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PATHCHAT

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Chronic kidney disease:

Updated recommendations on definition and classification

Introduction

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for longer than three months, with implications for health.

The most recent Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines (2012) recommend that CKD should be classified using the CGA staging system. This includes **C**ause, **G**lomerular filtration rate (GFR) category and **A**lbuminuria category (as marker for kidney damage), as the combination of these factors relates to risks of adverse outcomes.

Criteria for CKD: (one of the following must be present for more than **three months**):

1. **Decreased GFR** (<60 ml/min/1.73m^2) (GFR categories G3a-G5)
2. Markers of **kidney damage** (one or more):
   a. **Albuminuria**: Albumin excretion rate (AER) ≥ 30mg/day or albumin-to-creatinine ratio (ACR) ≥ 3 mg/mmol
   b. Urine sediment abnormalities (e.g. haematuria, red cell/white cell/granular casts, etc)
   c. Electrolyte and other abnormalities due to tubular disorders
   d. Abnormalities detected by histology
   e. Structural abnormalities detected by imaging
   f. History of kidney transplantation

Classification of CKD using the CGA system:

Previous CKD guidelines included only the level of GFR for staging. By using the CGA system, the cause and albuminuria category are also used. CKD is not a disease in itself, and the assignment of cause is important for determination of prognosis and to guide treatment decisions.

1. Assignment of the cause of CKD:

The cause of CKD is assigned based on the presence or absence of systemic disease and the location of observed or assumed pathology within the kidney. In developed countries, hypertension and diabetes are the most frequent causes of CKD. Examples are supplied in Table 1.

Table1: Classification of CKD based on systemic disease and location of pathology within kidney

	Examples of systemic diseases affecting the kidney	Examples of primary kidney diseases (absence of systemic diseases)
Glomerular diseases	Diabetes, systemic auto-immune diseases, systemic infections, drugs, neoplasia (including amyloidosis)	Diffuse, focal or concentric proliferative glomerulonephritis, focal and segmental glomerulosclerosis, membranous nephropathy, minimal change disease
Tubulointerstitial diseases	Systemic infections, auto-immune, sarcoidosis, drugs, urate, environmental toxins (lead, aristolochic acid found in Chinese herbal medicine), neoplasia (myeloma)	Urinary tract infections, stones, obstruction
Vascular diseases	Atherosclerosis, hypertension, ischaemia, cholesterol emboli, systemic vasculitis, thrombotic microangiopathy, systemic sclerosis	ANCA-associated renal limited vasculitis, fibromuscular dysplasia
Cystic and congenital diseases	Polycystic kidney disease, Alport syndrome, Fabry disease	Renal dysplasia, medullary cystic disease, podocytopathies

ANCA: Antineutrophil cytoplasmic antibody

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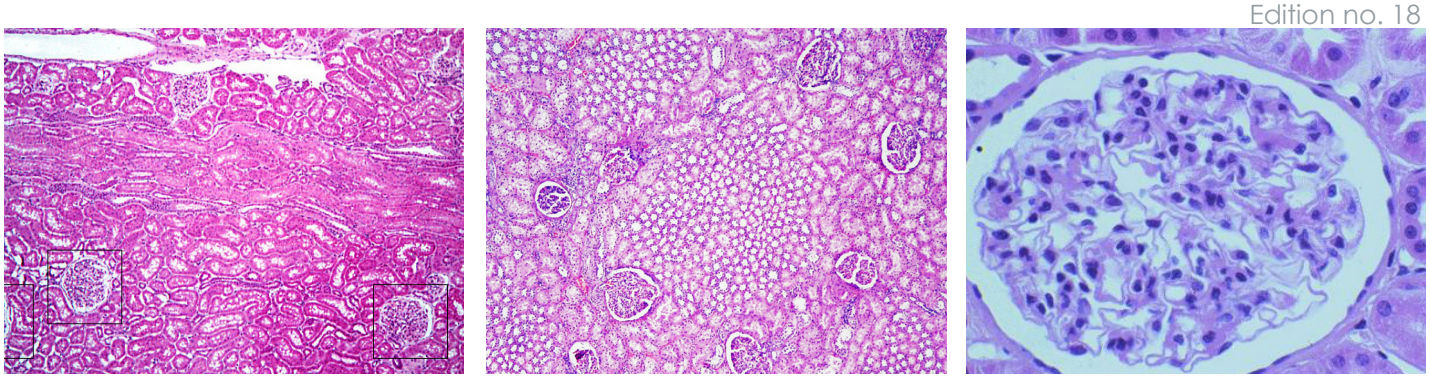

