to the vast majority of clinicians who encounter and can detect CKD. Importantly, the cause of CKD cannot always be determined despite extensive evaluation.

Thus, it is not practical to include the cause of CKD as part of the definition. However, CKD can be classified by cause, as described below.

1.B Classification of CKD (Table 4)
In principle, CKD could be classified according to severity, diagnosis, treatment and prognosis. Classification systems can be simple or complex. The choice of a classification system depends on answers to several questions:

- To whom is the classification system addressed?
- Can we build a system that is useful to most clinicians, with additional complexity that is useful to some?
- Can the classification system be linked to "Action Plans"? An action plan should be evidence-based, but modifiable based on considerations for different populations, and individualized based on patient circumstances.

I.B.1. Retain classification based on severity. There was agreement with initial classification based on level of GFR, using GFR estimating equations. This initial classification is simple, and can be linked to "Action Plans". Because of imprecision of GFR estimates at higher range of GFR, it may be difficult to distinguish Stages 1 and 2. Alternative terms such as "stage, class, or grade" can vary depending on local interpretation and language.

I.B.2. Add classification based on treatment by dialysis or transplantation. This is necessary to link with clinical care and policy, especially regarding reimbursement. To this end, use the following suffix:

- 'T' for all kidney transplant recipients, at any level of GFR (CKD Stages 1-5).
- 'D' for dialysis, for CKD stage 5 for patients treated by dialysis. Irrespective of the level of GFR at which dialysis is initiated, all patients treated by dialysis are CKD Stage 5D.

I.B.3. Encourage further consensus development on classification by cause of kidney disease. Clinical evaluation for CKD should include elucidation of the cause of disease. As discussed above, cause of disease cannot be ascertained in all cases. Classification based on cause of disease would be desirable, but would require a uniform taxonomy that does not currently exist. This would be an important area for further consensus development.

I.B.4. Further research is necessary to allow classification by prognosis. Stratification of risk for the major outcomes of CKD (loss of kidney function and CVD) is based in part, on level of GFR (CKD stage), and cause of kidney disease (Figure 2A). Other factors are also important and could be considered in risk stratification, such as magnitude of albuminuria (Figure 2B). It is likely that these and other risk factors contribute differentially to the risk of different outcomes (Table 5). Research is needed to elucidate risk factors and develop risk prediction instruments for CKD progression and CVD.

Implementation and audit

1. KCAT education programmes for primary health care providers should incorporate the CARI CKD classification system.

2. KHA and KCAT should commission audits of the awareness of the CARI CKD classification system among primary health care providers.

Suggestions for future research

1. Perform a study of the impact of dividing stage 3 into two stages: GFR 30–44 mL/min/1.73 m^2 compared with GFR 45–59 mL/min/1.73 m^2.

2. Perform prospective, longitudinal studies of the outcomes of low GFR in referred versus non-referred populations.

3. Determine whether or not there are different predictors of progression in different populations, thereby necessitating customisation of CKD classification systems.

4. Conduct ANZDATA Registry analysis of the impact of different levels of GFR post-kidney transplant for CKD progression and CVD outcomes.

5. Perform prospective longitudinal studies of the outcomes of patients with increased GFR.

6. Conduct studies to determine whether chronicity can be inferred by rate of change of kidney function over intervals shorter than 3 months (e.g. small or scarred kidneys plus GFR < 60 mL/min/1.73 m^2).

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Appendix

Table 1 Stages of chronic kidney disease (modified from NKF K/DOQI guidelines, 2002)

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage[a] with normal or ↑ GFR	≥ 90
2	Kidney damage[a] with mild ↓ GFR	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	Kidney failure	< 15 or on dialysis[b]

a. 'Kidney damage' is defined as persistent microalbuminuria, persistent proteinuria, persistent haematuria after exclusion of urological causes, or structural abnormalities on kidney imaging tests.

b. Dialysis patients should be denoted as '5D'.

c. Kidney transplant patients should be denoted by adding the suffix 'T' to the corresponding CKD stage.

d. Patients with at least moderate proteinuria (≥ 1 g/day) should be denoted by adding the suffix 'P' to the corresponding CKD stage.