Chapter e60: Evaluation of Kidney Function

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KEY CONCEPTS

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1. The stage of chronic kidney disease (CKD) should be determined for all individuals based on the level of kidney function, independent of etiology, in accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) classification system.
2. Persistent proteinuria indicates the presence of CKD and is associated with mortality and risk of end-stage kidney disease (ESKD).
3. Assessment of urine protein excretion, including measurement of a spot urine albumin-to-creatinine ratio, is critical for determining the severity of CKD and monitoring the rate of disease progression.
4. The glomerular filtration rate (GFR) is the single best indicator of kidney function.
5. Measurement of the GFR is most accurate when performed following administration of iohexol, iothalamate, or radioisotopes such as technetium-99m diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA).
6. Equations to estimate creatinine clearance (CL_{cr}) or GFR (eGFR) are commonly used in ambulatory and inpatient settings, and incorporate patient laboratory and demographic variables such as serum creatinine concentration (S_{cr}), cystatin C, age, sex, and weight.
7. Assessments of kidney structure and function, such as radiography, computed tomography, magnetic resonance imaging, sonography, and biopsy, are predominantly used for determining the diagnosis of a given condition.

BEYOND THE BOOK

BEYOND THE BOOK

Using the Drugs@FDA Website <https://www.accessdata.fda.gov/scripts/cder/daf/> or tertiary databases like Micromedex identify two commonly used drugs that require drug dose adjustments in patients with impaired kidney function. Compile a summary table of the dosing information including drug name, kidney estimation method and categories, and dose adjustment recommendation. Now consider the following patient scenarios: (1) 49-year-old Caucasian man with Scr 1.7 mg/dL (150 µmol/L), height 72 in. (183 cm), weight 100 kg; (2) 67-year-old female of African ancestry with Scr 1.5 mg/dL (133 µmol/L), height 65 in. (165 cm), weight 90 kg.

Calculate kidney function for each patient utilizing the Cockcroft–Gault equation, and the CKD EPI race free equation using Scr with and without indexing to body surface area. Compare and contrast the corresponding doses for the drugs identified using each kidney function equation. This activity is intended to build upon your understanding of kidney function and to familiarize you with how the various estimating equations may impact your dosing recommendations.

INTRODUCTION

Chronic kidney disease (CKD) continues to be a worldwide health concern, with over 2 million people in the United States estimated to require hemodialysis or kidney transplantation by 2030.[1,2] In response to this widespread problem, standardized approaches are now used for the identification of individuals with CKD and their subsequent stratification into risk categories for the development of end-stage kidney disease (ESKD) (see Chapter 62, Chronic Kidney Disease).[1,2] These efforts have heightened the awareness of the need for early identification of patients with CKD and the importance of monitoring the progression of kidney disease.

Comprehensive evaluation of kidney function requires use of qualitative, quantitative, and semi-quantitative methods. Estimation of creatinine clearance (CL_{cr}) was the clinical standard for assessment of kidney function for over 50 years. Although it continues to be used to assess kidney function for renal drug dosing purposes in pharmacokinetic studies, recent FDA guidance recommended use of estimated glomerular filtration rate (GFR) in addition to or in lieu of CL_{cr} for renal dosing recommendations.[3] Estimated GFR is routinely used across clinical settings to identify patients with CKD, and in large epidemiology studies to evaluate risks of mortality and progression to stage 5 CKD or ESKD.[4,5] Other tests, such as urinalysis, radiographic procedures, and biopsy, are also valuable tools in the assessment of kidney disease, and these qualitative assessments are useful for determining the pathology and etiology of kidney disease. Urinalysis, for example, may give clues to the primary location, such as glomerular or tubular, of the kidney disease. Follow-up studies, such as imaging procedures or kidney biopsy, may then further differentiate the specific cause, thereby guiding the selection of the optimal therapeutic intervention.

1 Quantitative indices of GFR or CL_{cr} are considered the most useful diagnostic tools for identifying the presence and monitoring the progression of CKD. These measures can also be used to quantify changes in function that may occur as a result of disease progression, therapeutic intervention, or an acute insult. The measurement or estimation of CL_{cr}, however, remains the most used index for individualizing medication dosage regimens in patients with acute and CKD. It is important to note that the term *kidney function* includes the combined processes of glomerular filtration, tubular secretion, and reabsorption, as well as endocrine and metabolic functions. Alterations in any or all these functions, whether declining or improving, are associated primarily with GFR. This chapter critically evaluates the various methods that can be used for the quantitative assessment of kidney function in individuals with normal kidney function as well as in those with CKD and acute kidney injury (AKI). Where appropriate, discussion regarding the qualitative assessment of the kidney function is also presented, including the role of imaging procedures and invasive tests such as kidney biopsy.

EXCRETORY FUNCTION

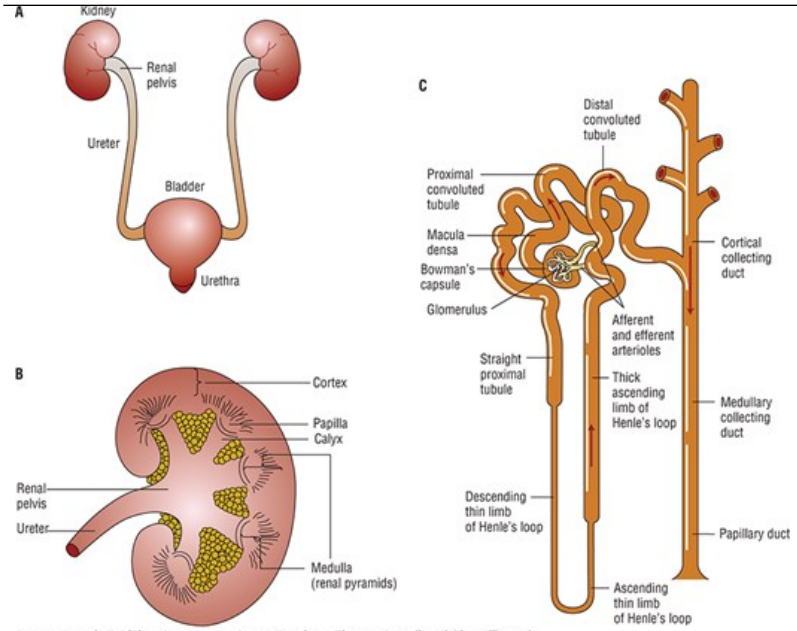
The kidney is largely responsible for the maintenance of body homeostasis via its role in regulating urinary excretion of water, electrolytes, and endogenous substances such as urea, medications, and environmental toxins. It accomplishes this through the combined processes of glomerular filtration, tubular secretion, and reabsorption.

Glomerular Filtration

Glomerular filtration is a passive process by which water and small-molecular-weight (less than 5-10 kDa) ions and molecules diffuse across the glomerular–capillary membrane into the Bowman capsule and then enter the proximal tubule (Fig. e60-1). Most proteins, such as albumin, are too large (greater than 60 kDa) to be substantially filtered, and their filtration is impeded by the electronegative charge on the epithelial surface of the glomerulus.[6] Thus, compounds presented to the glomerulus in the protein-bound state are usually not significantly filtered and remain in the peritubular circulation.

FIGURE e60-1

Structures of the (A) urinary system, (B) kidney, and (C) nephron, the functional unit of the kidney.

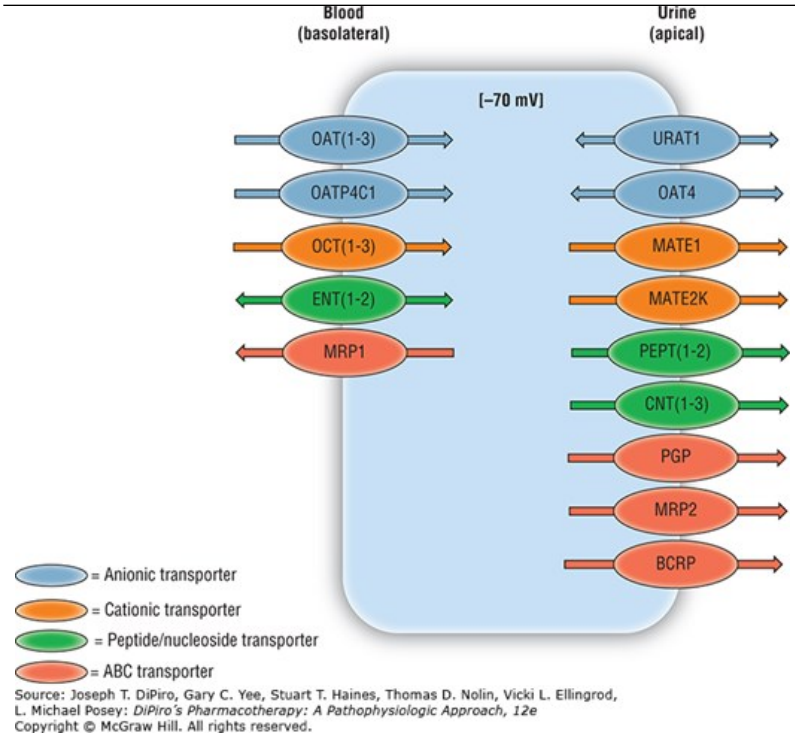


Secretion

Secretion is an active process that takes place predominantly in the proximal tubule and facilitates the elimination of compounds from the renal circulation into the tubular lumen. Several highly efficient transport pathways exist for a wide range of endogenous and exogenous substances, resulting in renal clearances of these actively secreted entities that often greatly exceed GFR and in some cases approximate renal blood flow. These transporters are typically found among the solute-linked carrier (SLC) and ATB-binding cassette (ABC) superfamilies. The primary SLC transporters include the organic anion transporting polypeptides (OATPs), organic cation transporters (OCTs), organic anion transporters (OATs), and multidrug and toxin extrusion proteins (MATEs) (Fig. e60-2). The key ABC transporters include multidrug resistance protein (MDR1 or P-glycoprotein (P-GP)), MRP1 and MRP2. Both group of transporters are expressed in a variety of different epithelial membranes throughout the body and play a role in intestinal absorption, blood–brain barrier penetration, and excretion into the bile and urine. The research has identified their localized role in drug uptake and efflux in kidney tissues, where the OCT (1-3) and OAT (1-3) are involved in basolateral influx of substrates, and P-GP, MRP, and MATE are apical efflux transporters.[7–9] Their presence in liver and kidney contributes to the hepatic and renal elimination of many drugs. For example, P-GP, which is located on the apical membrane of the proximal tubule, plays an important role in the kidney's elimination of a wide range of drugs, such as cimetidine, digoxin, and procainamide. Transporters also play a role in drug-induced kidney disease. For example, cobicisat, a CYP3A inhibitor that is used to enhance the response of several human immunodeficiency virus (HIV) regimens, has been associated with elevations in serum creatinine. The mechanism is attributed to combined inhibition of creatinine uptake (OCT2, OCT3) and efflux (MATE1).[7] The coordination of multiple drug transporters working together can result in a high degree of urinary excretion. For example, pramipexole undergoes OCT2-mediated uptake along with MATE-mediated efflux, resulting in extensive tubular secretion and renal clearance values of 500 to 800 mL/min (8.3-13.3 mL/s).[9] Overall, the net process of tubular secretion for drugs is likely a result of multiple secretory pathways acting simultaneously. For a summary table of transporters and substrates, we refer the reader to a summary by the International Transporter Consortium.[10]

FIGURE e60-2

Drug transporters in the renal proximal tubule.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Reabsorption

Reabsorption of water and solutes occurs throughout the nephron, whereas the reabsorption of most medications occurs predominantly along the distal tubule and collecting duct. Urine flow rate and physicochemical characteristics of the molecule influence these processes: highly ionized compounds are not reabsorbed unless pH changes within the urine increase the fraction unionized, so that reabsorption may be facilitated.

