MDRD and Drug Dosing
Has the MDRD's Time Arrived?

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Standardized Creatinine and MDRD

- The MDRD is now being used as a clinical tool for the detection, evaluation and management of kidney disease (>80% of clinical laboratories report eGFR).
- IDMS standardized, calibrated creatinine assays should in use by all laboratories by the end of 2010
- Standardized SCr are generally lower than non-standardized SCr values

IDMS-traceable MDRD Equation:

GFR (mL/min/1.73 m^2) =

$175 \times (Scr)^{-1.154} \times (Age)^{-0.203} \times (0.742$ if female) $\times (1.212$ if African American)

The equation does not require weight or height variables because the results are reported normalized to 1.73 m^2 body surface area, which is an accepted average adult surface area.

Clin Chem 2007;53:766-72
www.nkdep.nih.gov/professionals/drug-dosing-information 5/11

MDRD

- Original MDRD derived from a study population of 1,628 men and women with CKD, aged 18 to 70, predominantly Caucasian
- Widely validated

Cockroft-Gault Equation

CrCl = [(140-age) x weight]/(72 x Scr)

x 0.85 if female

- Derived from a study population of 249 Caucasian men aged 18 to 92, with and without CKD
- No women were included in the population, so the factor for female sex is hypothetical
- Widely validated

Nephron 1976;16:31-41

Staging CKD Using MDRD

Staging of CKD

Stage	Description	GFR (ml/min/1.73m²)
1	Kidney damage, normal GFR	≥ 90
2	Kidney damage, mild decrease GFR	60-89
3	Moderate decrease GFR	30-59
4	Severe decrease GFR	15-29
5	Kidney failure	<15

Ann Intern Med 2003;139:137-147

FDA - Pharmacokinetics in Impaired Renal Function

FDA Suggested Categories of Renal Function

Group	Description	Estimated Creatinine Clearance (ml/min)
1	Normal renal function	>80 ml/min
2	Mild renal impairment	50-80 ml/min
3	Moderate renal impairment	30-50 ml/min
4	Severe renal impairment	<30 ml/min
5	ESRD	Requiring dialysis

www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances (5/11)

FDA and Renal Function

- FDA suggests use of the non-modified Cockroft-Gault equation to estimate renal function (CrCl)
- FDA is considering whether to modify Guidance to Industry Pharmacokinetics in Impaired Renal Function. (latest update 5/98)
- Review took place in March 2008 and draft guidelines were put to public comment in March 2010
- Updating categories of renal function
- Use of MDRD being considered

NKDEP and Drug Dosing

- 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

www.nkdep.nih.gov/professionals/drug-dosing-information (5/11)

NKDEP and Drug Dosing

- 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
  - For individuals in whom eGFR and eCrCl provide different estimates of kidney function
  - For individuals in whom any estimates based on creatinine are likely to be inaccurate

NKDEP and Cockroft-Gault

- The CG equation estimates CrCl that is not adjusted for BSA
- CrCl systematically overestimates GFR due to tubular secretion of creatinine
- CrCl has more variability than eGFR
  - only 50-70% CrCl results are within 30% of measured GFR (vs. 83% eGFR within 30% of measured GFR)

NKDEP and Cockroft-Gault

"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"

"There is no evidence that these modifications are more accurate predictors of GFR or provide better drug-dosing guidelines"

The MDRD Equation

- Populations drawn from 1628 patients with chronic kidney disease (mean CrCl 39.8 ml/min/1.73m^2).
- GFR measured by iothalamate clearance and 24 hour urinary creatinine clearance
- Mean weight: 79.6 +/- 16.8 kg, mean BSA: 1.91+/- 0.23m^2, mean SCr: 2.3 mg/dl
- Urinary CrCl overestimated iothalamate GFR by 19%

