Chronic kidney disease (CKD) is an increasingly alarming worldwide health concern, with nearly 2 million people in the United States estimated to require hemodialysis or kidney transplantation by 2030. 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 end-stage renal disease (ESRD) (see Chap. 29). 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.

Assessment of kidney function using both qualitative and quantitative methods is an important part of the evaluation of patients and an essential characterization of individuals who participate in clinical research investigations. Estimation of creatinine clearance (CLE), has been considered the clinical standard for assessment of renal function for more than 40 years, and is the primary index of kidney function stratification used in drug pharmacokinetic studies. New equations to estimate glomerular filtration rate (GFR) are now used in many clinical settings to identify patients with CKD, and in large epidemiology studies to evaluate risks of mortality and progression to ESRD. 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 renal 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.

Quantitative indices of GFR or CLE are considered the most useful diagnostic tools for the identification of the presence 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 a toxic insult. The measurement or estimation of CLE has been the most commonly used index for individualizing medication dosage regimens in patients with acute and chronic kidney disease. Furthermore, CLE has been the predominant index used to stratify patients in pharmacokinetic studies which serve as the basis for the design of renal dosing algorithms in FDA-approved package inserts and tertiary drug information sources. The composite term renal function includes the processes of filtration, secretion, and reabsorption, as well as endocrine and metabolic functions. Alterations of all five renal 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 renal function, as well as in those with chronic kidney disease and acute kidney injury (AKI) (eTable 18-1). Where appropriate, discussion regarding the qualitative assessment of the renal 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, 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 (<5 to 10 kDa) ions and molecules diffuse across the glomerular–capillary membrane into the Bowman capsule and then enter the proximal tubule (eFig. 18-1). Most proteins are too large (>60 kDa) to be substantially filtered, and their filtration is impeded by the electronegative charge on the epithelial surface of the glomerulus. Thus, compounds presented to the glomerulus in the protein-bound state are usually not significantly filtered and remain in the peritubular circulation.

<table>
<thead>
<tr>
<th>eTABLE 18-1</th>
<th>Markers of Renal Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal plasma/blood flow</td>
<td>p-Aminohippurate (PAH)</td>
</tr>
<tr>
<td>Glomerular filtration rate</td>
<td>131I-Orthoiodohippurate (131I-OIH)</td>
</tr>
<tr>
<td>Glomerular filtration rate</td>
<td>99mTc-mercaptoacetyltriglycine (99mTc-MAG3)</td>
</tr>
<tr>
<td>Glomerular filtration rate</td>
<td>Inulin, sinistrin</td>
</tr>
<tr>
<td>Glomerular filtration rate</td>
<td>Iothalamate</td>
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<tr>
<td>Glomerular filtration rate</td>
<td>Iohexol</td>
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<tr>
<td>Glomerular filtration rate</td>
<td>99mTc-diethylenetriaminepentaacetic acid (99mTc-DTPA)</td>
</tr>
<tr>
<td>Tubular function</td>
<td>p-Aminohippurate (PAH)</td>
</tr>
<tr>
<td>Tubular function</td>
<td>N'-Methylnicotinamide (NMN)</td>
</tr>
<tr>
<td>Tubular function</td>
<td>Tetraethylammonium (TEA)</td>
</tr>
<tr>
<td>Tubular function</td>
<td>β2-Microglobulin</td>
</tr>
<tr>
<td>Tubular function</td>
<td>Retinol-binding protein (RBP)</td>
</tr>
<tr>
<td>Tubular function</td>
<td>Protein HC (α1-microglobulin)</td>
</tr>
<tr>
<td>Tubular function</td>
<td>N-Acetylglucosaminidase (NAG)</td>
</tr>
<tr>
<td>Tubular function</td>
<td>Alanine aminopeptidase (AAP)</td>
</tr>
<tr>
<td>Tubular function</td>
<td>Adenosine binding protein (ABP)</td>
</tr>
</tbody>
</table>