Intact Nephron Hypothesis

The "intact nephron hypothesis" described by Bricker,[11] over 50 years ago, proposed that "kidney function" of patients with kidney disease is the net result of a reduced number of appropriately functioning nephrons. As the number of nephrons is reduced from the initial complement of 2 million, unaffected nephrons compensate by hyperfunctioning to establish homeostasis and a new steady state. Extensive studies have demonstrated that single-nephron GFR increases in unaffected nephrons to maintain near normal whole-kidney GFR, which represents the sum of the single-nephron GFRs of the remaining functional nephrons. Based on this, one would presume that a measure of one component of nephron function, that is, GFR, could be used as an estimate of all functions (ie, secretion and reabsorption) of the kidney.

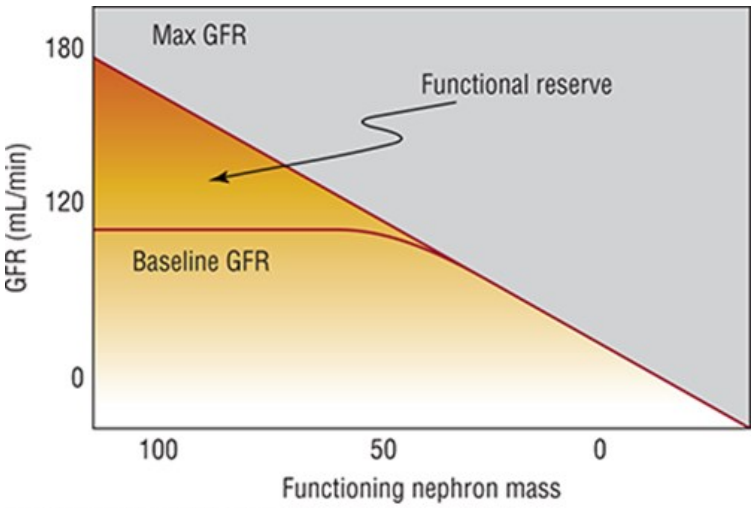
Glomerular Filtration Capacity

Glomerular filtration capacity and the corresponding GFR are dependent on numerous factors, one of which is protein load. The concept of renal functional reserve (RFR) has been defined as the capacity of the kidney to increase GFR in response to physiological or pathologic conditions.[12] This is similar in context to a cardiac stress test. The patient may have no hypoxic symptoms, for example, angina while resting, but it may become quite evident when the patient begins to exercise. Subjects with normal kidney function administered an oral or intravenous (IV) protein load prior to measurement of GFR have been noted to increase their GFR by as much as 50%. As kidney function declines, the kidneys usually compensate by increasing the single-nephron GFR. The RFR will be reduced in those individuals whose kidneys are already functioning at higher-than-normal levels because of preexisting kidney injury or subclinical loss of kidney mass (Fig. e60-3). Thus, RFR may be a complementary, insightful index of kidney function for many individuals with as yet unidentified CKD.

FIGURE e60-3

Structure–function relationship between GFR and nephron mass. GFR expressed in mL/min is converted to units of mL/s by multiplying by 0.0167.

(Reprinted, with permission, from Sharma A, Mucino MJ, Ronco C. Renal functional reserve and renal recovery after acute kidney injury. Nephron Clin Pract. 2014;127:94-100.)



Quantification of kidney function is not only an important component of a diagnostic evaluation, but it also serves as an important parameter for monitoring therapy directed at the etiology of the diminished function itself, thereby allowing for objective measurement of the success of treatment. Measurement of kidney function also serves as a useful indicator of the ability of the kidneys to eliminate drugs from the body. Furthermore, alterations of drug distribution and metabolism have been associated with loss of kidney function. The pharmacokinetic changes in patients with kidney disease are extensively reviewed in Chapter 67, Personalized Pharmacotherapy for Patients with Chronic Kidney Disease. Although several indices have been used for the measurement of GFR in the research setting, estimation of CL_{cr} and GFR are the primary approaches used in the clinical arena.

ENDOCRINE FUNCTION

The kidney synthesizes and secretes many hormones involved in maintaining fluid and electrolyte homeostasis. Secretion of renin by the cells of the juxtaglomerular apparatus and production and metabolism of prostaglandins and kinins are among the kidney's endocrine functions. Additionally, in response to decreased oxygen tension in the blood, which is sensed by the kidney, erythropoietin is produced and secreted by peritubular fibroblasts. Because these functions are related to kidney mass, decreased endocrine activity is associated with the loss of viable kidney cells. In patients with stages 3 to 5 CKD and those with moderate-to-severe AKI, secretion of erythropoietin is impaired leading to reduced red blood cell formation, normocytic anemia, and symptoms of reduced oxygen delivery to tissues such as fatigue, dyspnea, and angina (see Chapter 62, Chronic Kidney Disease). Indeed, anemia-induced kidney hypoxia results indirectly in erythropoietin gene activation, tubular necrosis, and apoptosis, thereby contributing to further kidney cell injury.

METABOLIC FUNCTION

The kidneys perform a wide variety of metabolic functions, including the activation of vitamin D, gluconeogenesis, and metabolism of endogenous compounds such as insulin, steroids, and xenobiotics. It is common for patients with diabetes and stages 4 to 5 CKD to have reduced requirements for exogenous insulin, and require supplemental therapy with activated vitamin D_3 (calcitriol) or other vitamin D analogs (paricalcitol, doxercalciferol) to avert the bone loss associated with CKD-associated metabolic bone disease (see Chapter 63, Chronic Kidney Disease: Management of Secondary Complications). Cytochrome P450 (CYP), *N*-acetyltransferase, glutathione transferase, renal peptidases, and other enzymes responsible for the degradation and activation of selected endogenous and exogenous substances have been identified in the kidney. The CYP enzymes in the kidneys are as active as those in the liver, when corrected for organ mass, and their function may be impaired in the presence of kidney failure or uremia. Impaired nonrenal clearance in the presence of kidney failure has been documented for a number of drugs with a fraction eliminated renally unchanged of less than 30%, including those that undergo extensive CYP metabolism by CYP1A2, CYP2D6, CYP3A4, and CYP2C9, such as duloxetine, rosuvastatin, and

telithromycin.[13]

QUALITATIVE AND SEMI-QUANTITATIVE INDICES OF KIDNEY FUNCTION

Patients who develop CKD remain relatively asymptomatic until they reach stage 4 to 5 and systemic manifestations and/or secondary complications become evident. As kidney function declines, patients may develop new onset or worsening hypertension, edema, electrolyte abnormalities, anemia, or other complications (see Chapter 62, Chronic Kidney Disease). The Kidney Disease Outcomes Quality Initiative (KDOQI) workgroup recommends that all patients with CKD, and at increased risk for CKD, undergo a comprehensive laboratory assessment that comprises (a) S_{cr} to estimate GFR; (b) albumin-to-ceatinine ratio in a spot urine specimen; (c) examination of urine sediment for red blood cell and white blood cell counts; (d) serum electrolytes, including sodium, potassium, chloride, and bicarbonate; (e) urine pH; and (f) urine specific gravity.[14] Kidney ultrasound and additional diagnostic tests such as urine electrolytes may aid in evaluating the etiology of kidney disease.

LABORATORY PROCEDURES TO DETECT THE PRESENCE OF KIDNEY DISEASE

Urinalysis is an important tool for detecting and differentiating various aspects of kidney disease, which often goes unnoticed as the result of its asymptomatic presentation. Urinalysis can be used to detect and monitor the progression of diseases such as diabetes, glomerulonephritis, and chronic urinary tract infections. A typical urinalysis provides information about physical and chemical composition, most of which can be completed quickly and inexpensively by visual observation (volume and color) and dipstick testing.

Chemical Analysis of Urine

pH

The normal urine pH typically ranges from 4.5 to 7.8, and an elevation above this may suggest the presence of urea-splitting bacteria. In patients with renal tubular acidosis, urine pH is usually more than 5.5 because of impaired hydrogen ion secretion in the distal tubule or collecting duct.

Glucose

Glucose is usually not present in the urine because the kidney normally completely reabsorbs all the glucose filtered at the glomerulus. When a patient's blood glucose concentration exceeds the maximum threshold for glucose reabsorption (~180 mg/dL [10.0 mmol/L]), glucosuria will be present. Routine assessment of glucosuria to monitor diabetes has been replaced by newer methods of direct blood glucose measurements. Urine glucose testing is now predominantly used as a screening tool for the detection of diabetes. Glucosuria may be used as a monitoring parameter for the efficacy of sodium glucose co-transporter 2 (SGLT2) inhibitors.

Ketones

Acetoacetate and acetone are not normally found in the urine; they are however excreted in patients with diabetic ketoacidosis. They are also present under conditions of fasting or starvation. Typically, values of acetoacetate excretion are reported as small (less than 20 mg/dL [2 mmol/L]), moderate (30-40 mg/dL [3-4 mmol/L]), and large (greater than 80 mg/dL [8 mmol/L]).

Nitrite

Nitrite is not usually present in urine. The presence of nitrite is most commonly the result of conversion from urinary nitrate by bacteria in the urine. The presence of nitrite suggests that the patient has a urinary tract infection, commonly caused by gram-negative rods such as *Escherichia coli*. Although false-positive results are very rare, false-negative results are more common and may be caused by lack of dietary nitrate, reduced urine nitrate concentration from diuresis, or infections caused by bacteria such as enterococci and *Acinetobacter*, which do not reduce nitrate, and pseudomonads, which convert nitrate to nitrogen gas.

Leukocyte Esterase

Leukocyte esterase is released from lysed granulocytes in the urine; its presence is suggestive of urinary tract infection. False-positive tests can result

from delayed processing of the urine sample, contamination of the sample with vaginal secretions (such as blood or heavy mucus discharge), or by *Trichomonas* infection (such as trichomoniasis). False-negative tests can be produced by the presence of high levels of protein or ascorbic acid.

Heme

The heme test indicates the presence of hemoglobin or myoglobin in the urine. A positive test without the presence of red blood cells suggests either red cell hemolysis or rhabdomyolysis. In patients with established CKD, the presence of hematuria (positive dipstick) may be a significant risk factor for worsening CKD and death.[15]

Protein or Albumin

2 Evaluation of urinary protein or albumin is a standard tool to characterize the severity of CKD and to monitor the rate of disease progression or regression.[14] Persistent proteinuria or albuminuria, which is present on at least three occasions over a period of 3 to 6 months, is now considered a principal marker of kidney damage. Under normal conditions, plasma proteins remain in the glomerular capillaries and thus do not cross the glomerular basement membrane or enter the urinary space. Some of these proteins, such as albumin and globulins, are not filtered by the glomerulus as a result of charge and size selectivity (albumin 69 kDa). Smaller proteins (less than 20 kDa) pass across the glomerular basement membrane but are usually readily reabsorbed in the proximal tubule. Most healthy individuals excrete between 30 and 150 mg/day of total protein consisting of approximately 30 mg/day of albumin. The other proteins that may be found in the urine are secreted by the tubules (Tamm-Horsfall, immunoglobulin A, and urokinase) or composed of smaller proteins such as β_2-microglobulin, apoproteins, enzymes, or peptide hormones. Increased renal excretion of these low-molecular-weight proteins is considered a sensitive marker of tubulointerstitial disease.

