

NEPHROLOGY I

CONTROVERSIES IN ASSESSING KIDNEY FUNCTION

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Learning Objectives

1. Evaluate methods to estimate and measure creatinine clearance and glomerular filtration rate (GFR) in patients with chronic kidney disease (CKD).
2. Given a case scenario, justify the use of CKD staging according to Kidney Disease Outcomes Quality Initiative (KDOQI) criteria.
3. Assess the use of serum creatinine-based estimates of kidney function in various patient populations including CKD, pediatrics, and the elderly.
4. Judge the appropriateness of using serum cystatin C concentration as a quantitative index of kidney function.
5. Compare and contrast the clinical limitations, economics, and practicability of various methods to evaluate proteinuria.
6. Design an individualized drug dosage regimen based on kidney function.

Introduction

Chronic kidney disease (CKD) is an increasingly alarming health problem in the United States, with 2 million people estimated to require hemodialysis or kidney transplantation by 2030. In response to this widespread problem, the National Kidney Foundation developed new approaches for identifying and classifying individuals with CKD and their subsequent stratification into risk categories for loss of kidney function. According to this approach, CKD is defined as the persistent presence (at least 3 months) of kidney damage (e.g., proteinuria), irrespective of cause or current glomerular filtration rate (GFR), or the presence of a GFR less than or equal to 60 mL/minute/1.73 m². Stratification of CKD into disease stage severity on the basis of GFR as proposed in 2000 is shown in Table 1-1. Individuals with stage 3 disease (i.e., having a GFR between 31 and 59 mL/minute/1.73 m²) are those most likely to begin

to exhibit the classic CKD systemic complications, such as anemia, hypertension, and calcium/phosphate imbalance.

After detection of CKD subsequent monitoring of kidney function is critical for evaluating disease progression, the impact of pharmacotherapy interventions, and the need for drug dose individualization (Figure 1-1). The variety of qualitative and quantitative methods for clinicians to assess kidney function in patients with CKD have demonstrated marked variability in their accuracy and use. This chapter addresses recent controversies associated with quantifying kidney function that affect the delivery of pharmaceutical care to patients with CKD.

Evaluation of Glomerular Filtration Rate

The GFR is the most comprehensive index of overall kidney function. Direct measurement of GFR using exogenous filtration markers such as iothalamate or inulin is the preferred but most costly means of quantification. Many approaches for estimating GFR are available; semi-quantitative methods such as the measurement of serum creatinine and cystatin C concentrations are of limited value, and their use is not recommended. The measurement or estimation of creatinine clearance has been extensively used even though creatinine is a crude index of kidney function. The method of choice for evaluating kidney function in a particular clinical scenario depends on a variety of patient, laboratory, and economic factors that are discussed below.

Serum Cystatin C

Serum cystatin C has been proposed as an endogenous marker of GFR, and its use has been extensively promoted in Canada and several European countries. This 132 amino acid (13.3 kDa) cysteine protease inhibitor appears to be constantly produced by nucleated cells under steady-state conditions. Recent studies have shown a strong association between serum cystatin C concentrations and cardiovascular disease, and a link between kidney disease and serum cystatin C concentrations has been demonstrated. Like creatinine, this low-molecular weight compound is freely filtered at the glomerulus, and its concentration in plasma is inversely correlated with GFR. However, unlike creatinine,

Abbreviations in this Chapter

BSA	Body surface area
CKD	Chronic kidney disease
eGFR	Estimated glomerular filtration rate
GFR	Glomerular filtration rate
KDOQI	Kidney Disease Outcomes Quality Initiative
MDRD	Modification of Diet in Renal Disease
MDRD4	4-variable Modification of Diet in Renal Disease
MDRD6	6-variable Modification of Diet in Renal Disease
SCr	Serum creatinine

it undergoes nearly complete reabsorption and catabolism within the proximal tubule, and thus, renal clearance values for cystatin C have not been reported. Implications of these complex tubular handling processes on the value of serum cystatin C concentration as a surrogate for GFR measurement are unknown. However, it is entirely possible that the presence of tubular damage can result in increased urinary excretion of cystatin C. This property is not associated with other traditional GFR markers such as iohexol, inulin, and iothalamate. Because cystatin C is not usually detected in urine, it is not possible to accurately identify the contributions of glomerular filtration and tubular reabsorption to total renal clearance of cystatin C. Equations to estimate GFR using cystatin C have been reported in some adult and pediatric populations, but they do not provide significant improvements in accuracy or precision compared with traditional approaches such as the Cockcroft-Gault, Modification of Diet in Renal Disease (MDRD), or Schwartz equations (see further discussion of these approaches in sections below). Furthermore, serum cystatin C concentrations are known to be influenced by age, gender, body mass, cigarette smoking, nutritional status, thyroid disease, and immunosuppressant drug therapy in recipients of kidney transplants. The impact of these non-renal factors on the “normal” reference range for serum Cystatin C, which has been reported based on age (less than age 50: 0.53–0.92 mg/L; 50 years of age or older: 0.58–1.02 mg/L) and sex (women: 0.62–1.15 mg/L; men: 0.51–1.25 mg/L), has not been fully evaluated. The Cystatin C test is not routinely available in clinical laboratories, but can be measured using a BNII nephelometer (Dade Behring Inc., Deerfield, IL) with a particle-enhanced immunonephelometric assay (N Latex Cystatin C, Dade Behring Inc.).

Recent claims that serum cystatin C concentration is more sensitive than serum creatinine concentration for detecting small changes in kidney function with minimal influence by non-renal factors are questionable. For example, it has been reported that serum creatinine and cystatin C concentrations begin to increase at GFR values of 75 mL/minute/1.73 m² and 88 mL/minute/1.73 m²,

respectively, suggesting that cystatin C is more sensitive at detecting reductions in kidney function than serum creatinine. However, cystatin C has been reported to have greater intra-individual variability than serum creatinine in healthy individuals, which may limit its use in longitudinal evaluations of kidney function. Furthermore, the lack of correlation between serum cystatin C and kidney function in patients with malignant disease, in recipients of a kidney transplant, and in those younger than age 18 is distressing.

In summary, the introduction of serum cystatin C concentration as a complementary or alternative renal biomarker to serum creatinine concentration has raised numerous questions and resolved few. Although cystatin C is not a quantitative index of GFR, it may provide useful information for comprehensive evaluations of health and cardiovascular status, including detection of acute and chronic changes in kidney function. However, further evaluations of intra-subject and inter-subject variability, mechanisms of renal handling, and identification of non-renal factors that contribute to serum cystatin C concentrations are warranted.