Secretion

Secretion is an active process that predominantly takes place in the proximal tubule and facilitates the elimination of compounds from the renal circulation into the tubular lumen. Several highly efficient anionic and cationic transport systems for a wide range of endogenous and exogenous substances have been identified and the renal clearance of these actively secreted entities can greatly exceed GFR and in some cases approximate renal blood flow. Probencid, p-aminohippurate (PAH), and cidofovir are examples of anionic substances, whereas creatinine, cimetidine, and procainamide are well-characterized cations. The anionic and cationic transport systems are not mutually exclusive, as probencid has been observed to compete with the tubular secretion of cimetidine. Other transport pathways, such as P-glycoprotein and multidrug resistance protein, are also present in several tissues, including the kidney, liver, jejunum, colon, and brain. These efflux proteins are now recognized as important contributors to the renal elimination of many drugs. For example, P-glycoprotein, which is located on the apical membrane of the proximal tubule, plays an important role in the renal elimination of a wide range of drugs, such as cimetidine, digoxin, and procainamide. Blockade of P-glycoprotein could result in decreased renal elimination of such compounds, leading to an increased drug exposure. Verapamil and cyclosporine are the two most widely studied agents that reduce the activity of this tubular transport mechanism. The net process of tubular secretion for drugs is therefore likely a result of multiple secretory pathways acting simultaneously.

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, more than 40 years ago, proposes that “kidney function” of patients with renal 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, those that are unaffected compensate; that is, they hyperfunction. The cornerstone of this hypothesis is that glomerulotubular balance is maintained, such that those nephrons capable of functioning will continue to perform in an appropriate fashion. Extensive studies have indeed shown that single-nephron GFR increases in the unaffected nephrons; thus, the whole-kidney GFR, which represents the sum of the single-nephron GFRs of the remaining functional nephrons, may remain close to normal until there is extensive injury. Based on this, one would presume that a measure of one component of nephron function could be used as an estimate of all renal functions. This, indeed, has been and remains our clinical approach. We estimate GFR and assume secretion and reabsorption remain proportionally intact.

**Glomerular Filtration Capacity**

GFR is dependent on numerous factors, one of which is protein load. Bosch suggested that an appropriate comprehensive evaluation of renal function should include the measurement of “filtration capacity” of the kidney. 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 renal function administered an oral or IV protein load prior to measurement of GFR have been noted to increase their GFR by as much as 50%. As renal function declines, the kidneys usually compensate by increasing the single-nephron GFR. The renal reserve, the maximal degree by which GFR can be increased, will be reduced in those individuals whose kidneys are already functioning at higher-than-normal levels because of pre-existing renal injury. Thus renal reserve may be a complementary, insightful index of renal function for many individuals with as yet unidentified CKD.

Quantification of renal 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 renal 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 the degree of renal function. A discussion of pharmacokinetic changes in patients with renal disease is extensively reviewed in Chapter 33. Although several indices have been used for the quantification of GFR in the research setting, estimation of CL\textsubscript{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. In addition 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 renal 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 acute kidney injuries, 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 Chap. 29). Indeed, anemia-induced renal hypoxia results indirectly in erythropoietin gene activation, tubular necrosis, and apoptosis, thereby contributing to further renal cell injury. This cyclic relationship between kidney disease, suppression of erythropoietin secretion, and cardiovascular disease is also referred to as the cardio-renal anemia syndrome.

**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 (calcitriol) or other vitamin D analogs (paricalcitol, doxercalciferol) to avert the bone loss and pain associated with CKD-associated metabolic bone disease. 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. In vitro and in vivo studies have shown that CYP-mediated metabolism is impaired in the presence of renal failure or uremia. In clinical studies using CYP3A probes in ESRD patients receiving hemodialysis, hepatic CYP3A activity was reported to be reduced by 28% from values observed in age-matched controls; partial correction was noted following the hemodialysis procedure. Impaired nonrenal clearance in the presence of renal 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.

**QUALITATIVE AND SEMIQUANTITATIVE 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 (eTable 18-2). As renal function declines, patients may develop de novo or experience an exacerbation of hypertension, edema, electrolyte abnormalities, anemia, or other complications (see Chap. 29). The National Kidney Foundation (NKF) currently recommends that all patients with CKD, and those at increased risk for CKD, undergo at least yearly a comprehensive laboratory assessment comprised of (a) serum creatinine concentration to estimate GFR; (b) albumin-to-creatinine ratio in a spot urine specimen; (c) examination of urine sediment for red blood cell and white blood cell counts; (d) renal ultrasonography; (e) serum electrolytes, including sodium, potassium, chloride, and bicarbonate; (f) urine pH; and (g) urine specific gravity. The role of each of these indices in the identification and monitoring of CKD is discussed in detail below.
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 mellitus, 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 >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 diabetics 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.