Dipstick tests are the most common means to determine in a semi-quantitative fashion a patient's urinary protein or albumin excretion. False-positive results can occur in the presence of alkaline urine (pH greater than 7.5), when the dipstick is immersed too long, in those with highly concentrated urine, in the presence of drugs such as penicillin, sulfonamides, or tolbutamide, as well as blood, pus, semen, or vaginal secretions. False-negative results occur with dilute urine (specific gravity less than 1.015) and when proteinuria is caused by non-albumin or low-molecular-weight proteins such as heavy or light chains or Bence Jones proteins. The results of these dipstick tests are graded as negative (less than 10 mg/dL [100 mg/L]), trace (10-20 mg/dL [100-200 mg/L]), 1+ (30 mg/dL [300 mg/L]), 2+ (100 mg/dL [1,000 mg/L]), 3+ (300 mg/dL [3,000 mg/L]), or 4+ (greater than 1,000 mg/dL [10,000 mg/L]). Benchtop portable analyzers designed for point-of-care testing are increasingly used as an alternative to visual urinalysis test-strip evaluation and provide rapid results for urinary albumin-to-creatinine ratio.

3 Dipstick test strips that are specific for low levels of albuminuria (30-300 mg/day) should be employed when one is screening individuals at risk for CKD. For example, the Accutest Microalbumin/Creatinine 2-1 Strips (Jant Pharmacal) is a semi-quantitative test for both albumin and creatinine in a spot urine sample. In patients with a positive protein or albumin dipstick test, a 24-hour urine collection with measurement of albumin excretion can be used to precisely quantitate the degree of albuminuria. However, this method requires a high degree of patient compliance and is being replaced by a similarly accurate but less cumbersome technique: calculation of the ratio of protein or albumin (in milligrams) to creatinine (in grams [or mmol]) in an untimed (spot) urine specimen. The normal ratio, KDIGO category A1, is less than 30 mg albumin or less than 150 mg protein per gram of creatinine (3 mg albumin per mmol of creatinine or 15 mg protein per mmol of creatinine).[2] Category A2 is values between 30 and 300 mg/g (3.4 to 33.9 mg/mmol)and A3 is greater than 300 mg/g (33.9 mg/mmol).[2] Positive test results should be repeated, particularly in patients without an underlying cause for CKD, such as diabetes or hypertension. Monitoring CKD progression involves routine measurement of the albumin-to-creatinine ratio (UACR), whereas for patients with advanced CKD or KDIGO category A3, the protein-to-creatinine ratio (PCR) can be used to monitor kidney disease progression.

The albumin-to-creatinine ratio has also been incorporated into a CKD classification system as recommended by a Work Group of the Kidney Disease: Improving Global Outcomes (KDIGO).[2] This standardized "CGA" scoring system requires evaluation of both estimated GFR (G1-G5) and albuminuria (A1-A3) in a given patient. This approach aids in evaluating prognosis of CKD outcomes rather than relying on estimated glomerular filtration rate (eGFR) alone. A detailed description of how to apply this CGA classification system in the monitoring plan for CKD patients is provided in Chapter 62, Chronic Kidney Disease.

Specific Gravity

Specific gravity is a measure of urine weight relative to water (1.00) that is performed using a refractometer. Thus, specific gravity is dependent on water intake and urine-concentrating ability. Normal values range from 1.003 to 1.030. Osmolality, which is a measure of the number of solute particles in the urine, is a more accurate measure of the kidney's ability to make a concentrated urine. Generally, the two values correlate; however, when large quantities of heavier molecules, such as glucose, are in the urine, the specific gravity may be elevated relative to the osmolality. These tests are used in the assessment of urine-concentrating ability and are most informative when interpreted along with the hydration status of the patient and plasma osmolality.

Microscopic Analysis of Urine

Microscopic examination of the urine is helpful to evaluate the etiology of kidney injury or disease. Formed elements that may be detected in the urine include erythrocytes and leukocytes, casts, and crystals which aids in the differential diagnosis. Hematuria may be glomerular, renal, or urologic in etiology. Hematuria is defined as more than three red blood cells per high-power field (HPF), and the presence of dysmorphic red blood cells suggest glomerular etiology. White blood cells may be present in the urine in association with infection or inflammatory conditions, such as interstitial nephritis. More than two cells/HPF for men and 5 cells/HPF for women is usually considered abnormal. Contamination of the sample should also be considered when there are many cells and may be a result of the presence of menses or of inadequate sample collection. Casts are cylindrical and composed of Tamm-Horsfall mucoprotein and contents of tubule lumen. They originate from the distal convoluted tubule or collecting duct during periods of urinary concentration or very low urinary pH. The predominant contents determine the type of cast: hyaline, erythrocyte, leukocyte, epithelial, granular, waxy, fatty, or broad.

A variety of crystals may be visualized in the urinary sediment in healthy individuals as well as those with kidney diseases. The most common crystals are those composed of uric acid, calcium oxalate, calcium phosphate, calcium magnesium ammonium pyrophosphate, and cystine. Many of these have a unique crystalline form, which permits them to be identified with microscopy. Images of common types of urinary casts and crystals can be found at publicly available Web sites such as https://openi.nlm.nih.gov/detailedresult?img=PMC4525130_cnr-4-137-g001&req=4 [Last Accessed August 4, 2022].

Serum or Blood Urea Nitrogen

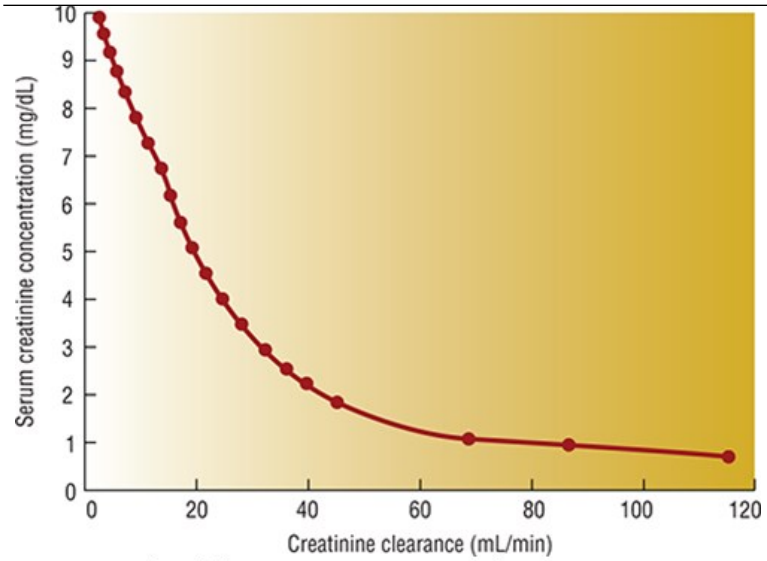
Amino acids metabolized to ammonia are subsequently converted in the liver to urea, the production of which is dependent on protein availability (diet) and hepatic function. Urea undergoes glomerular filtration followed by reabsorption of up to 50% of the filtered load in the proximal tubule. The normal blood urea nitrogen (BUN) is in the range of 5 to 20 mg/dL (1.8-7.1 mmol/L). The reabsorption rate of urea is predominantly dependent on the reabsorption of water. The excretion of urea may, therefore, be decreased under conditions that necessitate water conservation such as dehydration, although the GFR may be normal or only slightly reduced. This condition is evident when a patient exhibits prerenal azotemia, or an increase of the BUN to a greater extent than the S_{cr}. The normal BUN-to-creatinine ratio is 10 to 15:1 using conventional units (or 40-60:1 when both are expressed in identical molar units), and an elevated ratio is suggestive of a decreased effective circulating volume, which stimulates increased water, and hence, urea reabsorption. Creatinine is not reabsorbed to any significant extent by the kidneys. Despite these limitations, the BUN is usually used in combination with the S_{cr} as a simple screening test for the detection of kidney dysfunction.

Serum and Urine Creatinine

Creatinine remains the most widely used endogenous biomarker for the detection of kidney disease. The concentration of creatinine in serum is a function of creatinine production and kidney excretion. Creatinine is a product of creatine metabolism from muscle; therefore, its production is directly dependent on muscle mass. At steady state, the "normal" S_{cr} range is generally reported as 0.5 to 1.2 mg/dL (44-106 µmol/L) for males and females. Creatinine is eliminated primarily by glomerular filtration, and as GFR declines, the S_{cr} rises (Fig. e60-4).

FIGURE e60-4

Relationship between serum creatinine and creatinine clearance.



The National Health and Nutrition Examination Survey (NHANES) revealed a mean S_{cr} in Caucasian women and men of 0.73 mg/dL (65 µmol/L)and 0.95 mg/dL (84 µmol/L), respectively.[16] Values were lower among people of Mexican descent, and higher among those of African descent. For all groups, the S_{cr} increased with age. Although the S_{cr} alone is not an optimal measure of kidney function, it is often used as a marker for referral to a nephrologist. There is presently no accepted single standard for an "abnormal" S_{cr}, as it is dependent on gender, age, and lean body mass.

Standardized S_{cr} assays are now used in most hospital clinical laboratories.[17] The method involves calibration of creatinine values based on standardized reagents that are traceable to an isotope dilution-mass spectrometry (IDMS) method. This approach has significantly reduced interlaboratory variability in S_{cr} values, and has resulted in a downward shift of the "normal range" for S_{cr} values by 0.1 to 0.2 mg/dL (9-18 µmol/L) compared to noncalibrated ranges. Other modifications include reporting S_{cr} values in mg/dL to two decimal places (eg, 0.93 mg/dL), and values in µmol/L to the nearest whole number (eg, 82 µmol/L). This practice is aimed at reducing rounding errors which previously contributed to bias between creatinine-based GFR or CL_{cr} estimates, but it does not improve GFR estimation in those without CKD.

Despite alterations in creatinine assay methods, many drugs such as 5-flucytosine or dobutamine may interfere with these assays resulting in false elevations or reductions in S_{cr} values. Other compounds are known to increase S_{cr} by inhibition of active tubular secretion. Among these are cimetidine and trimethoprim, which compete for creatinine secretion at the cationic transport system in a dose-dependent fashion. Other drugs known to interfere with the active tubular secretion of creatinine include rilpivirine, dolutegravir, cobicistat, pyrimethamine, and amiodarone. These interactions typically result in S_{cr} elevations of 0.1 to 0.4 mg/dL (0.9-35 µmol/L) with apparent reductions in CL_{cr} of up to 30 mL/min/1.73 m^2 (0.29 mL/s/m^2).[18]

The S_{cr} is dependent on the "input" function, or formation rate, and "output" function, or elimination rate. Its formation rate depends on the zero-order production from creatine metabolism, as well as input from other sources, such as dietary intake. Over 95% of creatine stores are found in skeletal muscle, with creatine metabolism being directly proportional to muscle mass. Thus, individuals with more muscle mass have a higher S_{cr} at any given degree of kidney function than those with less muscle mass. Strenuous exercise is associated with an increase of approximately 10% in the S_{cr}. In contrast, cachectic patients, as the result of minimal muscle mass, will have very low S_{cr}, as do those with spinal cord injuries. Elderly patients and those with poor nutrition may also have low S_{cr} (less than 1.0 mg/dL [88 µmol/L]) secondary to decreased muscle mass.