Creatinine Clearance

The most practical approach to assessing kidney function in the majority of clinical settings is estimation of creatinine clearance. Even though it is well known that serum creatinine concentrations are influenced by many non-renal factors such as diet (e.g., vegetarian diet and creatine supplements), body mass (e.g., amputation, malnutrition, and emaciation), and drug therapies (e.g., cimetidine and trimethoprim), the fact that it is an endogenous compound has spawned the generation of several estimation equations. The Cockcroft-Gault equation provides a quantitative estimate of creatinine clearance in patients with CKD. The Cockcroft-Gault equation was derived from a predominantly male Canadian military veteran population who had a single measured 24-hour creatinine clearance. Equations such as Cockcroft-Gault depend on serum creatinine concentration and its associated measurement limitations, plus tubular secretion of creatinine, which results in overestimation of GFR by up to 20% in individuals with Stages 2–4 CKD. Despite these limitations, the Cockcroft-Gault equation remains the most appropriate method to determine drug dose individualization based on kidney function in the clinical setting. Concomitant administration of cimetidine (800 mg 3 times/day for 1 day) has dramatically improved the accuracy of creatinine clearance in estimating true GFR in adult CKD, kidney transplantation, and pediatric populations. Measured creatinine clearance requires serum and urine creatinine concentration determinations and the collection of a timed urine collection. This approach is less reliable than the Cockcroft-Gault equation, especially in ambulatory clinical settings where observation of timed urine collections is not possible. Thus, the measurement of creatinine clearance is not recommended for routine evaluation of kidney function. However, this method is acceptable for individuals with extremes in diet (e.g., vegetarian or high-protein diet) and body size (e.g., amputees or emaciated) as well as those with liver disease where assumptions associated with the creatinine clearance estimation formulas are not valid. In

Table 1-1. KDOQI Criteria for CKD Staging and Estimated United States Prevalence

CKD Stage	Description	Estimated GFR (mL/minute/1.73 m ²)	Prevalence in United States in millions (%)
1	Kidney damage with normal or ↑ GFR	≥ 90	5.9 (3.3)
2	Kidney damage with mild ↓ GFR	60–89	5.3 (3.0)
3	Moderate ↓ GFR	30–59	7.6 (4.3)
4	Severe ↓ GFR	15–29	0.4 (0.2)
5	Kidney failure (ESRD)	< 15	0.3 (0.1)

CKD = chronic kidney disease; ESRD = end-stage renal disease; GFR = glomerular filtration rate; KDOQI = Kidney Disease Outcomes Quality Initiative; ↑ = increased; ↓ = decreased.

these cases, use of an exogenous filtration marker for accurate measurement of GFR, such as iohalamate or iohexol, should be used if available.

Estimated GFR Using MDRD Equations

The traditional approach of estimating creatinine clearance and using it as a continuous variable of kidney function is now being replaced by estimation of GFR as a categorical variable for CKD staging. To overcome the limitations of creatinine clearance-based estimations, several new methods that estimate GFR were proposed in the past 8 years. For example, the original 6-variable equation (MDRD6, Table 1-2) was derived from the MDRD study population of 1628 patients with non-diabetic CKD (mean GFR 40 mL/minute/1.73 m²) who concomitantly had an iohalamate-GFR measurement. This equation was developed using patient variables such as age, serum

creatinine, blood urea nitrogen, albumin, race, and gender. Its performance (bias and precision) for predicting GFR was superior to the Cockcroft-Gault equation. An abbreviated 4-variable version of the MDRD (MDRD4) equation was introduced in 2000, and has demonstrated excellent precision and accuracy in the prediction of GFR. This version of the MDRD equation, hereby referred to as the “eGFR,” does not include albumin and blood urea nitrogen resulting in wider application in most outpatient clinical settings and is endorsed by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) and the National Institutes of Health National Kidney Disease Education Program for use in the identifying and stratifying individuals with CKD.

The validity of the eGFR equation for clinical use in all patient settings and use as a guide for drug dosage adjustment are controversial. This equation has not been

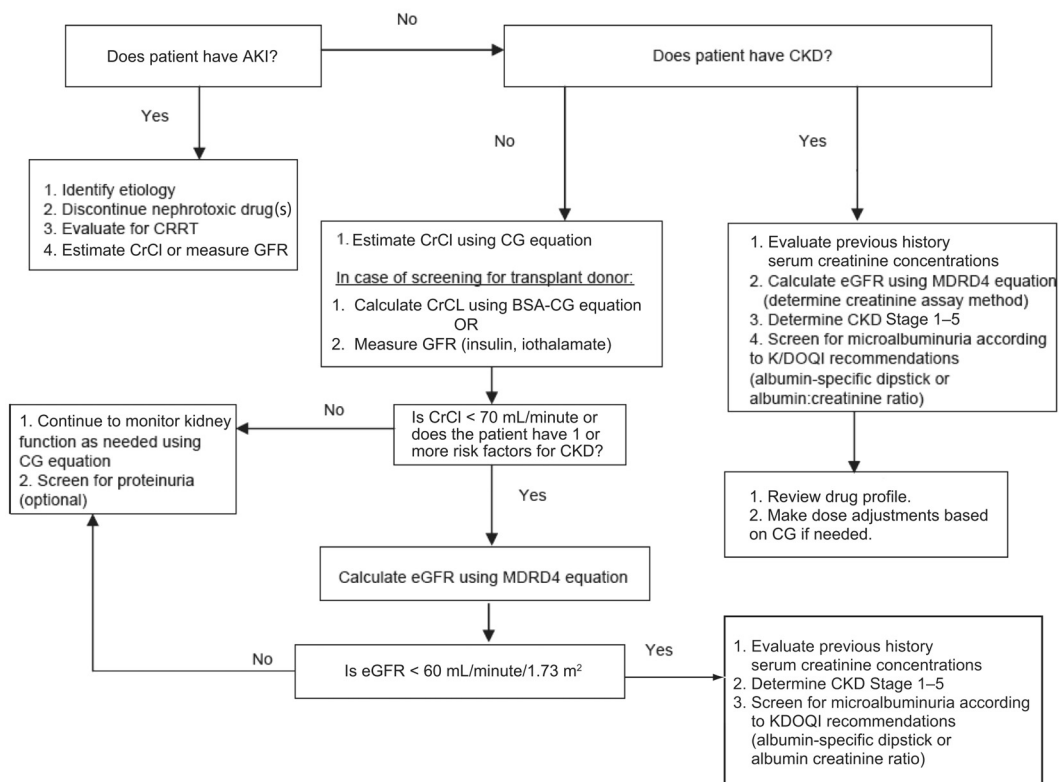


Figure 1-1. Algorithm for assessing kidney function.

AKI = acute kidney injury; BSA = body surface area; CG = Cockcroft-Gault equation; CKD = chronic kidney disease; CrCl = creatinine clearance; CRRT = continuous renal replacement therapy; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; KDOQI = Kidney Disease Outcomes Quality Initiative; MDRD4 = 4-variable Modification of Diet in Renal Disease.

validated in children, women who are pregnant, the elderly (age older than 70 years), racial or ethnic subgroups other than Caucasians and African Americans, patients with diabetes, and those with “normal” kidney function. The eGFR equation has yielded an underestimate of true GFR by up to 29% in healthy individuals, kidney donors, and patients with type 1 diabetes mellitus with normal serum creatinine concentrations. These discrepancies are likely due to the weaker association between serum creatinine and GFR among healthy persons compared with that of patients with CKD. Thus, an increasing serum creatinine concentration in patients with CKD is most likely due to a reduction in GFR, whereas variations in serum creatinine concentrations in healthy individuals are more likely due to non-renal causes such as increased muscle mass or protein intake. In individuals with normal kidney function, a body surface area (BSA) adjusted Cockcroft-Gault (calculated by multiplying the Cockcroft-Gault result by 1.73/the patient’s BSA) increases the accuracy and reduces the bias of the Cockcroft-Gault equation as an estimate of GFR. It is the preferred approach to estimating kidney function in those with serum creatinine concentrations in the “normal” range.