Levey Ann Intern Med. 1999;130:461-470

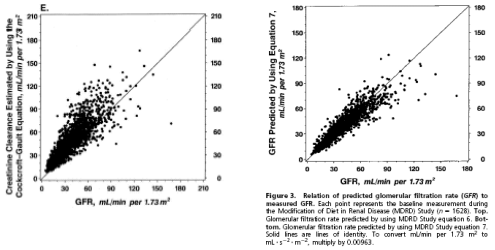


Figure 3. Relation of predicted glomerular filtration rate (GFR) to measured GFR. Each point represents the baseline measurement during the Modification of Diet in Renal Disease (MDRD) Study (n = 1628). Top, Glomerular filtration rate predicted by using MDRD Study equation 6. Bottom, Glomerular filtration rate predicted by using MDRD Study equation 7. Solid lines are lines of identity. To convert mL/min per 1.73 m^2 to mL · s^{-1} · m^{-2}, multiply by 0.00963.

Levey Ann Intern Med. 1999;130:461-470

Equations v. iGFR

- Cockroft-Gault vs. iothalamate GFR:
  - Cockroft-Gault: overestimated iothalamate GFR by 16%
  - Median absolute error: 6.8 ml/min/1.73m^2
  - Median percentage error:19.8%
  - R^2 = 0.842
- MDRD formula vs. iothalamate GFR:
  - Median absolute error: 3.8 ml/min/1.73m^2
  - Median percentage error: 11.5%
  - R^2 = .903

Levey Ann Intern Med.1999;130:461-470

4 Variable MDRD Equation

- R^2 = 0.892 for 4 variable MDRD
- 90% of subjects within 30% of actual GFR

Levey J Am Soc Nephrol. 2000; 11: 155A

NKDEP and Drug Dosing

"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"

Comparison of Drug Dosing Recommendations Based on Measured GFR and Kidney Function Estimating Equations

Lesley A. Stevens, MD, MS,[1] Thomas D. Nolin, PharmD, PhD,[2] Michelle M. Richardson, PharmD,[1] Harold I. Feldman, MD, MSCE,[3] Julia B. Lewis, MD,[3,4] Roger Rodby, MD,[5] Raymond Townsend, MD,[6] Aghogho Okparavero, MBBS, MPH,[1] Yaping (Lucy) Zhang, MS,[1] Christopher H. Schmid, PhD,[1] and Andrew S. Levey, MD,[1] on behalf of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)

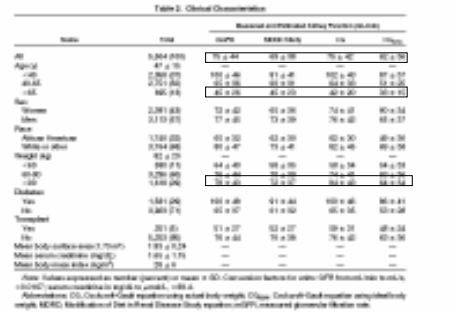
Am J Kidney Dis 54:33–42. © 2009 by the National Kidney Foundation, Inc.

Stevens 2009

- Objectives:
  - Estimate and compare kidney function estimates using I-125 iothalamate, MDRD, Cockroft-Gault and modified Cockroft-Gault equations
  - Determine concordance of assigned kidney function according to current FDA guidance
  - Determine concordance of recommended doses of 15 medications
- Study population: 5,504 participants (6 research studies, 4 clinical populations)

Stevens 2009

Stevens 2009



Stevens 2009

- Concordance was best for the MDRD and worst for the CG_{IBW}
- p<0.001 for difference in concordance among all equations
- Direction of discordance different for the 3 equations
  - CG_{IBW} is discordant low 29% of the time

Concordance to iGFR

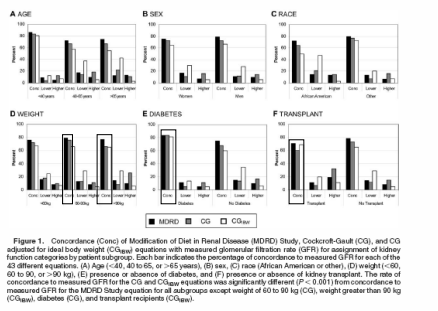
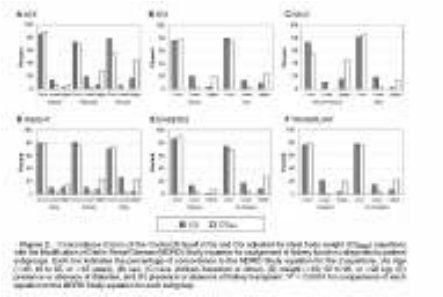