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 acetone excretion are reported as small (<20 mg/dL [<0.34 mMol/L]), moderate (30 to 40 mg/dL [0.5 to 0.69 mMol/L]), and large (>80 mg/dL [1.38 mMol/L]).

Nitrite Nitrite is not usually present in urine. The presence of nitrite is mostly common the result of conversion from urinary nitrate by bacteria in the urine. The presence of nitrite thus 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 as a consequence of 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.

Protein or Albumin Evaluation of urinary protein or albumin is now a standard tool to characterize the severity of CKD and to monitor the rate of disease progression or regression. Persistent proteinuria or albuminuria, that 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 (>40 kDa). Smaller proteins (<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 comprised of smaller proteins such as β2-microglobulin, apoproteins, enzymes, or peptide hormones. Increased renal excretion of these low-molecular-weight proteins is considered a sensitive marker of tubulointerstitial disease.

Historically, the sulfosalicylic acid test was used as a crude measure of proteinuria. This test is performed by adding sulfosalicylic acid to urine and then visually comparing this admixture with a tube of untreated urine; the degree of turbidity is then qualitatively graded (0 to 4 plus) as the index of the presence of proteinuria. Dipstick tests are now the most common means to determine in a semiquantitative fashion a patient’s urinary protein or albumin excretion. False-positive results can occur in the presence of alkaline urine (pH more 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 <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 (<10 mg/dL [<100 mg/L]), trace (10 to 20 mg/dL [100 to 200 mg/L]), 1+ (30 mg/dL [300 mg/L]), 2+ (100 mg/dL [1000 mg/L]), 3+ (300 mg/dL [3000 mg/L]), or 4+ (>1000 mg/L). Portable desktop analyzers such as the Chemstrip 101 Urine Analyzer (Roche Diagnostics) and Clinitek 50 Urine Chemistry Analyzer (Bayer Corporation) can also be used as an alternative to visual urinalysis test-strip evaluation, and provides rapid results for urinary albumin-to-creatinine ratio.

3 Dipstick test strips that are specific for low levels of albuminuria (30 to 300 mg/day) should be employed when one is screening individuals at risk for CKD. Microalbuminuria test strips, such as the Microalbumin 2-1 Combo Strip (Teco Diagnostics), is a semiquantitative test for both albumin and creatinine in a spot urine sample. When dipped into a urine sample, colors range from pale green to aqua blue (for albumin) and shades of purple-brown (for creatinine), depending on the amounts present in the sample. The presence of hemoglobin (>25 mg/dL [>250 mg/L]) or visibly bloody urine or bilirubin (>15 mg/dL [>257 μmol/L]) or visibly dark brown color urine) can interfere with test results from these strips, but no
interferences have been observed with ascorbic acid. In patients with a positive protein or albumin dipstick test, a 24-hour urine collection with a positive measurement of albumin excretion can be used to quantitate precisely 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 mg/s) to creatinine (in g [or mmol]) in an untimed (spot) urine specimen. The normal ratio is <30 mg albumin or <200 mg protein per gram of creatinine (<3.4 mg albumin or <22.6 mg protein per mmol of creatinine), with values between 30 and 300 mg of albumin per gram of creatinine (3.4 to 34.0 mg of albumin per mmol of creatinine) considered to be in the microalbuminuria range. Positive test results should be repeated, particularly in patients without an underlying cause for CKD, such as diabetes or hypertension. Monitoring of the degree of glomerular injury in CKD patients should use the albumin-to-creatinine ratio, whereas for patients with clinical proteinuria, that is, excretion of >500 mg per day or an albumin-to-creatinine ratio >500 mg/g (>56.6 mg/mmol), the protein-to-creatinine ratio can be used.

Clinical Controversy...

