Guidelines

Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: new developments and revised recommendations

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Australasian Creatinine Consensus Working Group

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After publication of the Australasian Creatinine Consensus Working Group's position statement in 2005 and revised statement in 2007, the group reconvened in 2010 to consider new issues. All recommendations contained in this position statement (Box) are endorsed by the Royal College of Pathologists of Australasia, Australasian Association of Clinical Biochemists, Royal Australian College of General Practitioners, Australian and New Zealand Paediatric Nephrology Association, Australian and New Zealand Society of Nephrology, Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists, and Kidney Health Australia.

Discussion of recommendations

1 Adoption of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula for calculating estimated glomerular filtration rate (eGFR)

Recently, the CKD Epidemiology Collaboration developed a new CKD-EPI eGFR formula from a pooled dataset that included 10 studies and 8254 participants with and without known CKD. Validation of this formula in a separate external dataset of 3896 participants in 16 studies showed that the CKD-EPI formula retained the precision and accuracy of the Modification of Diet in Renal Disease (MDRD) formula at GFR < 60 mL/min/1.73 m^2 with less bias and improved precision at GFR > 60 mL/min/1.73 m^2. Subsequent epidemiological evaluations in North American and Australian general population studies have shown that the CKD-EPI equation more appropriately categorises individuals with respect to long-term clinical risks of end-stage kidney disease, coronary heart disease, stroke and all-cause mortality than the MDRD equation.

2 Reporting limit for eGFR using the CKD-EPI formula

Although the CKD-EPI equation is more accurate (predominantly due to reduced bias) than the "175" MDRD equation at higher levels of kidney function, the working group could not reach consensus on a recommended eGFR reporting limit and concluded that all laboratories should report eGFR values as a precise figure to at least 90 mL/min/1.73 m^2.

3 Serum creatinine (SCr) assay performance in adult populations

A bias criterion of ± 5% is proposed, including any bias due to the manufacturer's calibration traceability. At a 5% bias level, about 5% of patients over 50 years of age would have their classification changed at the level of 60 mL/min/1.73 m^2.

Revised recommendations of the Australasian Creatinine Consensus Working Group and levels of evidence*

1 The method of calculating estimated glomerular filtration rate (eGFR) should be changed to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. **(1C)**

2 All laboratories should report eGFR values as a precise figure to at least 90 mL/min/1.73 m^2. **(1C)**

3 The performance of serum creatinine (SCr) assays should achieve a bias ± 5% (ie, 5 µmol/L at a value of 100 µmol/L) and a long-term within-laboratory coefficient of variation less than 4% for the measurement of SCr in adults. **(2C)**

4 Age-related decision points for eGFR are not recommended in adults. **(1C)**

5 Dose reduction of some drugs is recommended for patients with reduced kidney function. Both eGFR (mL/min/1.73 m^2) and estimated creatinine clearance (mL/min) provide an estimate of relative renal drug clearance. If using eGFR for drug dosing, body size should be considered, in addition to referring to the approved product information. For drugs with a narrow therapeutic index, therapeutic drug monitoring or a valid marker of drug effect should be used to individualise dosing. **(1C)**

6 The CKD-EPI formula is a useful tool to estimate GFR in all people, including various ethnic populations. The CKD-EPI formula has been validated as a tool to estimate GFR in some non-European populations, including South-East Asian, African, Indian and Chinese individuals living in Western countries. The different methods to estimate GFR from SCr concentration have not been validated in Indigenous Australians, although these studies are currently underway. **(2C)**

7 The validity of eGFR in pregnancy is not known. SCr concentration should be maintained as the standard test for kidney function in pregnant women. **(1C)**

8 The use of an enzymatic assay is recommended for the measurement of SCr concentration in children and youth (individuals aged less than 18 years). Other SCr assays that achieve a bias < 10% at low SCr values (ie, 5 µmol/L at a value of 50 µmol/L) and are not compromised by variations in albumin, bilirubin and haemoglobin F (neonates) would be satisfactory alternatives. Routine calculation of eGFR is not recommended in children and youth. Age-appropriate reference values for SCr concentration should be reported for individuals up to 18 years of age. **(1C)**

* Levels of evidence are defined in the 2006 position statement from Kidney Disease: Improving Global Outcomes (KDIGO), *Kidney Int* 2006; 70: 2058-2065. ◆

A long-term within-laboratory coefficient of variation (CV) less than 4% is proposed. The average within-subject biological variation for SCr (CVi) is described by a CV of 6.0%, so an assay with a CV below 4.5% (0.75% of CVi) contributes less than an additional 25% to the total result variation.