Renal histology slides.

2. Recommendations regarding GFR estimation:

- Current estimating equations for GFR **(eGFR)** are able to detect decreased GFRs < 60 and should be reported in addition to the S-Creatinine determined on an IDMS-standardised method. The eGFR should be reported in ml/min/1.73m^2 (relative to a standard BSA).
- Ampath currently uses the **Modification of Diet in Renal Disease (MDRD) equation** for GFR calculation as previously recommended by the National Kidney Disease Education Programme (NKDEP). However, in line with the most recent recommendations by KDIGO, Ampath will change to the **2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Equation during November 2014**.
- The **main advantages of changing to the CKD-EPI** Creatinine Equation are the following:
  - More accurate at GFR >60ml/min/1.73m^2 and GFR >90ml/min/1.73m^2 is reportable using the CKD-EPI Equation.
  - Less influenced by ethnic origin and reasonable to use without correction for race and ethnicity.
  - Significant reclassification from Stage 3 a (GFR 45-59) using MDRD equation to Stage 2 (GFR 60-89) when using CKD-EPI equation.
  - CKD-EPI classification shows better accuracy compared to gold standard methods of GFR estimation than MDRD, especially at high GFRs, in younger people and women.
  - Validated in older people.
- **Limitations of serum creatinine** (SCr) as a marker are still applicable – see Table 2.
- The use of **additional tests** (such as cystatin C or a clearance measurement) **for confirmatory testing** is recommended in specific circumstances (e.g. organ donors or dosing of toxic drugs). Determination of **cystatin C** and calculation of an eGFR based on its value (eGFRcys) will be offered in the near future. These equations are not influenced by race and are less affected by non-GFR determinants of S-Creatinine. Clearance measurements using an exogenous filtration marker are unfortunately not widely available in South Africa.
- **GFR categories in CKD:** Please take note that the previously used Stage 3 has been subdivided into Stage 3a and 3b, based on data supporting different risks and outcomes. These GFR categories can now also be used in children over the age of two years, provided that their GFR has been calculated with an appropriate equation (including height). Although some decline in GFR is expected with aging, levels below 60 ml/min/1.73m^2 are also regarded as decreased.

Table 2: Sources of error in GFR estimation using creatinine

Source of error	Example
Non-steady state	• AKI
Non-GFR determinants of SCr that differ from study populations in which equations were developed	
• Factors affecting creatinine generation	• Race/ethnicity other than US/European black and white • Extremes of muscle mass or body size • Diet and nutritional status (high protein diet/creatine supplements/ingestion of cooked meats) • Muscle-wasting diseases
• Factors affecting tubular secretion of creatinine	• Decrease by drug-induced inhibition: trimethoprim, cimetidine, fenofibrate
• Factors affecting extra-renal elimination of creatinine	• Dialysis • Decrease by inhibition of gut creatininase by antibiotics • Increased by large volume losses of extracellular fluids
Higher GFR	Higher biological variability in non-GFR determinants relative to GFR: • Higher measurement error in SCr and GFR
Interference with creatinine assay	• Spectral interferences (e.g. bilirubin, some drugs) • Chemical interferences (e.g. glucose, ketones, bilirubin, some drugs)