Figure 1. Concordance (Conc) of Modification of Diet in Renal Disease (MDRD) Study, Cockcroft-Gault (CG), and CG adjusted for ideal body weight (CG_{IBW}) equations with measured glomerular filtration rate (GFR) for assignment of kidney function categories by patient subgroup. Each bar indicates the percentage of concordance to measured GFR for each of the 43 different equations. (A) Age (<40, 40 to 65, or >65 years), (B) sex, (C) race (African American or other), (D) weight (<60, 60 to 90, or >90 kg), (E) presence or absence of diabetes, and (F) presence or absence of kidney transplant. The rate of concordance to measured GFR for the CG and CG_{IBW} equations was significantly different ($P < 0.001$) from concordance to measured GFR for the MDRD Study equation for all subgroups except weight of 60 to 90 kg (CG), weight greater than 90 kg (CG_{IBW}), diabetes (CG), and transplant recipients (CG_{IBW}).

Concordance to iGFR

- Rate of concordance to the measured GFR for the CG and CG_{IBW} was significantly different (p<0.001) from the rate of concordance to measured GFR for the MDRD equation for all subgroups except weight 60-90kg, weight >90, diabetes and transplant
  - CG or CG_{IBW} underperforms the MDRD in almost every subgroup of patients
  - CG or CG_{IBW} equivalent in only 3 subgroups

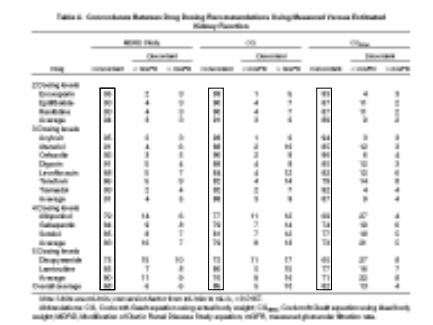
Concordance to the MDRD



Concordance to MDRD

- p<0.0001 for concordance in all subgroups
- CG, CG_{IBW} are **discordant** with MDRD
  - MDRD may not be concordant with CG, CG_{IBW}
  - Results of other dose concordance studies therefore are not surprising
  - Clinicians must recognize that there is going to be discordance among all equations
  - Equations are not meant to mimic each other
  - This study used the gold standard iGRF and the standardized, calibrated SCr measurement in a large pooled population

Concordance of Drug Dosing



CKD-EPI and MDRD Compared to iGFR

Table 3. Comparison of the CKD-EPI and MDRD Study Equations in Estimating Measured GFR in the Validation Data Set*

Variable and Equation	All Patients	Patients With Estimated GFR <60 mL/min per 1.73 m²	Patients With Estimated GFR ≥60 mL/min per 1.73 m²
Median difference (95% CI), mL/min per 1.73 m²†			
CKD-EPI	2.5 (2.1–2.9)	2.1 (1.7–2.4)	3.5 (2.4–4.5)
MDRD Study	5.5 (5.0–5.9)	3.4 (2.9–4.0)	10.6 (9.8–11.3)
Interquartile range for differences (95% CI), mL/min per 1.73 m²‡			
CKD-EPI	16.6 (15.9–17.3)	11.3 (10.7–12.1)	24.2 (22.8–26.3)
MDRD Study	18.3 (17.4–19.3)	12.9 (12.2–13.6)	29.7 (24.4–27.1)
P_{30} (95% CI), %‖			
CKD-EPI	84.1 (83.0–85.3)	79.9 (78.1–81.7)	88.3 (86.9–89.7)
MDRD Study	80.6 (79.5–82.0)	77.2 (75.5–79.0)	84.7 (83.0–86.3)
Root mean square error (95% CI)			
CKD-EPI	0.260 (0.241–0.269)	0.284 (0.270–0.298)	0.213 (0.203–0.223)
MDRD Study	0.274 (0.265–0.282)	0.294 (0.280–0.308)	0.248 (0.238–0.258)

