GFR Estimation in Children: Questions and Answers (and Questions)

Jeffrey J. Fadrowski and Susan L. Furth†*

Clin J Am Soc Nephrol 6: 1810–1812, 2011. doi: 10.2215/CJN.05900611

Accurate assessment of kidney function in children is essential from a clinical, research, and public health standpoint; however, in comparison with adults, this has received less attention, perhaps in part because of the lower burden of chronic kidney disease (CKD) in the pediatric population (1,2). Pediatricians must be experts in assessing the appropriateness of a clinical measure on the basis of characteristics such as the age, size, and/or gender of a child, and markers of kidney function are no exception. Serum creatinine, the most commonly used marker of kidney function in children, is proportional to muscle mass and varies greatly in children on the basis of age, gender, and race (3). A serum creatinine level of 1.0 mg/dl in a 17-year-old boy would be considered normal; this same creatinine level in a 4-year-old would represent advanced CKD. Given the challenges that serum creatinine presents to clinicians in distinguishing normal from abnormal and to researchers in assessing and comparing kidney function among children of all ages and sizes, the utility of accurate GFR estimation is obvious.

In this issue, Chavers *et al.* (4) report reference values for serum creatinine and cystatin C, another marker of kidney function, for healthy adolescents who were aged 12 to 17 years and participated in the National Health and Nutrition Examination Survey (NHANES) 1999–2008. As expected, serum creatinine and cystatin C varied on the basis of age, gender, and race. This study also compares the distribution of estimated GFR (eGFR) from two of the most commonly used estimating equations in children: The traditional "Schwartz" equation and the more recent complete "CKiD" equation derived from participants in the ongoing National Institutes of Health–sponsored Chronic Kidney Disease in Children (CKiD) Study (5–7). The distributions of eGFR from these equations vary greatly and prompt several questions for clinicians.

What Is the Normal Range of *Measured* Glomerular Filtration in Healthy Adolescents?

eGFR is intended to be a clinically efficient surrogate for measured GFR (mGFR). The renal clearance of inulin has traditionally been considered the gold standard for the evaluation of mGFR in children and adults. A few studies have measured GFR *via* inulin clearance in adolescents *without* kidney disease and inform the basis of "normal" in this age group. The mean ± SD GFRs in these studies ranged from 112 ± 13 to 117 ± 16 ml/min per 1.73 m^2 (3,8,9). Notably, the SDs are relatively large, likely due in part to the small sample sizes of the studies (n = 12 and 27 patients, respectively) and in part to biological variation in GFR. On the basis of these small studies, GFR would be expected to range between approximately 85 and 150 ml/min per 1.73 m^2 in 95% of healthy adolescents, with approximately 16% having GFRs <100 ml/min per 1.73 m^2 (1 SD below the mean).

Median eGFR, as examined by Chavers *et al.*, was 143 ml/min per 1.73 m^2 using the creatinine-based Schwartz equation and 96 ml/min per 1.73 m^2 using the creatinine and cystatin C–based complete CKiD equation. Examining NHANES data from 1999 through 2002 for adolescents 12 to 17 years of age, Fadrowski *et al.* (10) reported the percentile distribution of eGFR determined by the Schwartz, creatinine-based "bedside CKiD," and complete CKiD equations. The medians (5th, 95th percentiles) were 140 (107, 193), 97 (71, 132), and 97 (80, 121) ml/min per 1.73 m^2, respectively. Two aspects of these studies are noteworthy: (*1*) eGFR distributions between the Schwartz equation and the CKiD equations are strikingly different, and (*2*) the median and overall distribution of eGFR by any equation significantly differs from mGFR in similarly aged healthy teens.

What Are the Potential Sources of the Variation between the Schwartz and CKiD Equations, and How Well Do They Estimate GFR in the "General Population"?

The Schwartz and bedside CKiD equations, both of which account for the relationship between creatinine production and muscle mass by using height as a surrogate, are clinically easy to use because the only measures required are height (meters) and serum creatinine. Changes in creatinine laboratory assays over time have affected the accuracy of the Schwartz equation. Many laboratories now determine creatinine levels using a more sensitive and specific enzymatic assay, the assay used to derive the CKiD equations (11,12). Compared with the Jaffé (alkaline picrate) method used to derive the Schwartz equation, the enzymatic method results in lower creatinine values

*Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland; †Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Correspondence: Dr. Jeffrey J. Fadrowski, Department of Pediatrics, Johns Hopkins University School of Medicine, David M. Rubenstein Child Health Building, Room 3055, 200 N. Wolfe Street, Baltimore, MD 21287. Phone: 410-955-2467; Fax: 410-614-3680; E-mail: jfadrow1@jhmi.edu

(13). The lower constant in the bedside CKiD equation, 41.3, compared with the constants in the Schwartz equation, 55 and 70 for female and male adolescents, respectively, reflects this change. Thus, if the traditional Schwartz equation is used with enzymatic creatinine values, then the Schwartz equation would be expected to overestimate GFR. The median eGFR reported by Chavers *et al.* using the Schwartz equation of 143 ml/min per 1.73 m^2 supports the likelihood of overestimation.