In the past, measurement of urinary protein excretion rate was accomplished using a 24-hour urine collection in patients who were at risk for CKD. However, many now advocate the use of an untimed “spot” urine sample with either an albumin-specific dipstick or measurement of the albumin-to-creatinine ratio.

**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 more informative when interpreted along with the hydration status of the patient and plasma osmolality.

**Microscopic Analysis of Urine**

Microscopic examination is a critical aspect of urinalysis. Formed elements that may be detected in the urine include erythrocytes and leukocytes, casts, and crystals. An important consideration in the assessment of hematuria is whether the cells are of renal origin. More than two cells per high-power field is abnormal, and the presence of dysmorphic cells suggest renal parenchymal origin either because they were damaged as they passed through the glomerulus or due to exposure to the varying osmotic environments of the tubular lumen. White blood cells may be present in the urine in association with infection or inflammatory conditions, such as interstitial nephritis. More than one cell per high-power field 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 forms composed of protein, with or without cells that take the shape of the collecting tubules, where they are formed. Casts without cells are labeled hyaline casts and consist of the Tamm-Horsfall mucoprotein, secreted by the renal tubules. They are nonspecific and may appear in concentrated urine. In the presence of red or white blood cells, casts may be formed that include the cells, indicating that the cells were of renal origin. Solubility of the Tamm-Horsfall protein is increased as urine pH rises; therefore, sample collection for casts should occur with the first morning void when the urine is most acidic. Otherwise, casts may dissolve and elude detection.

A variety of crystals may be visualized in the urinary sediment in healthy individuals as well as with 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 multiple websites such as [http://www.ndt-educational.org/fogazzislidepart3.htm](http://www.ndt-educational.org/fogazzislidepart3.htm)

**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 nitrogen component of urea in serum (SUN) or blood (BUN) is considered normal if it is in the range of 5 to 20 mg/dL (1.8 to 5.1 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 blood urea nitrogen to a greater extent than the serum creatinine concentration. The normal blood urea nitrogen-to-creatinine ratio is 10 to 15:1 using conventional units (or 0.04 to 0.06 mmol/L:μmol/L using SI 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 blood urea nitrogen is usually used in combination with the serum creatinine concentration as a simple screening test for the detection of renal dysfunction.

**Serum and Urine Creatinine**

Creatinine remains the most important endogenous biomarker used for the detection of kidney disease. The concentration of creatinine in serum is a function of creatinine production and renal excretion. Creatinine is a product of creatine metabolism from muscle; therefore, its production is directly dependent on muscle mass. At steady state, the “normal” serum creatinine concentration range is generally reported as 0.5 to 1.5 mg/dL (44 to 133 μmol/L) for males and females.

Creatinine is eliminated primarily by glomerular filtration, and as GFR declines, the serum creatinine concentration rises (eFig. 18-2).

The third National Health and Nutrition Examination Survey (NHANES III) revealed a mean serum creatinine concentration in white women and men of 0.96 mg/dL (85 μmol/L) and 1.16 mg/dL (103 μmol/L), respectively. Values were lower among Mexican Americans, and higher among African Americans. For all groups, the serum creatinine concentration increased with age. The report also estimated that among U.S. community-dwelling adults, 10.9 million have a serum creatinine concentration greater than 1.5 mg/dL (133 μmol/L); 3.0 million have a serum creatinine concentration greater than 1.7 mg/dL (150 μmol/L); and 0.8 million have a serum creatinine concentration greater than 2.0 mg/dL (177 μmol/L). Although the serum creatinine concentration 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” serum creatinine concentration, as it is dependent on gender, race, age, and lean body mass.

Several methods have been used for the determination of the serum creatinine concentration. The kinetic Jaffe reaction remains the cornerstone of routine quantification of creatinine in most
eFIGURE 18-2 Relationship between serum creatinine and creatinine clearance.

Clinical laboratories. This colorimetric method is based on the reaction of creatinine with alkaline picrate. This nonspecific method also reacts with noncreatinine chromogens in the serum, including bilirubin and proteins such as albumin, and hemoglobin, which may result in a falsely increased serum creatinine concentration. The noncreatinine chromogens are not present in the urine in sufficient quantities to interfere with the urinary creatinine measurement, because the concentration of creatinine in urine is several-fold greater than the serum concentration.