Levey Ann Intern Med 2009;150:604-612

ARTICLE | Annals of Internal Medicine

A New Equation to Estimate Glomerular Filtration Rate

Andrew S. Levey, MD; Lesley A. Stevens, MD, MS; Christopher H. Schmid, PhD; Yaping (Lucy) Zhang, MS; Alejandro F. Castro III, MPH; Harold I. Feldman, MD, MSCE; John W. Kusek, PhD; Paul Eggers, PhD; Frederick Van Lente, PhD; Tom Greene, PhD; and Josef Coresh, M.D., PhD, MHS, for the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration)*

Table 2. The CKD-EPI Equation for Estimating GFR on the Natural Scale*

Race and Sex	Serum Creatinine Level, μmol/L (mg/dL)	Equation
Black		
Female	≤62 (≤0.7)	$GFR = 166 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 166 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 163 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 163 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$
White or other		
Female	≤62 (≤0.7)	$GFR = 144 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 144 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 141 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 141 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; GFR = glomerular filtration rate.

Ann Intern Med 2009;150:604-612

CKD-EPI, MDRD and CG_{IBW}

Table 4. Mean Difference in Cockcroft-Gault, CKD-EPI, and MDRD Equations[a,7]

Characteristic	Cockcroft-Gault GFR (mL/min), Mean ± SD	CKD-EPI GFR (mL/min), Mean ± SD	MDRD (mL/min), Mean ± SD	p Value[b]
Overall (n = 409)	34.8 ± 12.0	39.9 ± 12.5	40.2 ± 12.2	<0.001
Female (n = 208)	30.3 ± 10.9	34.5 ± 10.6	34.9 ± 10.3	<0.001
Male (n = 201)	39.5 ± 11.3	45.5 ± 11.9	45.7 ± 11.5	<0.001
White (n = 331)	35.4 ± 12.0	39.8 ± 12.4	40.0 ± 12.0	<0.001
African American (n = 78)	32.3 ± 11.7	40.2 ± 13.2	40.8 ± 13.1	<0.001

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease.
[a]Based on demographics.
[b]Statistical significance existed when comparing Cockcroft-Gault with both the CKD-EPI and the MDRD equations; no significant differences were observed when comparing CKD-EPI and MDRD.

- Calculated values only, iGFR not measured

Wargo Ann Pharmacother 2010;44:439-46

CKD-EPI, MDRD and CG_{IBW}

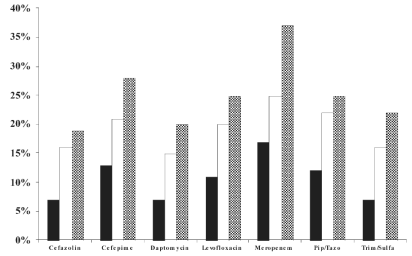


Figure 3. Antimicrobial dosage discordance rate when comparing the MDRD and CKD-EPI estimations of GFR with the manufacturer-recommended dosage adjustment using the Cockcroft-Gault estimation.[1] CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; Pip/Tazo = piperacillin/tazobactam; Trim/Sulfa = trimethoprim/sulfamethoxazole.
Black bars = MDRD vs CKD-EPI.
White bars = Cockcroft-Gault vs CKD-EPI.
Dotted bars = Cockcroft-Gault vs MDRD.

Wargo Ann Pharmacother 2010;44:439-46

CG or MDRD?

- Creatinine standardization has affected calculation of CrCl
- MDRD more accurately measures iGFR
- CG_{IBW} may not be as accurate as pharmacists assume
- MDRD is more difficult to use
- Discordance inevitable unless standards change