Because the eGFR equation provides less precise estimates of GFR in patients with normal kidney function and Stage 1 and 2 CKD, it is recommended that reporting of eGFR results be reserved for patients with an eGFR less than 60 mL/minute/1.73 m². For example, the eGFR for a 64-year-old African-American woman with a history of CKD and a serum creatinine concentration of 1.9 mg/dL would be reported as 33.7 mL/minute/1.73 m² in the

medical chart. However, because the eGFR concentration for a 53-year-old Caucasian man with no history of CKD and a serum creatinine value of 1.0 mg/dL is 80.0 mL/minute/1.73 m², the eGFR should be reported as “greater than 60 mL/minute/1.73 m².” This approach is important for evaluating potential kidney donors, where underestimation of true GFR using the eGFR equation may lead to a false clinical decision regarding the suitability of the donor. Here, creatinine clearance using the Cockcroft-Gault equation (BSA adjusted or unadjusted) should be reported, or a direct measure of GFR using iothalamate or iothexol clearance should be performed if available.

Other controversial issues associated with the eGFR equation include automated reporting and serum creatinine assay standardization by clinical laboratories, its use in the elderly and acutely ill, and application to drug dosing in patients with decreased kidney function. Each area is discussed in further detail below.

Standardization of Creatinine Assay in Clinical Laboratories

There has been increasing attention on differences in serum creatinine assays and variability between clinical laboratories, and to the resultant systematic bias associated with creatinine clearance estimation equations. The majority of clinical laboratories in the United States use the kinetic alkaline picrate method for serum creatinine measurement, which also detects non-creatinine chromogens. In 2003, a survey of 5624 clinical laboratories reported that the mean bias for a serum creatinine sample containing 0.902 mg/dL,

Table 1-2. Equations for Estimating Glomerular Filtration Rate and Creatinine Clearance^a

PREFERRED:

Equation 1: Cockcroft-Gault formula

$$\text{CrCl} = [(140 - \text{Age}) \times \text{Wt}] / (72 \times \text{SCr}) \times 0.85 \text{ if female}$$

Equation 2: BSA-adjusted Cockcroft-Gault formula

$$\text{CrCl} = [\text{Cockcroft-Gault formula}] \times 1.73 \text{ m}^2 / \text{BSA}$$

Equation 3: eGFR (abbreviated 4-variable MDRD)

$$\text{GFR} = 186 \times [\text{SCr}]^{-1.154} \times [\text{Age}]^{-0.203} \times [0.742 \text{ if female}] \times [1.210 \text{ if African American}]$$

$$\text{GFR}^b = 175 \times [\text{SCr}]^{-1.154} \times [\text{Age}]^{-0.203} \times [0.742 \text{ if female}] \times [1.210 \text{ if African American}]$$

NOT RECOMMENDED:

Equation 4: SCr

$$\text{GFR} = 0.69 \times [100 / \text{SCr}]$$

Equation 5: Measured CrCl

$$\text{GFR} = 0.81 \times [\text{CrCl}]$$

Equation 6: Average of CrCl and CL_{urea}

$$\text{GFR} = 1.11 \times [(\text{CrCl} + \text{CL}_{\text{urea}}) / 2]$$

Equation 7: CrCl, CL_{urea}, and demographic variables

$$\text{GFR} = 1.04 \times [\text{CrCl}]^{+0.751} \times [\text{CL}_{\text{urea}}]^{+0.226} \times [1.109 \text{ if African American}]$$

Equation 8: eGFR (6-variable with UUN)

$$\text{GFR} = 198 \times [\text{SCr}]^{-0.858} \times [\text{Age}]^{-0.167} \times [0.822 \text{ if female}] \times [1.178 \text{ if African American}] \times [\text{BUN}]^{-0.293} \times [\text{UUN}]^{+0.249}$$

Equation 9: eGFR (6-variable with albumin)

$$\text{GFR} = 170 \times [\text{SCr}]^{-0.999} \times [\text{Age}]^{-0.176} \times [0.762 \text{ if female}] \times [1.180 \text{ if African American}] \times [\text{BUN}]^{-0.170} \times [\text{Alb}]^{+0.318}$$

^aUnits are mL/minute /1.73 m² except for Equations 2, 3, 8, 9 (in mL/minute/1.73 m²).

^bIDMS-traceable MDRD Study equation.

Alb = albumin; BSA = body surface area; BUN = blood urea nitrogen; CrCl = creatinine clearance; CL_{urea} = urea clearance; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; IDMS = isotope dilution mass spectrometry; MDRD = Modification of Diet in Renal Disease; SCr = serum creatinine; UUN = urine urea nitrogen.

analyzed using the alkaline picrate method, ranged from 0.06 mg/dL to 0.31 mg/dL. According to the National Institutes of Health National Kidney Disease Education Program Working Group, assay errors are most significant at “lower creatinine values near the upper limit of the reference interval”, such as those values in the range of 1.2 mg/dL to 1.5 mg/dL.

In an effort to reduce interlaboratory bias in serum creatinine measurements, the National Kidney Disease Education Program recommends that clinical laboratories report serum creatinine concentrations using a “calibrated” assay, which is based on a sensitive isotope dilution mass spectrometry reference method. Widespread calibration of all clinical laboratories to a single reference research laboratory is a daunting task. The impact of using uncalibrated serum creatinine concentrations for eGFR has recently been evaluated. Errors in GFR estimates using uncalibrated serum creatinine concentrations were lowest in individuals with a GFR less than 60 mL/minute/1.73 m². For example, a GFR estimate of 30 mL/minute/1.73 m² would have an expected error range of 25 mL/minute/1.73 m² to 31 mL/minute/1.73 m² (-17% to +3%), which is not likely to be of clinical significance. However, an estimated GFR of 90 mL/minute/1.73 m² was associated with an error range of 62 mL/minute/1.73 m² to 100 mL/minute/1.73 m² (-31% to +11%), which is likely to be clinically significant. For clinical laboratories using a calibrated serum creatinine assay, the recently developed isotope dilution mass spectrometry-traceable MDRD Study equation should be used (see Table 1-2). The National Kidney Disease Education Program also recommends reporting serum creatinine concentrations in mg/dL to two decimal places (e.g., 0.93 mg/dL), and values in μ mol/L to the nearest whole number (e.g., 84 μ mol/L). This practice will likely reduce rounding errors that can further bias the eGFR value.

In summary, pharmacists should be aware of their laboratory’s use of calibrated serum creatinine assays, and understand the impact of assay methods on eGFR results. In the majority of clinical settings where serum creatinine assays are not calibrated, the National Kidney Foundation recommends that specific values for eGFR be reported only when the eGFR is less than 60 mL/minute/1.73 m². For higher eGFR values the recommended report language is “eGFR is greater than or equal to 60 mL/minute/1.73 m²,” with the use of Cockcroft-Gault estimates to monitor kidney function.

Elderly

Only about 30% of elderly individuals maintain normal kidney function, whereas most have experienced a reduction of at least 50% of GFR by the time they reach age 80. The high frequency of age-related kidney dysfunction provides a rationale for accurate estimation of kidney function in the elderly. Although the original Cockcroft-Gault study included few individuals older than age 65 and lacked validation against an accurate measure of GFR such as inulin or iothalamate clearance, it is widely accepted. However, a common misconception in the elderly is that low serum creatinine concentrations (i.e., less than 0.7 mg/dL) require correction (or rounding up) to 1.0 mg/dL, thereby lowering the Cockcroft-Gault equation estimate of

creatinine clearance. In the elderly, the competing influences of reduced muscle mass and reduced dietary protein intake (decreased production) and decreased GFR (decreased elimination) may result in an apparently normal serum creatinine concentration. Thus, interpretation of kidney function based on serum creatinine concentration alone should be avoided. Furthermore, the intentional “rounding up” of serum creatinine concentrations can lead to underestimation of creatinine clearance and underdosing of many drugs.