The “normal” interference results in an increase in the serum creatinine concentration of approximately 10% and thereby the measured \( C_{\text{IN}} \) would underestimate the true GFR by 10%. In subjects with normal renal function, this tends to counterbalance the effect of the contribution of tubular secretion of creatinine, which increases urine creatinine by nearly 10%. Thus, a measured \( C_{\text{IN}} \) effect of the contribution of tubular secretion to the renal clearance of creatinine.30 This becomes of major importance when kidney function is reduced to less than 50%.

Diabetic ketoacidosis may produce increased concentrations of acetoacetate, which serves as a chromophore in the Jaffe reaction, thereby increasing the serum creatinine concentration. Other substances that also react with this procedure in the serum include glucose, protein, pyruvate, fructose, uric acid, and ascorbic acid (eTable 18-3). In addition, some antibiotics are associated with a false increase in the serum creatinine concentration, including cephalexin, cefazolin, cephalaxin, cefotaxin, cefaclor, cephradine, and clavulanic acid,31,32 whereas other agents, such as the fluoroquinolones (ciprofloxacin, fleroxacin, lomefloxacin, ofloxacin, levofloxacin, sparfloxacin, and temafloxacin), do not produce a false elevation in serum creatinine concentration.33 The degree of interference is dependent on the serum concentration of the antibiotic, so blood samples for creatinine should be obtained when the antibiotic concentration is lowest (at the end of a dosing interval). These interferences are not observed when the serum creatinine concentration is measured using an enzymatic technique employing creatinine iminohydrolase, creatininase, creatinase, or sarcosine oxidase.

Endogenous and drug interferences continue to plague creatinine measurements for both the Jaffe and enzymatic methods. Recent modifications to the Jaffe method have been employed to address some nonspecific aspects of the assay.34 For example, the “compensated Jaffe” method is used on the Roche Diagnostics, and Siemens analyzers. Here, a fixed concentration is subtracted from all results in order to adjust for nonspecific protein influence. The “uncompensated Jaffe” method used by Abbott, Beckman, and Siemens has been reported to be less susceptible to interferences by bilirubin when compared to other Jaffe methods.35

A new approach to standardize serum creatinine concentration assays between manufacturers and institutions has been implemented in most hospital clinical laboratories.36 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 improved interlaboratory variability in serum creatinine concentration values, and has resulted in a downward shift of the “normal range” for serum creatinine concentration values by 0.1 to 0.2 mg/dL (9 to 18 μmol/L) when compared to noncalibrated ranges. For example, the normal reference range reported by the UNC Hospitals laboratory for healthy males was reduced from 0.8 to 1.4 mg/dL (71 to 124 μmol/L; pre-IDMS) to 0.7 to 1.3 mg/dL (62 to 115 μmol/L; post-IDMS).37 Other recent modifications include reporting serum creatinine concentration values in mg/dL to two decimal places (e.g., 0.93 mg/dL), and values in μmol/L to the nearest whole number (e.g., 82 μmol/L). This practice is aimed at reducing rounding errors that in the past contributed to bias between creatinine-based GFR or \( C_{\text{IN}} \) estimates, but it does not improve GFR estimation in those without CKD.

Despite alterations in creatinine assay methods, many drugs still interfere with these assays resulting in false elevations or reductions in serum creatinine concentration values. The antifungal agent 5-flucytosine cross-reacts with creatinine when measured using the Ektachem enzymatic system, but does not interact with the Jaffe method.38 Daly et al.39 reported a false-negative effect of dobutamine and dopamine on the serum creatinine concentration value when measured using the Ektachem system. The interference is concentration dependent and results in a 10% to 100% decrease of the serum creatinine concentration. The authors hypothesized that both drugs compete with the chromogenic dye for oxidation by hydrogen peroxide in a concentration-dependent manner. The problem is most evident when blood samples are contaminated with residual IV solution containing the interfering drug. Thus, standardization of procedures within the clinic setting and awareness of the creatinine assay method used at the institution are critical to properly interpret each patient’s serum creatinine concentration value.