Creatine or methyl guanidine acetic acid is found in many commonly ingested food sources such as fish and red meat. During the cooking of meat, some creatine is converted to creatinine, which is rapidly absorbed following ingestion. S_{cr} may rise as much as 50% within 2 hours of a meat meal and

remain elevated for as long as 8 to 24 hours.[19] Creatine is used as a dietary supplement to increase skeletal muscle stores of phosphocreatine, leading to adenosine triphosphate (ATP) resynthesis of adenosine diphosphate (ADP). The effect of creatine ingestion on the S_{cr} concentration is unclear. Short- and long-term administration of creatine increases S_{cr} by 25% to 40%[20] Thus, it is important to question ambulatory patients regarding their dietary intake for the 24 hours preceding the measurement of S_{cr} or CL_{cr}.

Diurnal variation in S_{cr} may also affect the accuracy of the CL_{cr} determination. Although the fluctuation is minimal, the observed peak plasma creatinine concentration generally occurs at approximately 7:00 PM, whereas the nadir is in the morning. The impact of diurnal variation is minimized by using S_{cr} measurements that are drawn at similar times during longitudinal evaluations, or using 24-hour urine collections for CL_{cr} measurements.

Serum and Urine Cystatin C

Cystatin C (cysC) is a 132-amino-acid (13.3-kDa) cysteine protease inhibitor produced by all nucleated cells of the body that is considered a biomarker of kidney function. It is freely filtered at the glomerulus and undergoes both reabsorption and catabolism in the proximal tubule. The renal handling of this biomarker is distinctly different from creatinine and exogenous GFR markers such as inulin, iohexol, and iothalamate. Originally introduced in Europe, it was recommended as a biomarker of kidney function because of findings that serum concentrations significantly correlated with GFR and S_{cr}. The range of normal serum cysC values is 0.55 to 1.18 mg/L (41-88 nmol/L) for women and 0.60 to 1.11 mg/L (45-83 nmol/L) for men based on data from the NHANES study.[21] It was hypothesized that since cysC production is not affected by muscle mass, it would provide a more reliable estimate of kidney function than S_{cr}. It is known that serum cysC concentrations can be altered by many factors other than kidney function, such as age, nutritional status, gender, weight, height, cigarette smoking, serum C-reactive protein levels, steroid therapy, and rheumatoid arthritis.[22] Serum cysC concentration has been shown to perform better than S_{cr} for predicting contrast-induced kidney injury, resulting in a new definition of contrast-induced acute kidney injury (CI-AKI), consisting of a more than 10% increase in cysC within 24 hours after exposure to contrast media.[23] Serum cysC also detected AKI up to 2 days earlier than S_{cr} in critically ill patients,[24] and cysC concentration was a better predictor of AKI in pediatric cardiac surgery patients.[25] However, serum cysC may be a less sensitive biomarker than creatinine for detecting AKI in the postoperative period.[26] Post-op cardiac surgery patients with elevated urinary cysC-to-creatinine ratios had the highest prevalence of developing AKI.[27] S_{cr} does not peak until 48 hours after intensive care unit (ICU) admission, suggesting that urinary cysC may be beneficial in early diagnosis of AKI. Because it is normally reabsorbed and metabolized in the renal proximal tubule, it is hypothesized that tubular damage would lead to increased urinary excretion of cysC. These differential findings suggest that the role of cysC in assisting with the diagnosis of AKI is yet to be fully determined.

Urinary Biomarkers for Detection of Acute Kidney Injury

Urinary biomarkers, such as kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), among others, have shown promise in detecting AKI (see Chapter 61, Acute Kidney Injury). β-Trace protein (BTP) has also been proposed as an alternate endogenous marker of GFR. Similar to cysC, it is a low-molecular-weight glycoprotein (168 amino acids) that is filtered through the glomerular basement membrane and reabsorbed in the renal proximal tubule. Elevated serum concentrations of BTP may be seen in patients with CKD,[28] kidney transplant recipients,[29] and children.[30] Other markers of early AKI include urinary tissue inhibitor of metalloproteinase 2 (TIMP-2) and urinary insulin-like growth factor binding protein 7 (IGFBP-7). These two biomarkers are important because they are involved in G1 cell cycle arrest of renal tubular cells during the early period of cell injury. Combining these markers into a duplex "TIMP-2 × IGFBP-7" biomarker algorithm in over 500 patients accurately predicted AKI following cardiac surgery in high-risk patients.[31,32] These results supported the FDA approval of NephroCheck® (Astute Medical, Inc; https://www.nephrocheck.com/us/) as a urinary diagnostic device indicated for early detection of AKI.

MEASUREMENT OF KIDNEY FUNCTION

The gold standard quantitative index of kidney function is a measured GFR (mGFR). A variety of methods may be used to measure and estimate kidney function in the acute care and ambulatory settings. Measurement of GFR is important for early recognition and monitoring of patients with CKD.

It is important to recognize conditions that may alter kidney function independent of underlying renal pathology. For example, protein intake, such as

oral protein loading or an infusion of amino acid solution, may increase GFR. As a result, inter- and intrasubject variability must be considered when GFR is used as a longitudinal marker of kidney function. Dietary protein intake correlates with GFR in healthy subjects. Subjects who are vegetarian have a lower GFR because of their reduced dietary protein intake relative to individuals who consume a similar caloric but normal-protein-content diet. Findings from the nurses' health study[33] indicate that longitudinal changes in GFR are independent of the source of protein (nondairy animal, dairy, or vegetable) in women with normal kidney function. However, women with mild renal insufficiency (GFR 71 ± 7 mL/min [1.18 ± 0.12 mL/s]) who consumed the highest amount of protein (93 g/day) had a threefold greater risk of a more than or equal to 5 mL/min (0.08 mL/s) decline in GFR compared to the lowest protein group (60 g/day); rates of decline were highest in those consuming nondairy animal protein. The increased GFR following a protein load is the result of renal vasodilation accompanied by an increased renal plasma flow. Therefore, assessment of a mGFR must consider the dietary protein status of the patient at the time of the study.

Measurement of Glomerular Filtration Rate

4 A mGFR remains the single best index of kidney function, and this method is routinely employed worldwide in the evaluation of kidney transplant recipients and donors. As renal mass declines in the presence of age-related loss of nephrons or disease states such as hypertension or diabetes, there is a progressive decline in GFR. The rate of decline in GFR can be used to predict the time to onset of stage 5 CKD, and the risk of complications of CKD.

The GFR is expressed as the volume of plasma filtered across the glomerulus per unit time, based on total kidney blood flow and capillary hemodynamics. The normal values for GFR are 127 ± 20 mL/min/1.73 m^2 (1.22 ± 0.19 mL/s/m^2) and 118 ± 20 mL/min/1.73 m^2 (1.14 ± 0.19 mL/s/m^2) in healthy men and women, respectively. These measured values closely approximate what one would predict if the normal kidney blood flow was approximately 1000 mL/min/1.73 m^2 (9.63 mL/s/m^2), plasma volume was 60% of blood volume, and filtration fraction across the glomerulus was 20%. In that situation the normal GFR would be expected to be approximately 120 mL/min/1.73 m^2 (1.16 mL/s/m^2).

Optimal clinical measurement of GFR involves determining the renal clearance of a substance that is freely filtered without additional clearance because of tubular secretion or reduction as the result of reabsorption. Additionally, the substance should not be susceptible to metabolism within renal tissues and should not alter kidney function. Given these conditions, the mGFR is equivalent to the renal clearance of the solute marker:

$\text{GFR} = \text{renalCL} = (A_e)/\text{AUC}_{0-t}$GFR=renalCL=(Ae)/AUC0−t

where renal CL is renal clearance of the marker, A_e is the amount of marker excreted in the urine in a specified period of time, t, and $AUC_{0\text{-}t}$ is the area under the plasma-concentration-versus-time curve of the marker.

Under steady-state conditions, for example, during a continuous infusion of the marker, the expression simplifies to

$\text{GFR} = \text{renalCL} = (A_e)/[(C_{ss}) \times t]$GFR=renalCL=(Ae)/[(Css)×t]

where C_{ss} is the steady-state plasma concentration of the marker achieved during continuous infusion. The continuous infusion method can also be employed without urine collection, where plasma clearance is calculated as CL = infusion rate/C_{ss}. This method is dependent on the attainment of steady-state plasma concentrations and accurate measurement of infusate concentrations. Plasma clearance can also be determined following a single-dose IV injection with the collection of multiple blood samples to estimate area under the curve ($AUC_{0\text{-}\infty}$). Here, clearance is calculated as CL = dose/AUC. These plasma clearance methods commonly yield clearance values 10% to 15% higher than GFR measured by urine collection methods.[34]

5 Several markers have been used for the measurement of GFR and include both exogenous and endogenous compounds (see Table e60-1). Although they generally provide an accurate measurement, use of exogenous GFR markers such as inulin, sinistrin, iothalamate, iohexol, and radioisotopes requires specialized administration techniques and detection methods for the quantification of concentrations in serum and urine so are not practical for routine clinical use. They are most commonly used in the research setting. Conversely, methods that employ endogenous compounds, such as creatinine or cysC, require less technical expertise, but produce results with greater variability. The GFR marker of choice depends on the purpose and cost of the compound. Radiolabeled compounds such as ^{125}I-iothalamate are more expensive than nonradiolabeled iothalamate (Conray-60, Mallincrodt) or iohexol.

TABLE e60-1

Markers of Kidney Function

Renal plasma/blood flow	PAH ^{131}I-OIH ^{99m}Tc-MAG3
Glomerular filtration rate	Inulin, sinistrin Iothalamate Iohexol ^{99m}Tc-DTPA ^{125}I- Iothalamate Creatinine cysC
Tubular function	PAH NMN TEA β_2-Microglobulin RBP Protein HC (α_1-microglobulin) NAG AAP ABP

^{1}I-OIH, ^{131}I-orthoiodohippurate; ^{99m}Tc-DTPA, ^{99m}Tc-diethylenetriaminepentaacetic acid; ^{99m}Tc-MAG3, ^{99m}Tc-mercaptoacetyltriglycine; AAP, alanine aminopeptidase; ABP, adenosine binding protein; cysC, cystatin C; NAG, *N*-acetylglucosaminidase; NMN, N^1-methylnicotinamide; PAH, *p*-aminohippurate; RBP, retinol-binding protein; TEA, tetraethylammonium.