Recent studies examining the reliability of eGFR in elderly patients have reported mixed results. In hospitalized geriatric patients over age 80 with measured 24-hour creatinine clearances, fewer than 20% of the values from the eGFR and Cockcroft-Gault equations fell within the limits of agreement (-10% and +10%). A recent study evaluated the precision and bias of the eGFR and Cockcroft-Gault equations compared with chromium-labeled ethylenediaminetetraacetic acid GFR in 52 outpatients who were elderly (mean age 80 years, range 69–92 years). Here, the Cockcroft-Gault formula was more precise than eGFR with a mean bias of -10.4% and a lower frequency of misclassification of CKD. The eGFR introduced a positive bias (8%) suggesting that this approach may slightly overestimate GFR in this elderly population. The eGFR method should be avoided in elderly individuals until further studies validate its use when compared with accurate measures of GFR. At this time, the Cockcroft-Gault equation or a timed 24-hour creatinine clearance is preferred.

Patients who are Critically Ill and Hospitalized

Estimation of kidney function in patients who are critically ill and hospitalized presents many challenges. The underlying presence of CKD, identification of any acute injury or insult to the kidney, and the use of continuous renal replacement therapy complicates the estimation of kidney function. Other factors to consider in the critically ill population include the likely presence of non-steady-state serum creatinine concentrations, comorbid conditions that contribute to malnutrition, and the use of drugs that are either associated with the development of acute kidney injury or known to interfere with the creatinine assay.

Few studies have evaluated GFR estimation equations in patients who are critically ill and hospitalized with kidney dysfunction. The MDRD₆ equation had less bias and better accuracy than the MDRD₄ or BSA-adjusted Cockcroft-Gault equations when compared with measured GFR. These findings may be explained in part by the incorporation of additional variables such as albumin and blood urea nitrogen, where hypoalbuminemia and azotemia may provide better indications of overall disease severity in those patients who are hypercatabolic. Further evaluation of eGFR methods in this population is clearly needed.

Drug Dosing in Kidney Disease

Drugs that are excreted by the kidneys often require dose adjustments to optimize their use in patients with kidney disease. The pharmacist plays a critical role in this process by incorporating basic pharmacokinetic principles and an estimate of kidney function to determine the optimal dose

and interval for individual patients. The recent introduction of the MDRD equation has created controversy regarding the choice of equations for estimating kidney function (e.g., Cockcroft-Gault vs. eGFR) for drug dose individualization. There are numerous approaches to estimate kidney function, and the approach to be chosen for an individual patient/drug scenario should be based on the Food and Drug Administration-approved prescribing information (i.e., package insert) and/or the primary clinical pharmacokinetic literature. Most prescribing information includes dose recommendations based on the relationship between Cockcroft-Gault-estimated creatinine clearance (mL/minute) and the drug's pharmacokinetic characteristics. However, some recommendations are based on creatinine clearance with BSA correction (mL/minute/1.73 m²), and a very few are based on measured GFR (mL/minute/1.73 m²). To date, no Food and Drug Administration prescribing information includes dose recommendations based on eGFR.

The substitution of eGFR in place of Cockcroft-Gault may lead to suboptimal dosing, especially in patients with Stage 2 CKD as GFR declines near 60 mL/minute/1.73 m². For example, prescribing information for the nucleoside analog didanosine includes a dose adjustment recommendation based on kidney function using creatinine clearance (in mL/minute). For patients with reduced creatinine clearance values in the range of 30 mL/minute to 59 mL/minute, a 50% dose reduction is recommended. However, in a patient with a Cockcroft-Gault estimated creatinine clearance of 63 mL/minute, but an eGFR result of 53 mL/minute/1.73 m², a less than optimal dose adjustment decision may be made if one were using this categorical approach for drug dosing.

In rare cases, a product label may provide dosing recommendations based on creatinine clearance values reported in mL/minute/1.73 m², such as that reported for topiramate. The BSA-corrected value for creatinine clearance is calculated for an individual as the product of the Cockcroft-Gault estimate (mL/minute) and the ratio (1.73/patient's BSA), where BSA = (weight in kg)^{0.425} x (height in cm)^{0.725} x 0.007184. Use of the eGFR in this case should be avoided because the lower GFR estimate compared with creatinine clearance estimate will likely result in suboptimal dosing.

Update in Pediatrics

Kidney disease in children (younger than age 18) is relatively uncommon, with this population accounting for less than 1% of all patients with kidney failure treated by dialysis. Unlike adults, the major causes of kidney impairment in pediatric patients are obstructive uropathy and glomerular disease. Other disease-related complications specific to pediatric patients treated with dialysis include growth failure and cognitive impairment. Regardless of etiology, the primary index of kidney function is GFR, which is highly dependent on age, gender, and body size. Normal values for GFR increase dramatically over a short time period, ranging from 41 mL/minute/1.73 m² ± 15 mL/minute/1.73 m² at birth to 96 ± 22 mL/minute/1.73 m² at 8 weeks of life. The GFR at 2 years of age is similar to the adult normal GFR of 130–140 mL/minute/1.73 m².

Thus, the GFR ranges described in the KDOQI guidelines for CKD stratification are applicable to children age 2 and older.

Several methods for estimating kidney function in children (younger than age 12) have been used over the past 3 decades. The two most commonly used equations in research and clinical settings are the Schwartz formula and the Counahan-Barratt formula. Both approaches use two clinical variables: height and serum creatinine concentration. The Schwartz formula provides an estimate of creatinine clearance, whereas the Counahan-Barratt formula provides an estimate of GFR:

$$\text{Schwartz: creatinine clearance (mL/minute/1.73 m}^2\text{)} = \frac{[K * \text{Height in cm}]}{\text{serum creatinine (SCr)}}$$

Where K = 0.45 for infants (younger than 1 year),
K = 0.55 for children and adolescent girls and K = 0.7 for adolescent boys.

$$\text{Counahan-Barratt: GFR (mL/minute/1.73 m}^2\text{)} = \frac{[0.45 * \text{Height in cm}]}{\text{serum creatinine (SCr)}}$$

The primary differences between the two equations relate to the index of kidney function used to derive the equation (e.g., BSA-adjusted creatinine clearance vs. GFR) and the presence of a “K” constant (0.45 vs. 0.55 based on age and gender). A recent evaluation in 267 pediatric patients (average age 10 years) who had GFR measured by technetium-99m-DTPA showed that the Schwartz formula was more accurate than the Counahan-Barratt and MDRD4 equations (see Table 1-2), with 86% sensitivity and 97% specificity to detect a GFR value less than 60 mL/minute/1.73 m². The most recent KDOQI guidelines recommend use of either the Schwartz or Counahan-Barratt method to estimate GFR in children and adolescents younger than age 12. The MDRD equations, which were developed for use in adults with CKD, are not recommended for use in pediatric patients until further evaluations are conducted in this population.