4 Age-related reference intervals for eGFR in adults

The CKD Prognosis Consortium recently published findings of collaborative meta-analyses of data from general and high-risk populations, and populations with kidney disease, showing that eGFR < 60 mL/min/1.73 m^2 was associated with increased risks of all-cause mortality, cardiovascular mortality, end-stage kidney disease, acute kidney injury and progression of CKD without consistent age interactions. In particular, for the controversial category of

eGFR 45–59 mL/min/1.73 m^2 with normal albuminuria, the relative hazards of all outcomes except all-cause mortality were similar above and below the age of 65 years in the general population cohorts. These observations are not consistent with the interpretation that decreased GFR with ageing is "normal" or "physiological". Consequently, the working group concluded that age-related decision points for eGFR are not recommended in adults.

5 The use of eGFR for adjusting drug dosing in patients with reduced kidney function

Most official recommendations for drug dosing in kidney impairment are traceable to the manufacturers' data by measured GFR or creatinine clearance estimated by the Cockcroft–Gault formula. Although the use of Cockcroft–Gault estimated creatinine clearance to guide drug dosing is supported by accumulated clinical experience, primary clinical outcome studies to support it are lacking. Few studies have been conducted directly linking dosing according to eGFR with pharmacokinetic or clinical outcomes. However, eGFR provides a valid estimate of GFR and is widely available on laboratory reports. The units of eGFR are mL/min/1.73 m^2 whereas the units of drug clearance are mL/min. To avoid overdosing small patients or underdosing large patients, eGFR should be adjusted for patient size. In CKD, factors other than renal drug clearance can also alter drug effects. Thus, for drugs with a narrow therapeutic index, drug effects (desired and adverse) or drug concentrations should be monitored. Detailed advice on drug dosing is outside the scope of this document.

6 The use of eGFR in various ethnic populations

Several studies have shown that performance of the MDRD equation in China and Japan improved when population-specific coefficients were introduced. A recent study evaluated a GFR-estimating equation that incorporated a four-level race variable (black, Asian, Native American and Hispanic, and white and other) against CKD-EPI eGFR (African American or not) in a validation cohort of 4014 patients from 17 studies from the United States and Europe, as well as in 1022 patients from China, Japan and South Africa. The study showed that the CKD-EPI equation could be successfully applied across a broad range of racial and ethnic groups living in Western countries.

Although GFR-estimating equations (including CKD-EPI) have yet to be validated in Aboriginal and Torres Strait Islander peoples and Maori and Pacific Islander peoples, it appears clinically appropriate for CKD-EPI eGFR to be calculated and used prudently in these ethnic groups, using the non-African American formulae.

7 The use of eGFR in pregnancy

Validation studies of eGFR in pregnant women have not been performed. A 24-hour creatinine clearance, when the collection is complete, does provide a valid estimate of kidney function. Reference ranges are available for the entire 40-week gestation, although the reference range will vary frequently, up to every 4 weeks.

8 Measurement of SCr concentration and calculation of eGFR in paediatric populations

Current publications have not convincingly shown that early detection of kidney disorders in children is cost-effective or will lead to a reduction in clinically significant outcomes. Moreover, calculation of eGFR is children is logistically problematic because the most commonly used equation, the Schwartz formula, requires height data, which are not routinely measured at the time of blood collection. Thus, the working group does not recommend routine reporting of eGFR in children.

SCr concentration in normal infants and children increases with age and is slightly higher at any age in males than females. Normative values have been published and are recommended for more accurate reporting of kidney function in children and adolescents. Enzymatic methods are generally preferred, particularly in young infants. Enzymatic methods are not affected by other substances (albumin, IgG and haemoglobin F) that are known to interfere with Jaffe creatinine assays and may lead to clinically important inaccuracies in the measurement of SCr concentration.

Conclusion

The available evidence indicates that introduction of automatic reporting of eGFR each time a test for SCr concentration is requested has increased the awareness of significant kidney dysfunction in clinical practice, augmented the detection of patients with CKD in the community and enhanced the quantity of appropriate referrals to specialist renal services. It has also led to improvements in the accuracy and standardisation of laboratory measurement of creatinine and reduction in the variability previously seen in Australasia and overseas. Progressive refinements in GFR estimating equations, from Cockcroft–Gault to "186" MDRD to "175" MDRD to CKD-EPI eGFR, have resulted in improved accuracy, particularly at normal and near-normal levels of kidney function, and in better kidney and cardiovascular risk prediction. Clinicians should also be aware that there is now overwhelming evidence that optimal detection and subsequent risk stratification of CKD patients requires simultaneous consideration of both eGFR and urinary albumin, rather than eGFR alone.

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