Iothalamate Clearance

Iothalamate is an iodine-containing radiocontrast agent that is available in both radiolabeled (^{125}I) and non-radiolabeled forms. This agent is handled in a manner similar to that of inulin; it is freely filtered at the glomerulus and does not undergo substantial tubular secretion or reabsorption. The non-radiolabeled form is most widely used to measure GFR in ambulatory and research settings, and can safely be administered by IV bolus, continuous infusion, or subcutaneous injection. Plasma clearance methods that do not require urine collections are highly correlated with renal clearance, making them particularly well-suited for longitudinal evaluations of kidney function.[35] These plasma clearance methods require two-compartment modeling approaches because accuracy is dependent on duration of sampling. For example, short sampling intervals can overestimate GFR, particularly in patients with severely reduced GFR.[35] In individuals with GFR more than 30 mL/min/1.73 m^2 (0.29 mL/s/m^2), a 2-hour sampling strategy yields GFR values that are up to 54% higher compared with 10-hour sampling, whereas the 5-hour sampling is 17% higher. In individuals with GFR less than 30 mL/min/1.73 m^2 (0.29 mL/s/m^2), 5-hour GFR is 36% higher and 2-hour GFR is 126% higher than the 10-hour measurement. Hence, a 5- to 7-hour sampling period with eight plasma samples may be the most appropriate and feasible approach for most GFR evaluations.

Iohexol

Iohexol, a nonionic, low osmolar, iodinated contrast agent, is widely used as a gold standard measure of GFR. Iohexol has a molecular weight of 821 Da, is low protein binding, and is eliminated almost entirely by glomerular filtration. Iohexol plasma and renal clearance strongly correlate with iothalamate and support use of iohexol as an alternative marker for the measurement of GFR. One advantage of this agent is that a limited number of plasma samples can be used to quantify iohexol plasma clearance, with as few as a single sample.[36] The sampling time depends on the subject's eGFR: 180 min if GFR is normal, 300 to 360 min if GFR between 30 and 60 mL/min (0.5 to 1 mL/s) and 600 to 1440 min if GFR is below 30 mL/min (0.5 mL/s).[37–39]

$$\text{Equation}: \text{GFR} = (1/(t/V + 0.0016) * \ln(\text{Dose}/(V * Ct)(\text{inmL min}))$$Equation:GFR=(1/(t/V+0.0016)*ln (Dose/(V*Ct)(inmLmin))
Vmale: 166 *W+ 2490

Vfemale: 95*W+ 6170

Ct is the sample concentration (μg/mL) at time t (minute), V is the apparent volume of distribution (mL), and W is the weight (kg).

In Sweden, a mGFR using plasma iohexol clearance is routinely employed to monitor advanced CKD progression during the pretransplant period.[40]

Radiolabeled Markers

The GFR has also been quantified using radiolabeled markers, such as ^{125}I-iothalamate (614 Da, radioactive half-life of 60 days), ^{99m}Tc-DPTA (393 Da, radioactive half-life of 6.03 hours), and ^{51}Cr-ethylenediaminetetraacetic acid (^{51}Cr-EDTA; 292 Da, radioactive half-life of 27 days).[41] These relatively small molecules are minimally bound to plasma proteins and do not undergo tubular secretion or reabsorption to any significant degree. ^{125}I-iothalamate and ^{99m}Tc-DPTA are used in the United States, whereas ^{51}Cr-EDTA is used extensively in Europe. The use of radiolabeled markers allows one to determine the individual contribution of each kidney to total kidney function. The nonrenal clearance of these agents is low (3-8 mL/min [0.05-0.13 mL/s]), suggesting that plasma clearance is an acceptable technique except in patients with severe renal insufficiency (GFR less than 30 mL/min [0.50 mL/s]). Indeed, highly significant correlations between renal clearance among radiolabeled markers has been demonstrated.[41] Although total radioactive exposure to patients is usually minimal, use of one of these agents does require compliance with radiation safety committees and appropriate biohazard waste disposal.

Optical Real-Time Glomerular Filtration Rate Markers

A clinically applicable technique to rapidly measure GFR, particularly in critically ill patients with unstable kidney function, is highly desirable. The currently available GFR measurement approaches, as outlined above, are technically demanding, time-consuming, and often cost-prohibitive, so they are not practical for routine clinical use. Rapid, accurate, safe, and inexpensive techniques are in development to address this need. For example, small, nontoxic, exogenously administered fluorescent tracers are being investigated for "real-time" GFR measurement, and at least two have entered early-phase clinical trials. Both methods involve administration of optically active compounds, with continuous detection of the fluorescence signal using fiber optic or photonics technologies. One system involving injection of fluorescent dextran molecules with blood sampling and rapid (bedside) detection over 120 minutes (FAST BioMedical; Indianapolis, IN).[42] Another method involves injection of a hydrophilic pegylated pyrazine dye (MB-102), with continuous detection using a transdermal noninvasive optical renal function monitor (ORFM) device (MediBeacon, LLC; St. Louis, MO).[43]

Measured Creatinine Clearance

Although the measured CL_{cr} (mCL_{cr}) has been used as an approximation of GFR for decades, it has limited clinical utility for a multiplicity of reasons. Short-duration witnessed mCL_{cr} correlates well with mGFR based on iothalamate clearance performed using the single-injection technique. However, diurnal variations in S_{cr} may impact CL_{cr}. This test is usually performed over a 24-hour period with the S_{cr} obtained in the morning. Inaccuracy can result from over- or under- collections, and interconversion between creatinine and creatine when urine is not maintained at a pH less than 6.

An important limitation of using creatinine as a filtration marker is that it undergoes tubular secretion. Tubular secretion augments the filtered creatinine by approximately 10% in subjects with normal kidney function. Tubular secretion, however, increases to as much as 100% in patients with kidney disease, resulting in mCL_{cr} values that markedly overestimate GFR. In CKD stage 4-5, one approach is to measure creatinine and urea in a 24-hour collection and take an average of the clearance of these small molecules. Since urea is freely filtered and reabsorbed, averaging its clearance with

creatinine adjusts the over-estimation based on creatinine alone.

Estimation of Glomerular Filtration Rate

Serum creatinine and other clinical variables are used to calculate eGFR. These estimates are commonly used for the detection, diagnosis, and management of kidney diseases. Creatinine-based eGFR guide our clinical decision making, especially as it pertains to the initiation, discontinuation, and dosing of medications. Clinical laboratories in the United States automatically calculate and report eGFR when reporting basic or comprehensive metabolic panels that contains serum creatinine. Many GFR estimating equations have been developed (see Table e60-2). The initial equation was derived from multiple regression analysis of data obtained from the 1,628 patients enrolled in the Modification of Diet in Renal Disease (MDRD) study where GFR was measured using the clearance of ^{125}I-iothalamate as a gold standard.[44] The original four-variable MDRD equation based on Scr, age, sex, and race was updated with the standardization of the Scr assay (MDRD4-IDMS). However, this equation was shown to be inaccurate at GFR greater than 60 mL/min/1.73 m^2, for reasons not associated with standardization of S_{cr} (IDMS) assay results. The MDRD equation is no longer recommended for clinical use and has since been replaced with newer eGFR equations described below.

TABLE e60-2

Equations for the Estimation of Glomerular Filtration Rate in Adults with Stable Kidney Function

Creatinine-based eGFR equations	
MDRD-IDMS[93]	$eGFR = 175 \times (S_{cr})^{-1.154} \times (age)^{-0.203} \times (0.742 \text{ if patient is female}) \times (1.210 \text{ if Black patient})$
CKD-EPI $_{creat}$[45]	$eGFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr/,}\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if Black patient]}$
CKD-EPI$_{creat}$ (race free)[58]	$eGFR = 142 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.2} \times 0.9938^{Age} \times 1.012 \text{ [if female]}$
Cystatin C–based eGFR equations	
CKD-EPI$_{cysC}$[49]	$eGFR = 133 \times \min(cysC/0.8, 1)^{-0.499} \times \max(cysC/0.8, 1)^{-1.328} \times 0.996(age) \times 0.932 \text{ [if female]}$
CKD-EPI$_{creat\text{-}cysC}$[49]	$eGFR = 135 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-0.601} \times \min(cysC/0.8, 1)^{-0.375} \times \max(cysC/0.8, 1)^{-0.711} \times 0.995^{Age} \times 0.969 \text{ [if female]} \times 1.08 \text{ [if Black patient]}$
CKD-EPI$_{creat\text{-}cysC}$ (race free)[58]	$eGFR = 135 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-0.544} \times \min(cysC/0.8, 1)^{-0.323} \times \max(cysC/0.8, 1)^{-0.778} \times 0.996^{Age} \times 0.963 \text{ [if female]}$

CKD, chronic kidney disease; cysC, cystatin C; eGFR, estimated glomerular filtration rate; min, minute; S_{cr}, serum or plasma creatinine (mg/dL).

κ is 0.7 for females and 0.9 for males, min indicates the minimum of S_{cr}/κ or 1, and max indicates the maximum of Scr/κ or 1. For SI conversion purposes serum/plasma creatinine is converted from µmol/L to mg/dL by multiplying by 0.0113. Conversion from eGFR conventional units of mL/min/1.73 m^2 to eGFR SI units of mL/s/m^2 requires multiplication by 0.00963; conversion from creatinine clearance or eGFR conventional units of mL/min to SI units of mL/s requires multiplication by 0.0167; cystatin C in nmol/L can be converted to mg/L by multiplication using 0.01335 as the conversion factor.

CKD-EPI Equation

A single eGFR equation may not be best suited for all populations, and choice of equation has been shown to impact CKD prevalence estimates. The Chronic Kidney Disease Epidemiology Collaboration (CKD–EPI)[45] was developed to improve the accuracy of GFR estimates across the spectrum of kidney function. The CKD-EPI equation was developed from pooled study data involving 5,500 patients (including the original MDRD population), with mean GFR values of 68 ± 40 mL/min/1.73 m^2 (range 2-190 mL/min/1.73 m^2). The CKD-EPI equation is less biased (2.5 vs 5.5 mL/min/1.73 m^2) but similarly imprecise compared to MDRD4.[46] Specifically, the bias of the CKD-EPI equation is 61% to 75% lower than the MDRD equation for patients with eGFR of 60 to 119 mL/min/1.73 m^2.[46] Based on these findings, the CKD-EPI equation was deemed more appropriate for estimating GFR in individuals with eGFR values over 60 mL/min/1.73 m^2. National and international guidelines subsequently recommended that clinical laboratories switch from the MDRD4 to CKD-EPI equation for routine automated reporting.[2]

Kidney function values derived using eGFR equations may overestimate CG equation derived values for eCL_{cr} and thus may impact corresponding dosing recommendations. For example, use of MDRD-derived eGFR (expressed in mL/min) resulted in a failure to make manufacturer-recommended dose reductions for enoxaparin and the glycoprotein IIb/IIIa inhibitor (GPI) eptifibatide in up to 50% of patients. The eGFR-derived doses were correlated with major bleeding episodes (odds ratio 1.57 [95% CI 1.35-1.84]).[47] To date, use of eGFR for individualized drug dosing has not been comprehensively evaluated and automatic substitution of eGFR in place of eCLcr or mCL_{cr} for drug dose calculations should be avoided.