Assessment of Proteinuria

The presence of urinary microalbuminuria (defined as albumin excretion of 30–300 mg/day) is a strong independent predictor of the presence of glomerular kidney disease and a high risk of progression to Stage 5 CKD. Reductions in urinary albumin excretion rates have been shown to provide cardiovascular benefit in patients with diabetes mellitus and hypertension. Therefore, quantification of urinary protein is an important aspect of identifying, characterizing, and monitoring the progression of CKD. Normal urinary protein excretion is less than 150 mg/day, with albumin (molecular weight 30 kDa) accounting for about 20% of total protein excretion (i.e. less than 30 mg/day). The presence of low-molecular weight globulins such as Tamm-Horsfall, immunoglobulin A, β₂-microglobulin, and enzymes typically indicate tubulointerstitial disease, which most likely occurs during the later stages of CKD (Stages 4–5). Thus, the term

proteinuria indicates total urinary protein excretion (i.e., albumin plus globulins and other proteins), whereas albuminuria refers specifically to urinary albumin.

A variety of methods can quantify urinary proteins in the clinical practice setting. Most methods that evaluate proteinuria involve non-specific visual dipstick tests. These semi-quantitative tests provide a range of categories, from negative (less than 10 mg/dL; less than 150 mg/day), trace (10–20 mg/dL; 150–300 mg/day), 1+ (30 mg/dL; 450 mg/day), 2+ (100 mg/dL; 1500 mg/day), 3+ (300 mg/dL; 4500 mg/day) to 4+ (>1000 mg/dL; greater than 15 g/day). Although assessment of total proteinuria is acceptable for screening purposes, it is currently recommended that all patients with known CKD and those with CKD risk factors (such as diabetes mellitus) should be tested for albuminuria using an albumin-specific dipstick test. Such semi-quantitative tests are relatively inexpensive (\$3 in the United States), easily conducted in a physician office or clinic, only require a small urine sample, provide rapid results (1 minute), and can detect low concentrations of urinary albumin. For example, the Chemstrip Micral test strips can detect urinary albumin concentrations at 0 mg/L, 20 mg/L, 50 mg/L, and 100 mg/L, with 20 mg/L corresponding to greater than 30 mg albumin excretion per day. This test may be influenced by urine-specific gravity at low albumin concentrations; false-negative readings (i.e. 0 mg/L, microalbuminuria absent) can occur when urine is dilute (specific gravity less than 1.025). Test results ranging from 20 mg/L to 50 mg/L are associated with a 19%–42% false-positive rate and require confirmation using a carefully conducted timed urine collection or urinary albumin:creatinine ratio.

In the past, the gold-standard quantitative approach for measuring urinary albumin excretion rate required a timed 24-hour urine collection. Significant collection errors due to either improper timing or incomplete urine collection were associated with errors in volume measurement. Shorter intervals such as overnight or daytime collections were less cumbersome, but still confounded by incomplete bladder emptying. More recently, the measured urinary albumin excretion rate has now been replaced by the measurement of the albumin:creatinine ratio obtained from an untimed (spot, first morning) urine aliquot. Here, urine creatinine concentration is used as a correction factor to account for urine dilution. This test is conducted by a clinical laboratory, with microalbuminuria defined as 30–300 mg albumin per g creatinine (mg/g). In patients with severe glomerular damage and significant clinical proteinuria (where the albumin:creatinine ratio is greater than 500 mg/g), the protein:creatinine ratio is the preferred index.

Newer methods for quantifying urinary albumin with improved sensitivity have recently been proposed. Albumin concentrations in the urine have traditionally been quantified using immunochemical methods such as enzyme-linked immunosorbent assay and radiolabeled immunoassay, based on the assumption that urinary albumin was excreted in a single intact form. However, recent studies indicate that albumin is present in multiple forms, as a mixture of intact (immunoreactive) and non-immunoreactive components such as albumin-derived peptides and non-immunoreactive intact albumin.

Microalbuminuria may be undiagnosed in patients with low amounts of non-immunoreactive albumin using radiolabeled immunoassay methods. Because these non-immunoreactive entities are not detected by radiolabeled immunoassay, new methods such as high performance liquid chromatography have been proposed to quantify each albumin component. Specific methods may be required to avoid false-negative results, especially in patients with early (Stages 1 and 2) CKD. It is important to determine the specific method used in each clinical laboratory to provide the most accurate interpretation of urinary albumin concentrations.

Conclusion

Accurate assessment of kidney function in the clinical setting is critical for identifying individuals with early CKD and monitoring kidney disease progression. The MDRD eGFR equation (MDRD4) appears to offer an improvement over serum creatinine or cystatin C concentrations alone and an estimated creatinine clearance using the Cockcroft-Gault equation for patients with CKD and GFR less than 60 mL/minute/1.73 m². Use of eGFR as a screening tool in healthy and non-CKD populations and as an index for individualization of drug dosage regimens requires further evaluation. The pharmacist should be aware that clinical laboratories are now reporting eGFR values in combination with serum creatinine concentrations, and it is important to understand the implications of this approach. Although the association with cardiovascular disease is convincing, the role of serum cystatin C concentration in the quantification of kidney function is yet to be defined. Both semi-quantitative and quantitative assessments of urinary protein and albumin excretion are important aspects of monitoring kidney disease progression and response to therapy. For the present time decisions regarding drug dose adjustments for patients with chronic kidney disease should be made based on estimated creatinine clearance using the Cockcroft-Gault equation.

Annotated Bibliography

1. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. 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;130:461–70.

This is the landmark article that introduced the MDRD equation for the first time as an estimate of GFR. A strength of the MDRD study design included direct GFR measurement (using iothalamate clearance) in all patients with non-diabetic CKD (GFR 40 ± 21 mL/minute/1.73 m²) enrolled in the original study. The authors derived a series of equations to estimate GFR based on a training sample set of 1070 patients and validated it in a separate cohort of 558 patients. The MDRD6 equation was used to estimate the incidence and prevalence of CKD in the United States based on the National Health and Nutrition Examination Survey III trial database. Development of this new eGFR has led to increased awareness and recognition of CKD in acute and ambulatory care settings. However, further studies are needed to evaluate its performance in non-CKD populations.

2. Bostom AG, Kronenberg F, Ritz E. Predictive performance of renal function equations for patients with chronic kidney disease and normal serum creatinine levels. *J Am Soc Nephrol* 2002;13:2140–4.

This study is the first of many to report that the MDRD eGFR equation may be inappropriate for use in patients with normal GFR values, even in the presence of CKD. This study included patients with non-diabetic CKD with a measured GFR (iohexol) and serum creatinine concentrations less than or equal to 1.5 mg/dL. Results showed that the Cockcroft-Gault equation had less bias and greater precision than both MDRD eGFR equations (MDRD4 and MDRD6). The eGFR equations significantly underestimated the measured GFR by 42–47 mL/minute/1.73 m², which has subsequently been confirmed in numerous populations of individuals with normal GFR values such as those with early type 1 diabetes mellitus and potential kidney donors. Taken together, these data form the basis for the most recent National Kidney Disease Education Program recommendation that actual eGFR values be reported only when eGFR is less than 60 mL/minute/1.73 m².

3. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003;139:137–47.

This summary report by the National Kidney Foundation KDOQI study group provides a standardized approach for estimating kidney function in patients with CKD. The authors discuss key problem areas, such as underdiagnosis of CKD and limitations of previous approaches to defining and classifying CKD. These National Kidney Foundation clinical practice guidelines include the five-stage classification system of CKD, risk factors, and a recommended approach for detecting kidney damage. This report recommends using either the MDRD eGFR (MDRD4) or Cockcroft-Gault equation for identifying kidney disease and monitoring GFR in CKD patients.