The CKiD equations benefited from being derived with current enzymatic creatinine methodology, a precise measurement of GFR (plasma disappearance of iohexol), and a relatively large pediatric cohort (14). When compared with previously published estimating equations in children, the complete CKiD equation performed favorably (7). Because the CKiD equations were derived from children with CKD with a median mGFR of 41 ml/min per 1.73 m^2, there has been interest in examining their performance in children with higher GFR, especially given evidence that equations for adults underestimate GFR in those with mildly decreased or normal kidney function (15–17). The studies by Chavers *et al.* and Fadrowski *et al.* of adolescents in NHANES are limited by the lack of mGFR, but given the extremely low prevalence of CKD in adolescents, it is a safe assumption that the vast majority of the cohort has normal kidney function. However, the 25th percentile for eGFR among adolescents in NHANES 1999–2002 was 84 and 90 ml/min per 1.73 m^2 for the bedside CKiD and complete CKiD equations, respectively. Thus, 25% of adolescents in the general population would be classified as having an eGFR consistent with Kidney Disease Outcomes Quality Initiative (KDOQI) stage 2 or higher kidney disease (eGFR $<$90 ml/min per 1.73 m^2), which is unlikely and suggests that these equations may underestimate GFR at higher levels of kidney function (1).

Studies comparing eGFR using the bedside CKiD equation with mGFR were recently published. Staples *et al.* (18) compared eGFR (enzymatic creatinine) with GFR measured *via* iothalamate clearance. Among 738 participants who were aged 1 to 16 years and had CKD, kidney transplant, or solid tumor, the mean ± SD mGFR was 111 ± 29 ml/min per 1.73 m^2, the mean bias (eGFR − mGFR) was −5.8 ml/min per 1.73 m^2, and 83% and 34% of eGFR values fell within 30% and 10%, respectively, of mGFR. When the analysis was limited to the 573 children with mGFR $>$90 ml/min per 1.73 m^2, the mean bias was −9.1 ml/min per 1.73 m^2, and 30% and 10% accuracy was similar. The degree of underestimation of eGFR increased in older age groups. Pottel *et al.* (19) also compared the bedside CKiD equation using creatinine determined by either an enzymatic (age $<$5 years) or modified Jaffé method to mGFR determined by ^{51}Cr-EDTA. Among 182 children who were aged 1 to 8 years and had CKD, the mean mGFR was 88 ml/min per 1.73 m^2, the mean bias was −15.4 ml/min per 1.73 m^2, and 54% of eGFR values were within 30% of mGFR. When limited to mGFR ≥90 ml/min per 1.73 m^2, 47% of eGFR values were within 30% of mGFR. Finally, Qayed *et al.* (20) compared the bedside CKiD equation (enzymatic creatinine) with mGFR (DTPA-Tc^{99m}) in children undergoing hematopoietic stem cell transplants. Among 107 children with a mean age of 9 ± 6 years, the mean mGFR was 107 ± 28 ml/min per 1.73 m^2, the mean eGFR was 96 ± 26 ml/min per 1.73 m^2, and 77% of estimates were within 30% of mGFR. Using a cutoff of 90 ml/min per 1.73 m^2 to classify normal or reduced kidney function, the bedside CKiD equation misclassified 40% of participants and most commonly underestimated mGFR.

Which Pediatric eGFR Equation Should Be Used for Children without Known Kidney Disease, and Is There a Cutoff or Range for "Normal"?

As observed with the Schwartz equation, the accuracy of an estimating equation decreases if the laboratory assay used to determine the creatinine level does not match that originally used to derive the equation. As more laboratories switch to enzymatic creatinine assays, the bedside CKiD equation, derived using the same method, is a suitable replacement for the Schwartz equation. CKiD investigators have demonstrated that the CKiD equations perform favorably in children with CKD and are useful to track CKD progression in the growing child and guide clinical care (7). In children with mildly decreased or normal kidney function and in older adolescents with normal and abnormal kidney function, these equations need further validation to inform clinical use. A GFR cutoff of ≥90 ml/min per 1.73 m^2, driven by KDOQI CKD staging and guidelines, has commonly been used to define "normal" kidney function, and this is supported by the range of mGFRs observed in healthy teenagers (1). However, examining NHANES data, the distribution of eGFR using the CKiD equations is shifted toward lower GFR in teenagers *without* evidence of kidney disease. This may partly be due to underestimation of GFR by the CKiD equations in children with higher levels of kidney function as the few studies comparing eGFR with mGFR have demonstrated to varying degrees. Thus, it is not yet possible to define a "normal" eGFR cutoff using the CKiD equations, but it is likely $<$90 ml/min per 1.73 m^2. Future validation and possibly modification of these equations in children with higher levels of kidney function will allow for better characterization of the normal range, but until that time, the published distributions of creatinine and eGFR and the broader clinical context can help clinicians identify those at risk for loss of kidney function.