Other compounds are known to truly alter the serum creatinine concentration by inhibition of the active tubular secretion of creatinine. Among these are cimetidine and trimethoprim, which compete for creatinine secretion at the cationic transport system in a dose-dependent fashion. Cimetidine, given as a single 400-mg dose can result in a reduction of the CL \( C_{\text{IN}} \)-to-inulin clearance ratio from
1.30 to 1.03, without a change in inulin clearance. Ranitidine, an H₂-receptor antagonist similar to cimetidine, however, does not have a similar effect on creatinine secretion following single doses of 300 to 1,200 mg.39

The serum creatinine concentration 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 serum creatinine concentration 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 serum creatinine concentration. In contrast, cachectic patients, as the result of minimal muscle mass, will have very low serum creatinine concentrations, as do those with spinal cord injuries.40 Elderly patients and those with poor nutrition may also have low serum creatinine concentrations (<1.0 mg/dL [88 μmol/L]) secondary to decreased muscle mass.

Creatine or methyl guanidine acetic acid are found in many commonly ingested foods sources such as fish and red meat. During the cooking of meat, some creatine is converted to creatinine, which is rapidly absorbed following ingestion. Serum creatinine concentrations may rise as much as 50% within 2 hours of a meat meal and remain elevated for as long as 8 to 24 hours.41 Ingestion of creatine as an ergogenic dietary supplement is currently popular, as a means to increase skeletal muscle stores of phosphocreatine leading to adenosine triphosphate (ATP) resynthesis of adenosine diphosphate (ADP). There are conflicting reports as to the effect of creatine ingestion on the serum creatinine concentration. Poortsmans et al.42 evaluated a short-term regimen of 20 g creatine per day for 5 days in healthy subjects, and reported no significant change in the serum creatinine concentration, creatinine excretion rate, or CLcr. Robinson et al.43 and Jagim et al.,44 reported a 25% to 40% increase in the serum creatinine concentration after ingestion of 20 g creatine per day for either 5 days or 8 weeks. The renal excretion rate of creatinine was not measured. Spillane et al.45 reported that creatine ethyl ester intake at a dose of 20 g/day for 6 days had a nearly threefold greater increase in serum creatinine concentrations than creatine monohydrate, indicating that different forms of creatine likely have differing effects on serum creatinine concentration values.

The issue of whether, or not, creatine ingestion adversely affects kidney function was studied by Edmonds et al.46 They noted that creatine supplementation led to an increase in renal disease progression in a rat model for renal cystic disease, suggesting that creatine supplementation may be a risk factor in patients with pre-

Serum and Urine Cystatin C

Cystatin C 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 renal 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 as well as serum creatinine concentration. It was hypothesized that since cystatin C production was not affected by muscle mass, it would provide a more reliable estimate of renal function than serum creatinine concentration. However, it has now been shown that serum cystatin C 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.47,48 Recent studies have reported conflicting results about the sensitivity of cystatin C compared to creatinine in predicting various forms of AKI.49-52 Cystatin C has been shown to perform better than serum creatinine concentration for predicting contrast-induced kidney injury, resulting in a new definition of contrast-induced acute kidney injury (CIAKI), consisting of a >10% increase in cystatin C within 24 hours after exposure to contrast media.49,50 Serum cystatin C also detected AKI up to 2 days earlier than creatinine in critically ill patients,53 and cystatin C concentration was a better predictor of AKI in pediatric cardiac surgery patients.52 However, three prior studies did not show a clear advantage for serum cystatin C level in predicting AKI in cardiopulmonary bypass and cardiothoracic surgery.53-55 In a recent multicenter study of 1,150 adults followed after cardiac surgery, cystatin C was noted to be a less sensitive biomarker than creatinine for detecting AKI in the postoperative period.56 These differential findings suggest that the role of cystatin C in assisting with the diagnosis of AKI is yet to be fully determined.