Cystatin C–Based Equations

Addition of serum cysC as a covariate in equations to estimate GFR has been employed as a means to improve creatinine-based estimations of GFR that historically were limited to the following variables; lean body mass (LM), age, sex, race, and S_{cr}.[48,49] Combining cysC and S_{cr} in the CKD-EPI equation improves precision and accuracy of GFR estimates across the range of GFRs.[49]

A significant limitation of serum cysC as a renal biomarker is the influence of body mass on serum concentrations. Fat-free mass is a significant covariate in GFR determination using cysC.[50,51] Using GFR measured as plasma inulin clearance, LM accounted for at least 16.3% of the variance in GFR values obtained using serum cysC. When using a serum cysC-based estimate of GFR, which incorporates the serum cysC, age, race, and sex, a higher prevalence of CKD was reported in obese patients compared to the MDRD4 equation.[51] Moreover, all-cause mortality rates may be significantly different between CKD-EPI and $CKD\text{-}EPI_{cysC}$ based estimates in older individuals. The CKD-EPI equation yields a U-shaped association, whereas the $CKD\text{-}EPI_{cysC}$ equation yields a linear relationship at eGFR values less than 60 mL/min/1.73 m^2, suggesting that cysC does not accurately predict mortality risk in older patients with low S_{cr}, reduced muscle mass, and malnutrition.[52] Because the combined use of serum cysC and serum creatinine in modified CKD-EPI equations generates improved estimates of GFR, the combined $CKD\text{-}EPI_{Scr\_cysC}$, equation (see Table e60-2) is recommended for use in patients where unreliable S_{cr} values are anticipated, such as extremes in body mass, diet, or creatinine assay interferences.[49]

A variety of online resources provide eGFR calculators to assist practitioners for the purpose of characterizing CKD stage. For example, NIH's NIDDK or the National Kidney Foundation websites provides an eGFR calculator using patient-specific data, with options to calculate eGFR using the MDRD4 or CKD-EPI equations. It should be noted that one must verify that a given equation is appropriate for the institutional creatinine reporting method.

Inclusion of a Race Coefficient in GFR Estimation

For over 20 years, GFR estimating equations used S_{cr}, age, sex (male or female), and race (Black or non-Black) to calculate an eGFR value. Originally, the race term in GFR estimating equations was found to improve equation accuracy since the mGFR was higher in people of African descent than Caucasian patients, and was meant to capture non-GFR determinants of S_{cr}.[53] Early work on the utility of eGFR equations in diverse ethnic groups resulted in modifications to them for use in some populations, including Japanese[54] and Chinese[55] populations. Recently, however, significant attention has been directed at addressing self-reported race as a social construct rather than a biological one. Since estimating equations that include a race coefficient use dichotomous response for Black race without regard to the proportion of a race or ancestry, and to reduce disparities in healthcare for Black individuals, many health systems began considering the use of alternative eGFR equations that do not require a race term.[53]

The potential implications of omitting race from eGFR equations that were originally developed with a race coefficient have been evaluated. Blending

or removing race coefficients resulted in decreased eGFR estimates as well as increased reclassifications of CKD stage.[56] For example, if the race coefficient is removed from the original CKD-EPI equation, which was developed for use with a race coefficient, then the estimated CKD prevalence among US Black adults doubles. Additionally, removing the race coefficient could impact dose adjustment of medications in up to 40% of Black adults.[57]

Recently, new race-free eGFR equations using data from the CKD-EPI cohort were developed.[58] The new race-free eGFR creatinine-based equation underestimates mGFR in Black participants by 3.6 mL/min/1.73 m^2 with 87.2% of values falling within 30% of mGFR. The new eGFRcys equation overestimates mGFR in Black participants by 0.1 mL/min/1.73 m^2 with 84.6% of estimated values within 30% of mGFR. Lastly, the new combined eGFRcr-cys equation had the best performance with a bias of 0.1 mL/min/1.73 m^2 and 90.5% of estimated values within 30% of mGFR. An expert task force from the National Kidney Foundation and American Society of Nephrology (NKF-ASN) published recommendations for race-free equations that are now widely endorsed.[59] The NKF-ASN Task Force recommends use of the new eGFR equation based on creatinine that does not require a race term, for use in categorizing and staging CKD. The Task Force also recommends use of the combined creatinine-cystatin C–based eGFR equation once implementation barriers including widespread availability in clinical laboratories and reimbursement for cystatin C are removed.[59]

Estimation of Creatinine Clearance

Many equations describe the mathematical relationships between various patient factors and mCL_{cr}. Most equations incorporate factors such as age, gender, weight, and S_{cr}, without the need for urine collection. The most widely used estimate of creatinine clearance is the CG equation, which identified age and body mass as important covariates.[60] This was based on observations from 249 male patients with stable kidney function in whom the creatinine production rates were estimated. The CG based eCL_{cr} is calculated as follows[60]:

$$\begin{matrix}\text{Men}: \mathrm{CL_{cr}} = [(140-\text{age})\mathrm{ABW}]/(\mathrm{S_{cr}} \times 72) \\ \text{Women}: \mathrm{CL_{cr}} \times 0.85\end{matrix}$$ Men:CLcr=[(140−age)ABW]/(Scr×72)Women:CLcr×0.85

where ABW is actual body weight (kg), CL_{cr} is creatinine clearance in mL/min, and S_{cr} is serum or plasma creatinine (mg/dL). For SI conversion purposes serum creatinine is converted from µmol/L to mg/dL by multiplying by 0.0113. Conversion from creatinine clearance conventional units of mL/min to SI units of mL/s requires multiplication by 0.0167.

Estimated creatinine clearance (eCL_{cr}), using the CG equation, is one of the methods recommended by the FDA for stratifying patients in drug development pharmacokinetic studies,[3] and has been included most often in FDA-approved package inserts for new drug entities since the 1990s.[61]

One of the key considerations with the use of this equation is whether to use a modified weight index in place of actual body weight. Several modified weight indices have been proposed and this remains a controversial issue. For obese individuals, defined as those with a body mass index (BMI) greater than or equal to 30 kg/m^2 but less than 40 kg/m,[2] it is generally recommended that total or actual body weight be used. In morbidly obese individuals (BMI ≥40 kg/m,[2] obesity class III) an alternate measure of body weight such as lean body weight (LBW) reduces bias in the CG equation, where LBW is calculated as follows:

$$\begin{matrix}\mathrm{LBW(kg,\,males)} = (9270 \times \mathrm{weight})/(6680 + 216 \times \mathrm{BMI}) \\ \mathrm{LBW(kg,\,females)} = (9270 \times \mathrm{weight})/(8780 + 216 \times \mathrm{BMI})\end{matrix}$$ LBW(kg,males)=(9270×weight)/(6680+216×BMI)LBW(kg,females)=(9270×weight)/(8780+216×BMI)

and BMI is calculated as follows:

$$\mathrm{BMI}\left(\mathrm{kg/m^2}\right) = \mathrm{weight(kg)}/\mathrm{height(m)}^2$$ BMI(kg/m2)=weight(kg)/height(m)2

Regardless of the approach used to estimate kidney function in obese patients, it is imperative that drug therapy outcomes be monitored closely in this population.

ASSESSMENT OF KIDNEY FUNCTION IN SPECIAL POPULATIONS

Liver Disease

Evaluation of renal hemodynamics is particularly complicated in patients with liver disease and cirrhosis, where filtration fraction is associated with the degree of ascites, renal artery vasoconstriction, and vascular resistance.[62] The estimation of CL_{cr} or GFR can be problematic in patients with

preexisting liver disease and renal impairment. Lower-than-expected S_{cr} values may result from reduced muscle mass, protein-poor diet, and diminished hepatic synthesis of creatine (a precursor of creatinine), and fluid overload. These lower S_{cr} values can lead to significant overestimation of CL_{cr}. In fact, CG may overestimate the mCL_{cr} by 40% to 100% in patients with severe liver disease.[63]

Cystatin-C based eGFR equations may be more accurate than eGFR equations based on creatinine alone in patients with advanced liver disease. The $CKD\text{-}EPI_{cr\text{-}cysC}$ equation is more precise than the CG, CKD-EPI, or $CKD\text{-}EPI_{cystatin\ C}$ when compared to iothalamate-mGFR.[64] The accuracy of the $CKD\text{-}EPI_{cr\text{-}cysC}$ equation, measured as percentage of eGFR that differs by more than 30% with respect to mGFR, and is significantly less than mCL_{cr}, CG, MDRD, and $CKD\text{-}EPI_{creatinine}$ equations. In summary, kidney function assessment in patients with hepatic disease should be performed by measuring glomerular filtration rate, and GFR estimation equations that combine creatinine and cystatin C are preferred.

Unstable Kidney Function

Patients with unstable kidney function or AKI present a unique situation because S_{cr} values are changing, breaking the underlying steady-state assumption of all the above-mentioned estimating equations. Methods to measure GFR include ^{125}I-iothalamate, ^{51}Cr-EDTA, or iohexol clearance. Moderately strong evidence suggests that renal clearance of ^{51}Cr-EDTA or iothalamate and plasma clearance of ^{51}Cr-EDTA or iohexol are sufficiently accurate methods to measure GFR.[65] Some of these methods are cumbersome and expensive, limiting their implementation in the clinical setting. Plasma clearance of iohexol is a simpler method that has been implemented in a few centers in the United States. However, it is unclear if this is being used for repetitive measures of kidney function as is frequently employed in AKI.

The CKD-EPI equations cannot be used in the critically ill population with unstable kidney function, because they require S_{cr} to be in steady state. The 1-hour mCL_{cr} correlates poorly with the CG and MDRD equations in critically ill patients.[66] Both equations are similarly imprecise with wide confidence intervals. The precision and accuracy of several estimating equations (CG, MDRD, CKD-EPI, CysC) is poor compared to a 4-hour mCLcr in ICU patients, showing suboptimal precision and a large bias.[67]

Equations for unstable kidney function include Jelliffe or kinetic GFR equations. The Jelliffe equation for unstable kidney function utilizes volume of distribution of creatinine and creatinine kinetics to estimate CL_{cr} and has less bias compared to other estimating equations in the critically ill population.[68] Adjusting the Jelliffe equation for fluid balance in AKI results in values closest to mCL_{cr}.[69] An alternative kinetic eGFR equation, which estimates GFR on the basis of initial creatinine content, volume of distribution, creatinine production rate, and the quantitative difference between consecutive S_{cr} in a defined time period is also available.[70] The kinetic eGFR has been applied in AKI to evaluate the impact on drug dosing. The concordance between CG and kinetic eGFR for drug dosing is only 62%, compared to 75% with MDRD and kinetic eGFR.[71] Others found a maximum discordance rate of 16.4% for drug dosing when comparing different estimating equations (CG, MDRD, Jelliffe, modified Jelliffe) to mCL_{cr} for antimicrobial dosing. When using CG or MDRD estimates, the drug doses were all higher compared to modified Jelliffe eGFR.[72] It is anticipated that using the modified Jelliffe or kinetic eGFR in place of steady-state estimating equations will result in different drug dosing recommendations in AKI and careful consideration of the risk:benefit of each dosing regimen is warranted.