4. Myers GL, Miller WG, Coresh J, Fleming J, Greenberg N, Hostetter T, et al. Recommendations for improving serum creatinine measurement: a Report from the Laboratory Working Group of the National Kidney Disease Education Program. *Clin Chem* 2006;52:5–18.

Since the introduction of the MDRD eGFR equation, attention has been focused on the need for more accurate methods to estimate GFR in the clinical setting. Because serum creatinine concentration is a critical element of all estimation approaches, this has spawned a renewed interest in determining the accuracy, precision, and interlaboratory variability of creatinine assays. This article from the National Kidney Disease Education Program working group provides an excellent analysis of the available methods and their performance, resources for assay standardization, in vitro diagnostic manufacturers, and sources of variability. A key finding in this paper is that uncalibrated creatinine methods begin to lose accuracy as serum creatinine concentrations drop into the near normal to slightly increased range (less than 1.5 mg/dL). Thus, many available uncalibrated serum creatinine assays will only provide acceptable results in patients with a GFR less than 60 mL/minute/1.73 m². For those laboratories that implement calibration procedures, a new creatinine reference range will require use of a modified version of the eGFR MDRD equation (isotope dilution mass spectrometry traceable).

5. Lamb EJ, Webb MC, Simpson DE, Coakley AJ, Newmann DJ, Oriordan SE. Estimation of glomerular filtration rate in older patients with chronic renal insufficiency: is the Modification of Diet in Renal Disease formula an improvement? *J Am Geriatr Soc* 2003;51:1012–7.

Serum creatinine concentrations in the elderly population are influenced by age-dependent changes in kidney function and reduced muscle mass. This study evaluated the performance of the MDRD6 and MDRD4 and Cockcroft-Gault equations in 52 elderly patients (age 68 and older) with GFR measured by chromium-labeled ethylenediaminetetraacetic acid. Both eGFR and Cockcroft-Gault equations performed reasonably well, but they were significantly positively (8%) and negatively (-10%) biased, respectively, compared with measured GFR. This well-designed study demonstrated that the MDRD eGFR equations do not provide a significant improvement over the Cockcroft-Gault equation in the elderly.

6. Macisac RJ, Tsalamandris C, Thomas MC, Premaratne E, Panagiotopoulos S, Smith TJ, et al. Estimating glomerular filtration rate in diabetes: a comparison of cystatin-C- and creatinine-based methods. *Diabetologia* 2006;49(7):1686–9.

This study evaluated the performance of a new serum cystatin C GFR equation, the MDRD eGFR (MDRD4), and Cockcroft-Gault equations compared with measured GFR in patients with type 2 diabetes mellitus. An important aspect of this study was inclusion of patients with diabetes mellitus whom were excluded from the original MDRD study population. This large cross-sectional study included 251 patients with a wide range of kidney function (mean GFR 88 ± 2, range 9–181 mL/minute/1.73 m²). The bias and precision of the cystatin C-GFR equation was similar to MDRD and Cockcroft-Gault equations. The findings indicate that a serum cystatin C-GFR equation does not provide improvement over traditional methods of GFR estimation.

7. Perkins BA, Nelson RG, Ostrander BE, Blouch KL, Krolewski AS, Myers BD, et al. Detection of renal function decline in patients with diabetes and normal or elevated GFR by serial measurements of serum cystatin C concentration: results of a 4-year follow-up study. *J Am Soc Nephrol* 2005;16(5):1404–12.

This was one of the first prospective studies evaluated the ability of serial cystatin C concentrations to detect changes in GFR. Yearly GFR measurements (using iothalamate clearance) were made in 30 patients with type 2 diabetes mellitus. The authors reported a stronger relationship between the reciprocal serum cystatin C index (100/cystatin C) and GFR compared with creatinine-based measures (100/serum creatinine; Cockcroft-Gault equation) and GFR was observed. Results of this well-designed, prospective study suggest that serum cystatin C concentrations may play a role in longitudinal evaluations of kidney function, where increasing serum cystatin C concentrations are associated with reductions in GFR.

8. Tkaczyk M, Nowicki M, Lukamowicz J. Increased cystatin C concentration in urine of nephrotic children. *Pediatr Nephrol* 2004;19:1278–80.

One of the controversial aspects of using serum cystatin C as a glomerular filtration marker is its reliance on renal tubular function. This study evaluated serum and urine concentrations of cystatin C in children with a relapse of the idiopathic nephrotic syndrome. Urinary cystatin C

concentrations were detectable only in cases where proteinuria was present, which is contradictory to renal markers such as creatinine where urinary recovery is reduced in the presence of kidney disease. This study identifies an important limitation of using serum cystatin C concentration as a renal biomarker, where renal clearance may be increased in CKD where macroalbuminuria (albumin excretion greater than 300 mg/day) is most likely present.

9. Comper WD, Osicka TM, Clark M, MacIsaac RJ, Jerums G. Earlier detection of microalbuminuria in diabetic patients using a new urinary albumin assay. *Kidney Int* 2004;65:1850–5.

It is well-known that microalbuminuria is a strong independent risk factor for developing kidney failure in patients with CKD, and early detection is critically important. This article focuses on a new method for quantifying very low concentrations of urinary albumin using high performance liquid chromatography. Traditional approaches to quantifying urinary albumin used immunoassays such as radiolabeled immunoassay to detect immunoreactive albumin. However, other forms of albumin have been identified, including non-immunoreactive components. The authors describe a new high performance liquid chromatography method that measures total albumin (immunoreactive plus non-immunoreactive). Study results suggest that measurement of total albumin may allow earlier detection of microalbuminuria associated with type 1 and type 2 diabetic nephropathy. High performance liquid chromatography methods are capable of detecting lower concentrations of urinary albumin than traditional radiolabeled immunoassay methods, which may result in less false-negatives and a significant increase in the reported prevalence of microalbuminuria in a given study population.

10. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the MDRD study equation for estimating GFR. *Ann Intern Med* 2006;145:247–54.

This paper is important because it provides a rigorous performance evaluation of the MDRD4 equation based on the isotope dilution mass spectrometry-calibrated creatinine assay. A major limitation of previous MDRD equations is reduced accuracy at GFR greater than 60 mL/minute/1.73 m². Investigators analyzed plasma samples obtained from 1628 patients with CKD who were enrolled in the original MDRD study (n=219 with GFR greater than 60 mL/minute/1.73 m²) using a re-expressed MDRD4 equation (MDRD4-IDMS with coefficient 175 vs. 186). Compared with measured GFR (iothalamate), the performance of the MDRD4-IDMS as measured by percent of estimates within 30% of GFR was not significantly different from the original MDRD6 equation. Both equations had similar sensitivity (97%) and specificity (67%–70%) to predict a measured GFR less than 60 mL/minute/1.73 m². This study provides evidence that the MDRD6 can be replaced by the abbreviated MDRD4 in patients with CKD and a measured GFR of less than 90 mL/minute/1.73 m².

11. Brosius FC 3rd, Hostetter TH, Kelepouris E, Mitsnefes MM, Moe SM, Moore MA, et al. Detection of chronic kidney disease in patients with or at increased risk of cardiovascular disease. *Circulation* 2006;114:1083–7.