The recent development of automated immunoassay techniques for cystatin C is based on a latex enhanced immunoturbidimetric assay. Here, cystatin C in the sample binds to anti-cystatin C antibody, which is coated on latex particles, resulting in agglutination. The degree of the turbidity caused by agglutination is measured optically (at 540 nm) and is proportional to the amount of cystatin C in the sample. The range of values is 0.13 mg/L to 8.0 mg/L (10 to 599 nmol/L), with normal values of 0.55 to 1.18 mg/L (41 to 88 nmol/L) for women and 0.60 to 1.11 mg/L (45 to 83 nmol/L) for men based on data from the NHANES study.56

The utility of cystatin C as a quantitative measure of GFR is gaining acceptance in the clinical and research settings. In a 4-year longitudinal study in 30 Pima Indians without CKD, the reciprocal cystatin C index (100/cystatin C) was shown to be a better predictor of declining GFR than estimated GFR, or Clcr.57 However in patients being treated for malignant disease, Page et al.58 reported increased cystatin C concentrations that were independent of Clcr. Cystatin C concentrations were also noted to be independent of GFR and weakly associated with measured Clcr in pediatric and adult renal transplant recipients, possibly because of the formation of cystatin–immunoglobulin complexes or reduced tubular catabolism.59,60 Two additional studies have shown a strong association between serum cystatin C and cardiovascular disease in elderly and non-CKD patients, suggesting that it may provide useful prognostic information in some populations.51,62

Alternative Methodologies to Identify Kidney Injury

Biomarkers measured in urine, such as kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), and cystatin C have shown promise in detecting AKI (see Chap. 28). 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 cystatin C. Koyner et al.54 showed that postop cardiac surgery patients with early elevated urinary cystatin C-to-creatine ratios had the highest prevalence of developing AKI. Here, plasma creatinine concentrations did not peak until 48 hours after intensive care unit (ICU) admission, suggesting that
urinary biomarkers such as cystatin C may be beneficial in early diagnosis of AKI. Use of cystatin C as a quantitative measure of GFR requires further evaluation, and may yield useful information for comprehensive evaluations of health and cardiovascular status, including detection of acute and chronic changes in kidney function.

β-Trace protein (BTP) has recently been proposed as a new alternate endogenous marker of GFR. Similar to cystatin C, 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 concentrations of BTP in serum have been reported in patients with chronic kidney disease, kidney transplant recipients, and children. Equations to estimate GFR from BTP concentrations in adults and pediatric populations are currently being evaluated.

MEASUREMENT OF KIDNEY FUNCTION

The gold standard quantitative index of kidney function is a measured GFR. 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 chronic kidney disease and as a guide for drug dose adjustment.

It is important to recognize conditions that may alter renal 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 it is used as a longitudinal marker of renal function. Dietary protein intake has been demonstrated to correlate with GFR in healthy subjects. Brändle et al. evaluated renal function in four groups of healthy volunteers, each ingesting a diet controlled for protein over a 4-month period. The GFR was nonlinearly related to the urine nitrogen excretion, with an observed maximum of 181.7 mL/min (3.03 mL/s) at a urine nitrogen excretion rate of 20 g/day (1.43 mol/d), or 125 g/day protein intake. 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. When challenged with a protein load, the vegetarian subjects are able to increase their GFR to the “normal” range. Findings from the Nurses’ Health Study indicate that longitudinal changes in GFR are independent of the source of protein (nondairy animal, dairy, or vegetable) in women with normal renal 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 ≥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. The exact mechanism of the renal response to protein is unknown, but may be related to extrarenal factors such as glucagon, prostaglandins, and angiotensin II, or intrarenal mechanisms, such as alterations in tubular transport and tubuloglomerular feedback.

Despite the evidence of a “renal reserve,” standardized evaluation techniques have not been developed. Therefore, assessment of a measured GFR must consider the dietary protein status of the patient at the time of the study.

Measurement of Glomerular Filtration Rate

A measured GFR remains the single best index of kidney function. 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, as well as the risk of complications of CKD. Accurate measurement of GFR in clinical practice is a critical variable for the individualization of the dosage regimens of renally excreted medications so that one can maximize their therapeutic efficacy and avoid potential toxicity.

The GFR is expressed as the volume of plasma filtered across the glomerulus per unit time, based on total renal blood flow and capillary hemodynamics. The normal values for GFR are 127 ± 20 mL/min/1.73 m² (1.22 ± 0.19 mL/s/m²) and 118 ± 20 mL/min/1.73 m² (1.14 ± 0.19 mL/s/m²) in healthy men and women, respectively. These measured values closely approximate what one would predict if the normal renal blood flow were approximately 1.0 L/min/1.73 m² (0.01 mL/s/m²), plasma volume was 60% of blood volume, and filtration fraction across the glomerulus was 20%: then the normal GFR would be expected to be approximately 120 mL/min/1.73 m² (1.16 mL/s/m²).