The Acute Disease Quality Initiative (ADQI) group published a consensus report on acute kidney disease and renal recovery where they recommend that additional research is needed to validate the use of non-steady-state estimating equations in AKI.[73] Their current recommendation is for the use of timed mCLcr in the setting of persistent AKI which is in steady state.[73]

Children

Neonatal kidney function is difficult to assess because of challenges in the collection of urine and blood samples, the frequent presence of a non-steady-state S_{cr}, maternal placental transfer of creatinine early after birth, and apparent disparity between development of glomerular and tubular function. Preterm infants demonstrate significantly reduced GFR prior to 34 weeks, which rapidly increases to that of term infants within the first week of life.[74] Thus, estimation of GFR is not recommended for infants younger than 1 week. Kidney function expressed as GFR standardized to body surface

area (BSA) increases with age and stabilizes at approximately 1 year. In older children, GFR is best assessed using standard measurement techniques for GFR. Subcutaneous administration of ^{125}I-iothalamate has been effectively used to measure GFR in children ranging in age from 1 to 20 years.[75] The Schwartz equation[76] was developed from a population of 349 children (1-19 years) with mild-to-moderate CKD enrolled in the Chronic Kidney Disease in Children (CKiD) study. This simple equation is commonly referred to as the Schwartz "Bedside" formula:

$$\mathrm{eGFR_{CKiDbed}} = 41.3 * [\text{height (m)}/\mathrm{S_{cr}inmg/dL}]$$
eGFRCKiDbed=41.3*[height (m)/Scrinmg/dL]

For SI conversion purposes serum creatinine is converted from µmol/L to mg/dL by multiplying by 0.0113. Schwartz et al.[77] developed another equation, CKiD full equation, adding cysC measurements in addition to Scr, and found high accuracy and precision and minimal bias in the CKiD population. For SI conversion purposes serum urea is converted from mmol/L to mg/dL by multiplying by 2.801, and serum cystatin C is converted from nmol/L to mg/L by multiplying by 0.01335.

$$\mathrm{eGFR_{CKiDfull}} = 39.8 \times (\text{height[m]}/\mathrm{Scr[mg/dL]})^{0.456} \times (1.8/\mathrm{cystatinC[mg/L]})^{0.418} \times (30/\mathrm{SUN[mg/dL]})^{0.079} \times 1.076(\text{ifmale}) \times (\text{height[m]}/1.4)^{0.179}$$
eGFRCKiDfull=39.8×(height[m]/Scr[mg/dL])0.456×(1.8/cystatinC[mg/L])0.418×(30/SUN[mg/dL])0.079×1.076(ifmale)×(height[m]/1.4)0.179

Older Adults

Generally, GFR is considered to decline as a function of age. The Baltimore Longitudinal Study on Aging (BLSA) showed that mCL_{cr} decreases at the rate of approximately 0.75 mL/min/1.73 m^2/yr (0.0072 mL/s/m^2/yr) beginning at the fourth decade of life.[78] Interestingly, after up to 23 years of follow-up, approximately one-third of the participants showed no change in kidney function from their baseline value, and a small number showed an increased clearance.[78] These changes may be a result of normal physiologic changes or of subclinical insults to the kidneys initiating the events leading to chronic progressive loss of kidney function.

Interpretation of S_{cr} alone is difficult in older adult patients primarily because of decreased muscle mass and the resultant lower production rate of creatinine. Thus, the S_{cr} often remains within the normal range despite a reduction in the number of functional nephrons. The adoption of standardized creatinine assays by clinical laboratories and reporting of S_{cr} values to two decimal places will likely improve the accuracy of kidney function estimation in older adults.

The CG formula provides a valid estimate of CL_{cr} in older populations.[60] In an analysis of the BLSA data set, the CG equation yielded the least biased estimate of mCl_{cr}, whereas the MDRD4 and CKD-EPI equations significantly overestimated the CG and mCl_{cr} values by 30% to 47%.[79] Rounding low S_{cr} values up to an arbitrary value of 1.0 mg/dL (88 µmol/L) result in CG values that significantly underestimate mCl_{cr} and uncorrected CG. The commonly accepted practice of fixing or rounding S_{cr} to an arbitrary value in older patients should be avoided.

IMPACT ON DRUG DOSING RECOMMENDATIONS

The automated reporting of eGFR in the clinical setting has led some practitioners to consider substituting eGFR in place of eCL_{cr} for drug dose adjustments as recommended in regulatory agency–approved product labeling. The prime concern with this approach, particularly in older adults, is that substitution of eGFR values in CL_{cr}-based dosage adjustment algorithms may result in dosing errors and toxicity especially for drugs with narrow therapeutic indices since eGFR tends to overestimate eCL_{cr}. For instance, MDRD eGFR values overestimate gentamicin clearance by up to 29%, whereas the CG CL_{cr} yields only 10% overestimation, and MDRD overestimates kidney function more as age increases.[80] Although use of an eGFR value (MDRD4 equation in mL/min based on a calculated BSA) yields dosage regimens for a subset of drugs that are similar to doses calculated using mGFR,[81] overestimation of kidney function using the MDRD4 equation may result in up to 30% to 60% higher doses for digoxin, amantadine, and various antimicrobials compared to doses calculated using eCL_{cr}.[82,83] It must be cautioned that use of eGFR in place of eCL_{cr} for drug dose adjustments does not align with the majority of drug development studies (and as reported in the product label) for FDA-approved drugs currently marketed. Moreover, although dosing concordance between eGFR and eCL_{cr} based estimates is high, drug dosing based on eGFR can lead to clinically significant dosing errors for drugs such as eptifibatide, tirofiban, and enoxaparin and in high-risk older adult populations.[84,85]

Use of modified eGFR and newer CKD-EPI equations including race free estimates to adjust drug doses has also been reported, but not fully validated. For example, the deindexed CKD-EPI$_{cr\text{-}cysC}$ equation (converted to mL/min) yields a 2.5-fold improvement in achieving target vancomycin trough values in critically ill patients, when compared to eCL$_{cr}$.[86] Of note, predicted trough values improve among those with normal GFR (greater than 120 mL/min [2 mL/s]), where underdosing is often problematic. Future areas yet to be fully evaluated include use of newer eGFR equations and deindexing values for drug dosing. A more detailed discussion of the utilization of kidney function estimates and renal dosing approaches is provided in Chapter 67, Personalized Pharmacotherapy for Patients with Chronic Kidney Disease.

MEASUREMENT OF RENAL PLASMA AND BLOOD FLOW

While rare in the clinical setting, renal plasma and blood flow are occasionally measured in research settings to evaluate hemodynamic changes related to disease or drug therapy. The kidneys receive approximately 20% of cardiac output. Representative values of renal blood flow in men and women are about 1,200 mL/min/1.73 m^2 and 1,000 mL/min/1.73 m^2 (11.6 and 9.6 mL/s/m^2), respectively. Renal plasma flow (RPF) is estimated to be 60% of blood flow assuming that the average hematocrit (HCT) is 40% (0.40) and that it can be measured by the use of model compounds that are eliminated from the plasma compartment on a single pass through the kidneys. Para-aminohippuric acid (PAH) is an organic anion that has been used extensively for the quantification of RPF. PAH is approximately 17% bound to plasma proteins and is eliminated extensively by active tubular secretion. Because PAH elimination is active, saturation of the transport processes should be anticipated, and concentrations of PAH in plasma should not exceed 10 mg/L.[87] The extraction ratio (ER) for PAH is 70% to 90% at plasma concentrations of 10 to 20 mg/L; hence, the term “effective” renal plasma flow (ERPF) has been used when the clearance of PAH is not corrected for the ER or if it is assumed to be 1. Normal values are about 650 mL/min (10.9 mL/s) for men and 600 mL/min (10.0 mL/s) for women. Children will reach normalized adult values by 3 years of age, and ERPF will begin to decline as a function of age after 30 years, reaching about one-half of its peak value by 90 years. The method for calculation of ERPF is based on the relationship between organ clearance, ER, and flow:

$$\mathrm{ERPF} = \mathrm{renalPAHCL} = \mathrm{RPF} \times \mathrm{ER}$$ ERPF=renalPAHCL=RPF×ER

Effective renal blood flow (ERBF) can be estimated from ERPF by assuming the extraction ratio is 1 and correcting for the red blood cell volume of the blood (HCT):

$$\mathrm{ERBF} = \mathrm{ERPF}/(1 - \mathrm{HCT})$$ ERBF=ERPF/(1−HCT)

ASSESSMENT OF TUBULAR FUNCTION

Although GFR is the best overall indicator of kidney function, it may not provide an accurate measure of tubular function (either secretory capacity or cellular function) suitable for use in the research environment. Since renal tubular function is directly related to renal blood flow, tubular secretion can be measured using surrogate markers such as PAH, as described above. Other compounds that are substrates for the organic cationic transporter (OCT) such as *N*^{1}-methylnicotinamide (NMN) and tetraethylammonium may be used as markers of cationic secretory capacity.

Semi-quantitative measures of tubular function are more widely used in clinical settings, focusing on detection of tubular injury within the nephron. Low-molecular-weight proteins located in the proximal tubule, such as β_2-microglobulin, can be used as urinary biomarkers to detect early tubular toxicity of some drugs including carboplatin, ifosfamide, and etoposide.[88] Other low-molecular-weight proteins used as markers of tubular function include retinol-binding protein (21 kDa), protein HC (also known as α_1-microglobulin, 27 kDa), KIM-1, NGAL, interleukin-18, and fatty-acid binding proteins (FABPs).[89] Under normal conditions, these proteins are freely filtered at the glomerulus and then completely reabsorbed by the proximal tubule. In the presence of tubular injury, these enzymes are increasingly excreted and appear in the urine. Although suggestive of tubular pathology, they are not entirely specific. For example, increased excretion could be due to an overload of the maximal reabsorptive capacity, leading to net excretion of the protein.

Examples of other biomarkers used to detect early renal tubular damage include *N*-acetylglucosaminidase, alanine aminopeptidase, alkaline phosphatase, γ-glutamyltransferase, pyruvate kinase, glutathione transferase, lysozyme, and pancreatic ribonuclease. *N*-acetylglucosaminidase and alanine aminopeptidase may be early predictors of early renal allograft rejection in kidney transplant patients.[90] *N*-acetylglucosaminidase is an enzyme

contained within the lysosome of the tubular cell and is released when the lysosome is damaged, whereas alanine aminopeptidase is an enzyme of the brush border. Both markers are increased approximately 2 days earlier than S_{cr} in patients with transplant rejection. Other biomarkers associated with fibrosis and collagen degradation in the kidney such as matrix metalloproteinases (ProMMP9) may also be associated with acute allograft rejection, interstitial fibrosis, and tubular atrophy.[91]

QUALITATIVE DIAGNOSTIC PROCEDURES

Radiologic Studies

7 The etiology of kidney disease can be evaluated using several qualitative diagnostic techniques, including radiography, ultrasonography, magnetic resonance imaging, and biopsy.[92] The standard radiograph of the kidneys, ureters, and bladder (the KUB) provides a gross estimate of kidney size and identifies the presence of calcifications. Although easy to perform, the value of the information is minimal, and more detailed evaluations are often necessary. The *IV urogram* (formerly known as IV pyelogram) involves the administration of a contrast agent to facilitate visualization of the urinary collecting system. It is primarily used in the assessment of structural changes that may be associated with hematuria, pyuria, or flank pain, resulting from recurrent urinary tract infections, obstruction, or stone formation. For patients with low GFRs, retrograde administration of dye into the ureters may be performed to facilitate visualization of the collecting system. Contrast agents are also employed during renal angiography for the assessment of renovascular disease. The captopril (angiotensin-converting enzyme inhibitor) test is also a useful adjunct. Under conditions of unilateral renal artery stenosis, the affected kidney produces large quantities of angiotensin II, which constricts the efferent arteriole to maintain GFR. The administration of captopril results in reduced uptake of the contrast agent because the efferent arteriole is dilated, thereby decreasing the perfusion pressure of the affected kidney. For patients with bilateral disease, a decrease in uptake is observed in both kidneys. Computed tomography is a cross-sectional anatomic imaging procedure. The procedure is frequently performed with contrast to enhance imaging. Spiral, or helical, computed tomography provides for three-dimensional visualization of tissues. Computed tomography is performed as a test for the evaluation of obstructive uropathy, malignancy, and infections of the kidney.