This joint position statement by the American Heart Association and National Kidney Foundation recommends combined screening of microalbuminuria and estimating GFR

in patients with cardiovascular disease. The proposed approach includes estimation of GFR using the MDRD4 equation and detection of microalbuminuria using a spot urine albumin-to-creatinine ratio. Of note, the MDRD equation provided in this paper is the original MDRD4 with coefficient 186 using the uncalibrated serum creatinine assay. For patients with GFR values less than 60 mL/minute/1.73 m² and albumin-to-creatinine ratio values greater than 30 mg albumin per 1 g creatinine, repeat determination of GFR and albumin-to-creatinine ratio in 3 months is recommended. This approach is expected to improve the monitoring and care of CKD in patients with cardiovascular risk factors, such as diabetes mellitus and hypertension.

12. Redon J, Morales-Olivas F, Galgo A, Brito MA, Mediavilla J, Marin R, et al. Urinary albumin excretion and glomerular filtration rate across the spectrum of glucose abnormalities in essential hypertension. *J Am Soc Nephrol* 2006;17(12 suppl 3):S236–45.

This large cross-sectional study evaluated the relationship between urinary albumin excretion rate and degree of glucose intolerance in 6227 patients with essential hypertension. The method used to estimate GFR in this study was the MDRD4 equation. The authors reported that the prevalence of microalbuminuria (urinary albumin excretion greater 30 mg/day) was strongly associated with the degree of glucose intolerance. As expected, the urinary albumin excretion was positively associated with increasing systolic blood pressure and reductions in GFR. The study results demonstrate that abnormalities in kidney function are common in patients with hypertension who have prediabetic conditions, and close monitoring of CKD and its complications are needed in this population.

13. Schiff J, Paraskevas S, Keith D, Tchervenkov J, Metrakos P, Cantarovich M. Prediction of the glomerular filtration rate using equations in kidney-pancreas transplant patients receiving cimetidine. *Transplantation* 2006;81:469–72.

This study addresses the important issue of estimating kidney function in recipients of kidney-pancreas transplants, many of whom subsequently develop drug-induced kidney disease or chronic allograft nephropathy. This is the first study to report the effect of cimetidine administration on the performance of creatinine clearance (Cockcroft-Gault and 24-hour measured) and GFR (MDRD6) estimation relative to GFR measured by technetium-99m-DTPA in this population. The authors used the most commonly reported regimen for cimetidine (800 mg 3 times/day for 1 day before kidney function assessment) in 15 recipients with kidney-pancreas transplants. The mean GFR in the study population was 62 mL/minute/1.73 m². Here, the cimetidine-aided Cockcroft-Gault estimate provided an acceptable estimate of measured GFR (mean bias 4.2 mL/minute/1.73 m²; r = 0.71). Although a repeated measures study design in this small study would have been preferred, the results suggest that use of cimetidine-aided Cockcroft-Gault assessment may be a suitable alternate to measured GFR in quantifying kidney function in the kidney transplant population.

SELF-ASSESSMENT QUESTIONS

Questions 1–4 pertain to the following case.

G.H. is a 64-year-old African-American woman (66 kg, 5'5") with a history of type 2 diabetes mellitus and chronic kidney disease (CKD). Her serum creatinine concentration (uncalibrated, non-isotope dilution mass spectrometry) is 2.40 mg/dL, which is unchanged since her clinic visit last month. No serum laboratory results were requested for this clinic visit. Her estimate glomerular filtration rate (eGFR) as determined by the Modification of Diet in Renal Disease (MDRD) equation is 26.1 mL/minute/1.73 m² and her Cockcroft and Gault equation creatinine clearance (CrCl) estimate is 24.7 mL/minute, which places her into Stage 4 CKD. While reviewing her list of drugs, you identify several that require dosing adjustments in patients with kidney dysfunction.

1. Which one of the following is the best approach to use to determine the correct dose of G.H.'s drugs?
 - A. Calibrated serum creatinine concentration.
 - B. Estimated glomerular filtration rate.
 - C. Cockcroft-Gault equation.
 - D. Body surface area-adjusted creatinine clearance estimate.
2. The pharmacy resident on rotation with you notices that the eGFR is unusually higher than the CrCl estimate. Which one of the following best explains this finding in G.H.?
 - A. Race.
 - B. Sex.
 - C. Body weight.
 - D. Diabetes mellitus.

While reviewing the patient's prior medical records, the pharmacy resident also notices that the eGFR 5 years ago was listed as greater than 60 mL/minute/1.73 m² and that microalbuminuria was reported on several occasions.

3. Which one of the following is the best interpretation of these results 5 years ago?
 - A. Stage 3 CKD was present.
 - B. Chronic kidney disease was not present at that time.
 - C. A Cockcroft-Gault estimate is needed to make any interpretation.
 - D. The MDRD equation is not precise enough to report an actual number.
4. Which one of the following is the most appropriate CKD screening test to conduct for G.H.?
 - A. A 24-hour urine collection to determine urinary protein excretion rate.
 - B. A high performance liquid chromatography quantification of urine albumin components.
 - C. A spot urinary albumin:creatinine ratio.
 - D. A urine albumin-specific dipstick test.

5. R.T. is an 82-year-old Caucasian man (54 kg, 5'8") with a history of hypertension, cerebral stroke, and benign prostatic hypertrophy. He presents to his primary care physician today for a routine examination. R.T. is an active man. Although he is officially retired, he practices law 30 hours/week. His serum creatinine concentration today is 0.61 mg/dL. Which one of the following is the best approach for assessing R.T.'s kidney function?
 - A. Measure a chromium-labeled ethylenediaminetetraacetic acid GFR.
 - B. Estimate CrCl (Cockcroft-Gault equation) using a serum creatinine of 0.61 mg/dL.
 - C. Estimate GFR (MDRD equation) using a serum creatinine of 1.0 mg/dL.
 - D. Conduct a timed 24-hour urine collection.

Questions 6 and 7 pertain to the following case.

J.S. is a 3-year-old girl (13 kg, 94 cm) with a history of glomerulonephritis. She presents to the pediatric nephrology clinic today for a routine examination. Her serum creatinine concentration today is 1.1 mg/dL, which has increased from her last visit (0.9 mg/dL) 6 months ago.

6. Which one of the following is the best approach to assessing the potential change in J.S.'s CrCl?
 - A. Counahan-Barratt equation.
 - B. Schwartz equation.
 - C. The MDRD equation.
 - D. Cockcroft-Gault equation.
7. Which one of the following is the most appropriate method to stage J.S.'s CKD?
 - A. The Kidney Disease Outcomes Quality Initiative (KDOQI) Guidelines for CKD Stratification.
 - B. Measured GFR using iothalamate.
 - C. Serial cystatin C concentrations.
 - D. Estimated GFR using the MDRD 4 variable equation.

Questions 8–10 pertain to the following case.

A.J. is a 48-year-old Caucasian man (68 kg, 5'9") who is positive for the human immunodeficiency virus due to intravenous drug use. His serum creatinine concentration is currently 2.4 mg/dL (isotope dilution mass spectrometry-traceable) and stable. His drug therapy consists of efavirenz (600 mg orally at bedtime) and emtricitabine 200 mg every day. The plan is to add didanosine to his drug regimen today.

