Chronic Kidney Disease and Drug Dosing: Information for Providers

(Revised January 2010)

Estimation of Kidney Function for Prescription Medication Dosage in Adults

Knowledge of kidney function is important for dosage of medications that are excreted by the kidneys. Food and Drug Administration (FDA)-approved drug-labeling guides provide adjustments of drug dosages for patients with impaired kidney function. On these labels, serum creatinine; measured creatinine clearance (CrCl); or, most commonly, estimated creatinine clearance using the Cockcroft-Gault equation (eCrCl) are used to estimate kidney function. For most drugs, these labels were developed prior to standardized calibration of creatinine assays and reporting estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease (MDRD) Study equation.[1] This document describes the National Kidney Disease Education Program's (NKDEP) suggestions and rationales for assessment of kidney function for drug-dosing purposes.

NKDEP's Suggested Approach to Drug Dosing

Historically, there has been substantial variability in serum creatinine values reported by different clinical laboratory creatinine methods. Consequently, pharmacokinetic (PK) studies performed using non-standardized creatinine methods obtained results that were dependent upon the particular creatinine method used in a given PK study. The results from the PK studies were incorporated into FDA drug labels. As such, the PK studies' recommended drug dosages (i.e., the FDA drug labels) were inconsistently translated into clinical practice due to the variability among creatinine methods used in different laboratories.

Use of standardized creatinine methods will lead to less variation in estimating kidney function and more consistent drug dosing. For some drugs, the FDA or manufacturers may decide to perform studies to re-express drug labeling for standardized creatinine values. However, it will not be possible to re-express all current drug-dosing recommendations for use with standardized creatinine values.

A large simulation study compared eGFR and eCrCl calculated from standardized creatinine values to each other and to gold-standard measurements of GFR. The results suggested that for the majority of patients and for most drugs tested, there was little difference in the drug dose that would be administered using either equation to estimate kidney function.[2] Based on these and other considerations, we suggest the following:

- Use of a single kidney function estimate to guide detection, evaluation, and management of chronic kidney disease (CKD) and drug dosing is likely to facilitate delivery of high-quality health care.
- Utilize eGFR or eCrCl for drug dosing.

- If using eGFR in very large or very small patients, multiply the reported eGFR by the estimated body surface area (BSA) in order to obtain eGFR in units of mL/min:

$$\text{eGFR}/1.73\text{m}^2 \times \text{estimated BSA} = \text{eGFR for drug dosing}$$

Note: BSA can be obtained from a standard nomogram or can be calculated using equations such as[3]:

$$\text{m}^2 = \sqrt{\frac{\text{Height (in)} \times \text{Weight (lb)}}{3131}}$$

(See more on this in the MDRD Study Equation section.)

- Consider assessing kidney function using alternative methods such as measured CrCl or measured GFR using exogenous filtration markers when prescribing drugs with narrow therapeutic indices, or for individuals in whom eGFR and eCrCl provide different estimates of kidney function, or for individuals in whom any estimates based on creatinine are likely to be inaccurate.[4] (See more on this in the Limitations of Any Serum Creatinine-based Estimate section.)

Impact of IDMS-standardized Creatinine Values

National efforts to standardize serum creatinine assays by establishing calibration traceability to an isotope dilution mass spectrometry (IDMS) reference measurement procedure have been underway since 2005. All major global manufacturers have completed recalibration to be traceable to an IDMS reference measurement procedure, and all inventory with older calibration is expected to be no longer in use by the first half of 2010. (Individual manufacturers should be contacted for status regarding their products.) Previously, there was a large variability in serum creatinine results among clinical laboratories, with an overall positive bias by approximately 10 to 20 percent among laboratories surveyed.[5] When standardization of all creatinine methods to IDMS-traceable calibration is complete, there will be less variability in creatinine results used for managing patients. The following items describe the impact of standardized creatinine assays:

- Standardization of creatinine assays will lead to less variation in estimating kidney function and more consistent drug dosing.

- The relationship between creatinine results before and after standardization will be different for each specific method and instrument used in clinical laboratories.

- It is not possible to have a single, uniform conversion formula or factor to relate IDMS-standardized creatinine values back to non-IDMS-traceable values that can be applied to all laboratories where the PK studies were performed or to all clinical laboratories.

- Using standardized creatinine values, the accuracy of estimated kidney function will depend upon whether or not an equation was developed using IDMS-traceable creatinine values.

- Use of IDMS-traceable creatinine values in the IDMS-traceable MDRD Study equation will result in a more accurate eGFR.[1,6]

- Use of IDMS-traceable creatinine values in the Cockcroft-Gault formula will have a variable impact on eCrCl, depending upon the creatinine method/instrument used. However, because most nonstandardized methods had a positive bias, use of the Cockcroft-Gault formula with IDMS-traceable creatinine values will lead to higher eCrCl values than were determined prior to standardization.[6]

- Measured CrCl values based on measured serum and urine creatinine results may change for some methods that have independent calibration for serum and urine samples. Most methods use the same calibration scheme for both serum and urine and will be minimally affected by standardization of calibration because creatinine is used in both the numerator and denominator of the CrCl calculation.