Renal Ultrasonography

Ultrasonography uses sound waves to generate a two-dimensional image. Evaluation includes assessment of shape and size, echogenicity, the urinary space (including the lower urinary tract), vasculature, and presence of masses.[92] The echogenicity of the kidney is compared with that of an adjacent organ—liver on the right and spleen on the left—with an increased echogenicity indicating an abnormal finding. Ultrasonography can distinguish the renal pyramids, medulla, and cortex, and abnormalities in structure, such as occurs with obstruction. Renal ultrasonography is also used as a guide for site localization during percutaneous kidney biopsy.

Magnetic Resonance Imaging

Magnetic resonance imaging is based on aligning hydrogen nuclei in the body with the use of a powerful magnet and applying radiofrequency pulses. The signals emitted by the hydrogen nuclei during realignment on repeated pulses allows for generation of the tissue image. Realignment times can also be altered with the use of contrast agents (gadolinium, gadopentetate), leading to increased signal intensity and improved imaging. Magnetic resonance imaging is useful for the assessment of obstruction, malignancy, and renovascular lesions.

Biopsy

Renal biopsy is used in several situations to guide diagnosis, evaluate progression, and support clinical decision making when clinical, laboratory, and imaging findings do not suffice. Proteinuria and hematuria are both associated with renal parenchymal disease. When less-invasive studies are unsuccessful in differentiating the cause and the possible causes have different therapeutic approaches, biopsy may be indicated. Functional status of the kidney is not assessed with biopsy, and severity of disease and progression is best measured using quantitative tests discussed above. Contraindications to renal biopsy include a solitary kidney, severe hypertension, bleeding disorder, severe anemia, cystic kidney, and hydronephrosis, among others. Complications resulting from biopsy primarily include hematuria, which may last for several days, and perirenal hematoma.

CONCLUSION

Approaches to evaluate kidney function in CKD patients include the CG equation for estimating CL_{cr}, various CKD-EPI equations for estimation of GFR, and determination of UACR as a marker of the integrity of the glomerular basement membrane. Measurement of GFR using exogenous administration of iothalamate, iohexol, or radioisotope techniques such as ^{99m}Tc-DPTA is increasingly being employed to assess progression of disease or acceptability of an individual to be a kidney donor. Other qualitative assessments of kidney function, such as radiography, computed tomography, magnetic resonance imaging, sonography, and biopsy, are most useful to identify the underlying cause of kidney disease.

ABBREVIATIONS

AASK	African American Study of Kidney Disease and Hypertension
ABC	ATB-binding cassette
ADP	adenosine diphosphate
AKI	acute kidney injury
ATP	adenosine triphosphate
AUC	area under the plasma concentration versus time curve
BIS	Berlin Initiative Study
BLSA	Baltimore Longitudinal Study on Aging
BMI	body mass index
BSA	body surface area
BTP	β-trace protein
BUN	blood urea nitrogen
CG	Cockcroft–Gault
CIAKI	contrast-induced acute kidney injury
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CKiD	Chronic Kidney Disease in Children
CL	clearance
CL_{cr}	creatinine clearance
^{51}Cr-EDTA	^{51}Cr-ethylenediaminetetraacetic acid
C_{ss}	concentration of a substance in plasma under steady-state conditions

CYP	cytochrome P450
cysC	cystatin C
eCL_{cr}	estimated creatinine clearance
eGFR	estimated glomerular filtration rate
ER	extraction ratio
ERBF	effective renal blood flow
ERPF	effective renal plasma flow
ESKD	end-stage kidney disease
FABP	fatty-acid binding protein
FDA	Food and Drug Administration
GFR	glomerular filtration rate
GPI	glycoprotein IIb/IIIa inhibitor
HCT	hematocrit
HIV	human immunodeficiency virus
IBW	ideal body weight
ICU	intensive care unit
IDMS	isotope dilution-mass spectrometry
IGFBP-7	insulin-like growth factor binding protein 7
^{131}I-OIH	^{131}I-orthoiodohippurate
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
KIM1	kidney injury molecule-1
KUB	kidneys, ureters, and bladder
LBW	lean body weight
LM	lean body mass
MATEs	multidrug and toxin extrusion proteins

mCL_{cr}	measured creatinine clearance
MCQ	Mayo Clinic Quadratic Equation
MDR1	multidrug resistance protein
MDRD	Modification of Diet in Renal Disease
MDRD4	four-variable Modification of Diet in Renal Disease study equation
mGFR	measured glomerular filtration rate
NHANES	National Health and Nutrition Examination Survey
NGAL	neutrophil gelatinase–associated lipocalin
NKDEP	National Kidney Disease Education Program
NKF	National Kidney Foundation
NMN	N^1-methylnicotinamide
OATs	organic anion transporters
OATPs	organic anion transporting polypeptides
OCTs	organic cation transporters
PAH	para-aminohippuric acid
P-GP	P-glycoprotein
RFR	renal function reserve
RPF	renal plasma flow
S_{cr}	serum creatinine concentration
SLC	solute-linked carrier
SUN	serum urea nitrogen
^{99m}Tc-DTPA	technetium-99m diethylenetriamine pentaacetic acid
^{99m}Tc-MAG3	^{99m}Tc-mercaptoacetyltriglycine
TIMP-2	tissue inhibitor of metalloproteinase 2

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SELF-ASSESSMENT QUESTIONS

1. The glomerulus is primarily responsible for ___ of unbound drug in the kidney.
   A. filtration
   B. reabsorption
   C. secretion
   D. endocytosis
2. Active drug secretion occurs most often in which of the following nephron segments?
   A. Glomerulus
   B. Proximal tubule
   C. Loop of Henle
   D. Distal tubule
3. Which of the following is/are involved in drug influx at the basolateral membrane of the proximal tubule?
   A. OAT1-3
   B. OCT1-3
   C. OAT4

D. Both A and B

4. According to the intact nephron hypothesis, single nephron GFR ___ in the surviving nephrons.

   A. decreases

   B. increases

   C. remains the same

5. The kidney is responsible for synthesizing each of the following hormones, *except*:

   A. Erythropoietin

   B. Prostaglandin

   C. PTH

   D. Renin

6. Which of the following kidney function indices is most influenced by changes in fluid or volume status?

   A. Serum creatinine

   B. Blood urea nitrogen

   C. Urine specific gravity

   D. Urine albumin to creatinine ratio

7. Which of the following kidney function indices is least affected by dietary protein intake?

   A. Serum creatinine

   B. Blood urea nitrogen

   C. Creatinine clearance

   D. Urine sodium

8. Which is the most appropriate method to quantify proteinuria in a patient with CKD risk factors such as diabetes?

   A. Spot or random urine total protein:creatinine ratio

   B. Spot or random urine albumin:creatinine ratio

   C. 24-hour urine protein excretion

   D. Urinalysis

9. Which of the following equations is most appropriate for estimating a patient's GFR for the purpose of determining their CKD category/stage?

   A. MDRD equation

   B. CKD-EPI$_{creatinine}$ equation

   C. CKD_cysC equation

   D. Cockcroft–Gault equation

10. When using the Cockcroft–Gault equation to estimate creatinine clearance in obese patients, it is recommended that lean body weight be used in patients with:

    A. BMI ≥40 kg/m^2

    B. BMI 30-39 kg/m^2

    C. BMI 25-29 kg/m^2

    D. None of the above

11. J.S. is a 70-year-old male of African American ancestry (5 ft 8 in. [173 cm], 85 kg) with a history of hypertension and CKD. His serum creatinine today is 1.50 mg/dL (133 µmol/L) (using the IDMS calibrated assay). What is his estimated creatinine clearance?

    A. 55.0 mL/min

    B. 43.5 mL/min

    C. 37.2 mL/min

    D. 29.4 mL/min

12. What is J.S.'s estimated GFR (in mL/min/1.73 m^2)?

    A. 50 mL/min/1.73 m^2

    B. 45 mL/min/1.73 m^2

    C. 35 mL/min/1.73 m^2

    D. 30 mL/min/1.73 m^2

13. What is J.S.'s estimated GFR when expressed in mL/min?

    A. 50 mL/min

    B. 53 mL/min

    C. 55 mL/min

    D. 57 mL/min

14. Progression to end-stage kidney disease can be estimated using all the following *except*:

    A. Age

    B. Urinary albumin:creatinine ratio

    C. Urinary cystatin C concentration

    D. Estimated GFR

15. In the clinical setting, the renal clearance of PAH is considered an index of ____.

    A. fractional excretion of sodium

B. renal plasma or blood flow

C. glomerular filtration rate

D. renal tubular reabsorption

SELF-ASSESSMENT QUESTION-ANSWERS

1. **A.** The glomerulus is the primary filtering unit in the kidney.
2. **B.** Secretion is an active process taking place in the proximal tubule and facilitates the elimination of compounds from kidney circulation into the tubular lumen.
3. **D.** OAT1-3 and OCT1-3 are influx transporters known to be involved in transport of drugs into the proximal tubule.
4. **C.** In kidney disease, the remaining intact nephrons hyperfilter to maintain the total GFR.
5. **C.** PTH is produced by the parathyroid gland.
6. **C.** Urine specific gravity would be most influenced by volume status. The urine albumin to creatinine ratio would be less influenced since urine concentration impact is in the numerator and denominator of the ratio.
7. **D.** Urine sodium is not impacted by dietary protein intake but would be impacted by dietary sodium intake or use of diuretics.
8. **B.** The random UACR is a sensitive test for quantifying proteinuria in early kidney disease (ie, stage 1-2, where GFR is intact or mildly reduced) in at-risk patients.
9. **B.** The CKD $EPI_{creatinine}$ equation is used by most laboratories to estimate GFR for the purpose of staging CKD.
10. **A.** Lean body weight should be used when the BMI is greater than 40 kg/m^2, which is considered morbid obesity.
11. **A.** The Cockcroft–Gault equation is used to estimate creatinine clearance. This patient has a BMI of 28.4 which is considered overweight, but actual body weight should be used to calculate his clearance.
12. **A.** The CKD $EPI_{creatinine}$ 2021 equation should be used to estimate GFR and does not require a race term.
13. **D.** The CKD EPI 2021 equation should be used to estimate GFR and when adjusting for his BSA, the estimate is higher at 57 mL/min.
14. **C.** Urinary cystatin C concentrations are not used in estimating progression of kidney disease. Serum cystatin C concentrations may be used to estimate GFR in addition to Scr.
15. **B.** PAH clearance is used to measure renal blood flow.