8. Which one of the following is the best representation of A.J.'s estimated GFR?
 - A. 37.3 mL/minute/1.73 m².
 - B. 30.8 mL/minute/1.73 m².
 - C. 29.0 mL/minute/1.73 m².
 - D. 22.9 mL/minute/1.73 m².

9. Which one of the following is the most appropriate interpretation of calibrated serum creatinine concentration?
- Fewer rounding errors to bias the eGFR result.
 - The error range around A.J.'s eGFR value is clinically insignificant.
 - To decrease error, reporting of A.J.'s eGFR should be limited to "less than 60 mL/minute/1.73 m²."
 - A.J.'s serum creatinine concentration is likely to be subject to significant assay error.
10. Which one of the following dosing regimens is the most appropriate for initiating didanosine therapy in A.J.?
- 400 mg/day.
 - 250 mg/day.
 - 200 mg/day.
 - 125 mg/day.

Questions 11–14 pertain to the following case.

J.R. is a 73-year-old African-American man (70 kg, 5'8") with a history of type 2 diabetes mellitus, hypertension, and heart failure. His serum creatinine is 1.32 mg/dL (uncalibrated) and serum cystatin C concentration is 1.44 mg/L. A urine protein dipstick test shows (1+) protein, and albumin:creatinine ratio is 42 mg/g.

11. Which one of the following is the most appropriate representation of J.R.'s kidney function and should appear in his automated laboratory results report?
- Estimated GFR greater than 60 mL/minute/1.73 m².
 - Serum creatinine of 1.3 mg/dL.
 - Serum creatinine of 1.32 mg/dL.
 - Estimated GFR of 68.4 mL/minute/1.73 m².
12. Which one of the following statements is the best interpretation of J.R.'s cystatin C results?
- The value is above the normal range.
 - Cystatin-C estimated GFR is higher than the MDRD eGFR.
 - The value is useful to indicate progression of J.R.'s kidney disease.
 - Acute kidney injury is present.
13. Which one of the following is the most appropriate diagnosis for J.R. based on his urinary protein results?
- Microalbuminuria.
 - Macroalbuminuria.
 - Idiopathic nephrotic syndrome.
 - Membranous glomerulonephritis.
14. Which one of the following best describes the measure components reported in J.R.'s urinary albumin:creatinine ratio?
- β₂-microglobulin.
 - Immunoreactive albumin.
 - Albumin-derived peptides.
 - Non-immunoreactive albumin.

Questions 15–17 pertain to the following case.

T.R. is a 32-year-old Caucasian man (85 kg, 5'10") who is undergoing initial evaluation as a potential kidney donor. His sister has stage 5 CKD and is a candidate for transplantation. Today is his first day of testing and assessment. His only medical history is a broken leg 15 years ago. He is married without children, and eats a regular diet. His serum creatinine concentration today is 0.98 mg/dL (uncalibrated), and he takes no prescription drugs.

15. Which one of the following is the best recommendation for a comprehensive evaluation of kidney function for T.R. at this time?
- The GFR should be calculated using the MDRD equation.
 - The Cockcroft-Gault equation should be used to estimate CrCl.
 - A serum cystatin C concentration is needed to evaluate kidney tubular function.
 - A GFR measurement using iothalamate or inulin is needed.
16. Which one of the following urine protein assessments is most appropriate to conduct for T.R.'s initial evaluation as a potential kidney donor?
- A 24-hour urine collection to determine urinary protein excretion rate.
 - A 24-hour urine collection to determine urinary albumin excretion rate.
 - A urine protein dipstick test.
 - A urine albumin-specific dipstick test.

Three months into T.R.'s evaluation as a kidney donor, he moves to another state. He wants to continue his evaluation and has found a new transplantation nephrologist. At his most recent visit to his new clinic, his serum creatinine concentration was 1.21 mg/dL (calibrated).

17. Which one of the following is the best course of action to take based on T.R.'s most recent serum creatinine concentration?
- Stop the transplantation donor evaluation because T.R. is not eligible.
 - Research the cause of T.R.'s change in kidney function.
 - Re-estimate T.R.'s eGFR using the MDRD equation.
 - Continue the transplantation donor evaluation as planned.
18. In the next month, your institution will be changing its serum creatinine assay to the isotope dilution mass spectrometry-traceable creatinine assay. You are giving a presentation to the pharmacy staff describing the impact of the change. In which one of the following CKD populations is it most important to discuss the impact of the assay change on GFR estimates?
- Stage 2.
 - Stage 3.
 - Stage 4.
 - Stage 5.

Questions 19 and 20 pertain to the following case.

K.M., a 45-year-old man with type 2 diabetes mellitus, is being seen in the outpatient clinic to be assessed before undergoing a non-urgent renal artery angiogram next week to assess for a cause of difficult to control hypertension. At his last clinic visit 3 months ago, he was told to lose weight. At that time, he weighed 240 pounds, his blood pressure was 150/95 mm Hg, and his serum creatinine concentration was 2.3 mg/dL. According to his glucometer log, his blood glucose concentrations were routinely between 300 mg/dL and 350 mg/dL. He reports having lost 15 pounds due to becoming a vegetarian. His blood pressure today is 140/90 mm Hg. For the past year, his drug list includes metoprolol, lisinopril, and glyburide. His serum creatinine concentration in today is 1.9 mg/dL and his glucometer log demonstrates improved blood glucose concentrations of 225–260 mg/dL.

19. Which one of the following clinical results is most likely to be skewed in K.M. at this clinic visit?
- A. Blood pressure.
 - B. Albuminuria.
 - C. Serum glucose concentration.
 - D. Serum creatinine concentration.
20. Which one of the following is the most appropriate method to assess K.M.'s kidney function before his renal artery angiogram?
- A. Iohexol.
 - B. Estimated GFR.
 - C. Cockcroft-Gault CrCl.
 - D. A 24-hour timed urine collection.
21. G.H. is a 75-year-old well-nourished man who resides in an assisted living complex. He is active and participates in the exercise classes offered. The staff report that in recent days G.H. has been getting confused at night and trying to sleep in the recreation room. G.H. is admitted to the hospital for evaluation. G.H. is going to be treated with a drug that is entirely eliminated by glomerular filtration and whose dosage is based on kidney function. Which one of the following methods is the best choice to accurately assess of G.H.'s kidney function?
- A. A 24-hour timed urine collection with cimetidine.
 - B. Cockcroft-Gault estimate of CrCl.
 - C. Quantitative proteinuria assessment.
 - D. Cystatin C concentration.
22. R.C. is a 65-year-old retired man with a history of coronary artery disease and type 2 diabetes mellitus. He lives alone and due to a work-related injury, he has limited use of his dominant arm. He presents to his primary care physician for an annual checkup. R.C. is adherent to the following drugs: aspirin 325 mg/day, metoprolol 50 mg/day, atorvastatin 20 mg/day, and metformin 500 mg 2 times/day. All his laboratory values are within normal limits. Urine analysis using a Chemstrip Micral test strip provides the following information pH 5, specific gravity 1.020, urinary albumin concentration 20 mg/L, and no blood, ketones,

glucose, or leukocyte esterase. Given the presence of albuminuria, R.C.'s physician is considering therapy to inhibit the progression of diabetic nephropathy. Which one of the following is the most appropriate next step to take?

- A. Repeat albumin-specific dipstick test today.
- B. Initiate drug therapy.
- C. Conduct a 24-hour timed urine collection.
- D. Request a spot urinary albumin:creatinine ratio.