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Table 3: GFR categories in CKD

GFR category	GFR (mℓ/min/1.73m²)	Terms
G1	≥ 90	Normal or high
G2	60–89	Mildly decreased*
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	< 15	Kidney failure

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*Relative to young adult level

In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

3. Albuminuria as a marker of kidney damage:

- **Albuminuria** is the preferred marker for assessment of kidney damage, and should be used in preference to proteinuria, as it is the earliest marker of **glomerular diseases**. There is a graded increase in risk for all-cause and cardiovascular mortality, kidney failure, acute kidney injury (AKI) and CKD progression for higher albuminuria categories across all GFR categories.
- For **screening** purposes, an early morning urine sample (first pass) to determine the **albumin-to-creatinine ratio (ACR)** is preferred.
- The term micro-albuminuria used for an ACR of 3-30 mg/mmol (Category A2) should no longer be used and has been replaced by the term **"moderately increased" albuminuria**.
- An abnormal screening test should be **confirmed** by an ACR on an early morning urine sample or an albumin excretion rate (AER) in a timed urine collection.
- The use of **reagent test strips is discouraged** due to poor sensitivity at lower concentrations and because the values are not adjusted for urinary concentration.
- If non-albuminuric proteinuria is suspected, use assays for **specific proteins**, e.g. determination of Bence Jones proteins in myeloma patients.
- In **children**, urine **protein determination is preferred** to albumin, due to the higher incidence of non-glomerular diseases.

Table 4: Albuminuria categories in CKD and relationship with proteinuria

	Categories		
Measure	**Normal to mildly increased (A1)**	**Moderately increased (A2)**	**Severely increased (A3)**
Albumin-to-creatinine ratio (ACR) (mg/mmol)	<3	3–30	>30
Albumin excretion rate (AER) (mg/24 hours)	<30	30–300	>300
Protein-to-creatinine ratio (PCR) (mg/mmol)	<15	15–50	>50
Protein excretion rate (PER) (mg/24 hours)	<150	150–500	>500
Protein reagent strip	Negative to trace	Trace to +	++ or greater

Nephrotic syndrome: ACR > 220 mg/mmol, AER > 2 200 mg/24 hours, PCR > 350 mg/mmol, PER > 3 500 mg/24 hours

4. Prognosis of CKD by GFR and albuminuria categories:

For all CKD complications, prognosis depends on the combination of the degree of GFR impairment, degree of albuminuria, cause and the presence of other comorbid conditions.

Risk for all-cause mortality, CVD and kidney failure increases as the degree of GFR declines and albuminuria increases. Risk scores for specific events/complications are under development.

Table 5: Prognosis of CKD.

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012				Peristent albuminuria categories description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (mℓ/min/1.73m²) description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severly decreased	15–29			
	G5	Kidney failure	<15			

Legend: Green: low risk; Yellow: moderately increased risk; Orange: high risk; Red: very high risk

Areas of controversy or confusion:

1. **CKD with isolated GFR decrease** without markers of kidney damage may be seen with heart failure, liver cirrhosis, hypothyroidism, malnutrition and in kidney donors.
2. **CKD with isolated persistent albuminuria** without decreased GFR is seen in obesity and the metabolic syndrome. CKD should be excluded in patients with orthostatic (postural) proteinuria with PER > 1 000 mg/24 hours.
3. If decreased GFR or markers of kidney damage resolve while on treatment, the patient is regarded as having **treated CKD**, similar to treated HT, DM or hypercholesterolaemia. If normalisation is maintained after discontinuation of treatment, the patient is regarded as having a **history of CKD**.
4. Kidney disease may rarely be present in the absence of decreased GFR and markers of kidney damage.

Reference:

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. 2012. *Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease*. *Kidney Inter*national, Supplement 2013: 3: 1-150. Available online at http://kdigo.org/home/guidelines/ckd-evaluation-management.