Disclosures

None.

References

1. Hogg RJ, Furth S, Lemley KV, Portman R, Schwartz GJ, Coresh J, Balk E, Lau J, Levin A, Kausz AT, Eknoyan G, Levey AS: National Kidney Foundation's Kidney Disease Outcomes Quality Initiative clinical practice guidelines for chronic kidney disease in children and adolescents: Evaluation, classification, and stratification. *Pediatrics* 111: 1416–1421, 2003
2. US Renal Data System: Renal function measures in the adolescent NHANES population. In: *USRDS 2009 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*, Vol 1, Bethesda, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2009, pp 49–58
3. Schwartz GJ, Work DF: Measurement and estimation of GFR in children and adolescents. *Clin J Am Soc Nephrol* 4: 1832–1843, 2009
4. Chavers BM, Rheault MN, Foley RN: Kidney function refer-

ence values in US adolescents: National Health and Nutrition Examination Survey 1999–2008. *Clin J Am Soc Nephrol* 6: 1956–1962, 2011
5. Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A: A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. *Pediatrics* 58: 259–263, 1976
6. Schwartz GJ, Gauthier B: A simple estimate of glomerular filtration rate in adolescent boys. *J Pediatr* 106: 522–526, 1985
7. Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL: New equations to estimate GFR in children with CKD. *J Am Soc Nephrol* 20: 629–637, 2009
8. Gibb DM, Dalton NR, Barratt MT: Measurement of glomerular filtration rate in children with insulin-dependent diabetes mellitus. *Clin Chim Acta* 182: 131–139, 1989
9. Brodehl J, Gellissen K, Weber HP: Postnatal development of tubular phosphate reabsorption. *Clin Nephrol* 17: 163–171, 1982
10. Fadrowski JJ, Neu AM, Schwartz GJ, Furth SL: Pediatric GFR estimating equations applied to adolescents in the general population. *Clin J Am Soc Nephrol* 6: 1427–1435, 2011
11. Myers GL, Miller WG, Coresh J, Fleming J, Greenberg N, Greene T, Hostetter T, Levey AS, Panteghini M, Welch M, Eckfeldt JH: Recommendations for improving serum creatinine measurement: A report from the Laboratory Working Group of the National Kidney Disease Education Program. *Clin Chem* 52: 5–18, 2006
12. Schwartz GJ, Kwong T, Erway B, Warady B, Sokoll L, Hellerstein S, Dharnidharka V, Furth S, Munoz A: Validation of creatinine assays utilizing HPLC and IDMS traceable standards in sera of children. *Pediatr Nephrol* 24: 113–119, 2009
13. Srivastava T, Alon US, Althahabi R, Garg U: Impact of standardization of creatinine methodology on the assessment of glomerular filtration rate in children. *Pediatr Res* 65: 113–116, 2009
14. Schwartz GJ, Abraham AG, Furth SL, Warady BA, Munoz A: Optimizing iohexol plasma disappearance curves to measure the glomerular filtration rate in children with chronic kidney disease. *Kidney Int* 77: 65–71, 2010
15. Poggio ED, Wang X, Greene T, Van Lente F, Hall PM: Performance of the modification of diet in renal disease and Cockcroft-Gault equations in the estimation of GFR in health and in chronic kidney disease. *J Am Soc Nephrol* 16: 459–466, 2005
16. Rule AD, Larson TS, Bergstralh EJ, Slezak JM, Jacobsen SJ, Cosio FG: Using serum creatinine to estimate glomerular filtration rate: Accuracy in good health and in chronic kidney disease. *Ann Intern Med* 141: 929–937, 2004
17. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J: A new equation to estimate glomerular filtration rate. *Ann Intern Med* 150: 604–612, 2009
18. Staples A, LeBlond R, Watkins S, Wong C, Brandt J: Validation of the revised Schwartz estimating equation in a predominantly non-CKD population. *Pediatr Nephrol* 25: 2321–2326, 2010
19. Pottel H, Mottaghy FM, Zaman Z, Martens F: On the relationship between glomerular filtration rate and serum creatinine in children. *Pediatr Nephrol* 25: 927–934, 2010
20. Qayed M, Thompson A, Applegate K, Haight A, Rogatko A, Chiang KY, Horan J: Is the updated Schwartz formula appropriate for assessing renal function prior to hematopoietic stem cell transplantation? *Pediatr Blood Cancer* 55: 199–201, 2010

See related article, "Kidney Function Reference Values in US Adolescents: National Health and Nutrition Examination Survey 1999–2008," on pages 1956–1962.