MDRD Study Equation

- The Modification of Diet in Renal Disease (MDRD) Study equation was derived from a study population of 1,628 men and women with CKD, aged 18 to 70, predominantly Caucasian, nondiabetic, and who were non-kidney-transplant recipients.[7]

- A large number of studies now show that the MDRD Study equation is suitable for use across populations with CKD, but underestimates measured GFR at higher levels.[8,9]

- The MDRD Study equation estimates GFR adjusted for BSA. Kidney function is proportional to kidney size, which is proportional to BSA. BSA of 1.73 m^2 is the normal mean value for young adults. Adjustment for BSA is necessary when comparing a patient's kidney function to normal values, or to the levels defining the stages of CKD. For most drugs, adjusting for BSA is not necessary for determining drug dosing. GFR estimates adjusted for BSA will generally be adequate except in patients whose body size is very different than average. (See NKDEP's Suggested Approach to Drug Dosing section.)

- The original MDRD Study equation is suitable for use with creatinine methods that DO NOT have calibration traceable to IDMS.

$$\text{eGFR} = 186 \times (S_{cr})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$$

Note: GFR is expressed in mL/min per 1.73 m^2, S_{cr} is serum creatinine expressed in mg/dL, and age is expressed in years.

- The MDRD Study equation has been re-expressed for use with standardized serum creatinine values.[1,10]

$$\text{eGFR} = 175 \times (\text{Standardized } S_{cr})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$$

Note: GFR is expressed in mL/min per 1.73 m^2, S_{cr} is serum creatinine expressed in mg/dL, and age is expressed in years.

Cockcroft-Gault Equation

- The Cockcroft-Gault (CG) equation was derived from a study population of 249 Caucasian men aged 18 to 92, with and without CKD. No women were included in the development population, so the factor for female sex is hypothetical.[11]

  $$eCrCl = [((140\text{-age}) \times \text{weight})/(72 \times S_{cr})] \times 0.85 \text{ if female}$$

  Note: eCrCl is expressed in mL/min, age is expressed in years, weight is expressed in kilograms, and S_{cr} is expressed in mg/dL.

- The CG equation cannot be re-expressed for IDMS-traceable creatinine values. The creatinine method used in the development of the equation is no longer in use and samples from the study are not available.

- The CG equation estimates CrCl that is not adjusted for BSA. Similar to measured CrCl, eCrCl systematically overestimates GFR due to tubular secretion of creatinine. Additionally, eCrCl has more variability than eGFR using the MDRD Study equation as evidenced by Cockcroft-Gault eCrCl having only 50 to 70 percent of results (vs. 83 percent for eGFR) within 30 percent of measured GFR.[6]

- Modifications of the CG equation, such as the use of ideal versus actual body weight, were developed in an attempt to overcome the imprecision with the use of measured body weight. However, there is no evidence that these modifications are more accurate predictors of GFR or provide better drug-dosing guidelines.

Limitations of Any Serum Creatinine-based Estimate

- The serum concentration of creatinine is influenced by factors other than the GFR, in particular, differences in rate of generation related to muscle mass and diet, as well as differences in the rate of tubular secretion. Estimating equations capture the average difference in rate of creatinine generation by age, sex, race, or weight, but do not capture all factors.

- Neither eGFR nor eCrCl will be accurate in individuals with extremes of body size or muscle mass, or those with unusual dietary habits. The limitations in creatinine-based estimating equations are particularly relevant for populations with reduced muscle mass, including the frail, elderly, critically ill, or cancer patients who are likely to require medications.[12]

- Use of any serum creatinine-based estimate requires that kidney function be at a steady state, so any estimate must be used cautiously in hospitalized patients with rapidly changing kidney function.

- Measurement of GFR using exogenous filtration markers and urine or plasma clearance or of CrCl using timed urine collections, should be considered when dosing medications with narrow therapeutic indices or with high toxicity, or in patients for whom serum creatinine based estimates may be inaccurate.[4]

[1] Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*. 2006;145:247-54.

[2] Stevens LA, Nolin T, Richardson M, et al. Comparison of drug dosing recommendations based on measured GFR and kidney function estimating equations. *Am J Kid Dis*. 2009;54(1):33-42.

[3] Mosteller, RD. Simplified Calculation of Body-Surface Area. *N Engl J Med*. 1987;317(17):1098.

[4] Stevens LA, Levey AS. Measured GFR as a Confirmatory test for estimated GFR: indications and interpretation. *J Am Soc Nephrol.* 2009;20:2305-13.

[5] Miller WG, Myers GL, Ashwood ER, et al. Creatinine measurement: state of the art in accuracy and interlaboratory harmonization. *Arch Pathol Lab Med*. 2005;129:297-304.

[6] Stevens LA, Manzi J, Levey AS, et al. Impact of creatinine calibration on performance of GFR estimating equations in a pooled individual patient database. *Am J Kidney Dis*. 2007;50:21-35.

[7] Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130:461-470.

[8] Stevens LA, Coresh J, Greene T, et al. Assessing kidney function--measured and estimated glomerular filtration rate. *N Engl J Med*. 2006;354:2473-83.

[9] Stevens LA, Coresh J, Feldman HI, et al. Evaluation of the modification of diet in renal disease study equation in a large diverse population. *J Am Soc Nephrol*. 2007;18:2749-57.

[10] Levey AS, Coresh J, Greene T, et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem*. 2007;53:766-72.

[11] Cockcroft D, Gault M. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31-41.

[12] Poggio ED, Nef PC, Wang X, et al. Performance of the Cockcroft-Gault and modification of diet in renal disease equations in estimating GFR in ill hospitalized patients. *Am J Kidney Dis*. 2005;46:242-52.

This information was originally posted to the NKDEP website in September 2009. Extra copies of this updated version can be printed by visiting: http://www.nkdep.nih.gov/professionals/drug-dosing-information.htm.

NKDEP is an initiative of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), U.S. Department of Health & Human Services (DHHS).