Schwartz et al. (1) have reported a new formula for estimating the glomerular filtration rate (GFR) in children with chronic kidney disease (CKD). This is an excellent analysis based on a carefully described, prospectively recruited cohort of children with various types of kidney diseases that have compromised function. The analysis is precise and the results seem to provide a more accurate, noninvasive method of estimating the GFR of children.

The obvious first question raised about a study is: Why is it important? In this case, aren’t there existing methods of estimating GFR in these children, and wouldn’t a measured GFR be more accurate and reliable? As indicated in the article, there are 2 important reasons to have an improved method for readily estimating GFR: Knowledge of the GFR would be valuable in adjusting the doses of nephrotoxic medications in children with CKD, and the method is a useful tool in plotting the decline of renal function if it is coupled with intermittent direct measures. As important as these reasons are, they may understate the importance and significance of this work.

First, some background. The nephrology community, including the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), professional associations such as the American Society of Nephrology and the American Society of Pediatric Nephrology, and patient advocacy and support organizations such as the National Kidney Foundation, have developed educational programs to alert both the professional and lay populations to the prevalence of CKD. One organization, the National Kidney Disease Education Program (http://www.nkdep.nih.gov/), was developed by NIDDK. Collectively, these organizations estimate that >15 million adult Americans suffer from CKD (http://kidney.niddk.nih.gov/kudiseases/pubs/kustats/index.htm). CKD is often asymptomatic until it has reached advanced stages, at which point it is both irreversible and untreatable. Thus, the development of methods for early detection of CKD is thought to be paramount in the attempts to interrupt its progression. In general, recommendations for early detection include 3 simple clinical measurements: blood pressure, urine protein, and serum creatinine to allow estimation of the GFR.

Creatinine is produced at a relatively constant rate and excreted by glomerular filtration, with limited renal tubular reabsorption in healthy individuals. The amount produced each day is generally related to the muscle mass of the individual and varies between 10 mg/kg/day in infants up to 25 mg/kg/day in muscular adult men. Because the production rate is constant and the removal rate is principally related to kidney function, the steady-state serum concentration of creatinine is inversely proportional to the GFR. For years, clinicians used the serum creatinine itself as a measure of kidney function. However, because the concentration is influenced by both the production rate and the excretion rate, the nephrology community concluded that serum creatinine should be interpreted in light of the expected rate of production of creatinine. Thus, formulas have been developed to estimate the GFR based on the serum creatinine and certain factors associated with muscle mass, such as sex and height. Two of the common formulas used for adults are the Cockcroft–Gault and the Modification of Diet in Renal Disease (MDRD) formulas, but these are not appropriate for use in children (2). The most widely used formula for children has been the Schwartz equation (3). It has been successful because it relates GFR to (patient’s height)/(serum creatinine) rather than to 1/(serum creatinine). Physicians need to recognize that the formula requires updating when analytically specific methods of measuring serum creatinine, such as enzymatic assays, are used in their institutions (4).

Many in the community have recommended that when the results of screening laboratory tests are reported, both the serum creatinine and the estimated GFR based on one of these formulas be listed. In some cases, a serum creatinine that is only slightly increased, or even within the typical reference interval, might be correlated with a significantly reduced GFR, especially if the patient is small or elderly. Use of the estimates of

References

1 Harvard Medical School, Children’s Hospital Boston, Boston, MA.
* Address correspondence to the author at: Children’s Hospital Boston, 300 Longwood Ave., Boston, MA 02115. Fax 617-730-0569; e-mail william.harmon @childrens.harvard.edu.

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Nonstandard abbreviations: GFR, glomerular filtration rate; CKD, chronic kidney disease; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; MDRD, Modification of Diet in Renal Disease; ACE, angiotensin-converting enzyme; BUN, blood urea nitrogen.
GFR is more likely to detect earlier stages of CKD than use of serum creatinine alone. With early detection, appropriate treatment options, such as weight loss, exercise, or blood pressure control, especially with angiotensin-converting enzyme (ACE) inhibitors, might be initiated early. There is evidence that early introduction of these measures will slow or even halt progression of renal dysfunction.

Children have age-dependent reference intervals for many laboratory tests, including serum creatinine. Thus, assessing renal function based on a single laboratory value with a single cutpoint is even more difficult for them. The new approach for estimating GFR (1) is a relatively simple method, based on measurements of creatinine, blood urea nitrogen (BUN), and cystatin, together with an accurate height measurement. The method seems to be more accurate than existing formulas. As the authors suggest, this method can certainly be used to adjust drug dosing and as a research tool. But it can also be used clinically to determine whether CKD in children is stable or progressing and whether interventions affect the rate. It can be used as a confirmatory screening tool for children with diminished renal function. It cannot yet be used as a general screening tool, since it has not yet been verified in a cohort of children with normal renal function. But we can expect that will be the next study.

A final word about the study cohort. About 8 years ago, NIDDK initiated an observational cohort study of adults with CKD to determine the rate of progression of renal insufficiency and to characterize the complications of CKD. At the time, NIDDK elected to develop a separate parallel pediatric cohort, the CKiD study, rather than include children in the larger study. That cohort, which was used for this study with initial recruitment starting in 2005, is now proving to be an extremely valuable resource for investigators of pediatric CKD. This model provides substantial guidance of how to undertake pediatric multicenter clinical trials, and we expect many more reports about CKD in children.

**References**