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

\[
GFR = \frac{\text{renal } CL}{A_g/AUC_\text{ss}}
\]

where renal CL is renal clearance of the marker, \(A_g\) is the amount of marker excreted in the urine in a specified period of time, \(t\), and \(AUC_{\text{ss}}\) 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

\[
GFR = \frac{\text{renal } CL}{(A_g/C^\text{ss}) \times \tau}
\]

where \(C^\text{ss}\) 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 \(CL = \text{infusion rate}/C^\text{ss}\). 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\text{ss}). Here, clearance is calculated as \(CL = \text{dose}/AUC\). These plasma clearance methods commonly yield clearance values 10% to 15% higher than GFR measured by urine collection methods. Several markers have been used for the measurement of GFR and include both exogenous and endogenous compounds. Those administered as exogenous agents, such as inulin, sinistrin, iothalamate, iohexol, and radioisotopes, require specialized administration techniques and detection methods for the quantification of concentrations in serum and urine, but generally provide an accurate measure of GFR. Methods that employ endogenous compounds, such as creatinine or cystatin C, require less technical expertise, but produce results with greater variability. The GFR marker of choice depends on the purpose and cost of the test, ranging from $2,000 per vial for radioactive 125I-iothalamate (Glofil-125, QOL Medical) to $6 per vial for nonradiolabeled iothalamate (Conray-60, Mallinckrodt or iohexol (Omnipaque-300, GE Medical) (eTable 18-4).

Inulin and Sinistrin Clearance

Inulin is a large fructose polysaccharide (5,200 Da), obtained from the Jerusalem artichoke, dahlia, and chicory plants. It is not bound
to plasma proteins, is freely filtered at the glomerulus, is not secreted or reabsorbed, and is not metabolized by the kidney. The volume of distribution of inulin approximates extracellular volume, or 20% of ideal body weight. Because it is eliminated by glomerular filtration, its elimination half-life is dependent on renal function and is approximately 1.3 hours in subjects with normal renal function. Measurement of plasma and urine inulin concentrations can be performed using high-performance liquid chromatography. Sinistrin, another polyfructosan, has similar characteristics to inulin; it is filtered at the glomerulus and not secreted or reabsorbed to any significant extent. It is a naturally occurring substance derived from the root of the North African vegetable red squill, *Urginea maritime*, which has a much higher degree of water solubility than inulin. Assay methods for sinistrin have been described using enzymatic procedures, as well as high-performance liquid chromatography with electrochemical detection. Alternatives have been sought for inulin as a marker for GFR because of the problems of availability, high cost, sample preparation, and assay variability.

### Iothalamate Clearance

Iothalamate is an iodine-containing radiocontrast agent that is available in both radiolabeled (125I) and nonradiolabeled 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 nonradiolabeled 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 and urine iothalamate concentrations can be measured using high-performance liquid chromatography. Plasma iothalamate clearance methods that do not require urine collections have been shown to be highly correlated with iothalamate renal clearance, making them particularly well-suited for longitudinal evaluations of renal function. These plasma clearance methods require two-compartment modeling approaches because accuracy is dependent on duration of sampling. For example, Agarwal et al. demonstrated that short sampling intervals can overestimate GFR, particularly in patients with severely reduced GFR. In individuals with GFR >30 mL/min/1.73 m² (>0.29 mL/s/m²), a 2-hour sampling strategy yielded GFR values that were 54% higher compared with a 10-hour sampling, whereas the 5-hour sampling was 17% higher. In individuals with GFR <30 mL/min/1.73 m² (<0.29 mL/s/m²), the 5-hour GFR was 36% higher and 2-hour GFR was 126% higher than the 10-hour measurement. The authors proposed a 5 to 7 hour sampling time period with eight plasma samples to be the most appropriate and feasible approach for most GFR evaluations.

### Iohexol

Iohexol, a nonionic, low osmolar, ionic contrast agent, has also been used for the determination of GFR. It is eliminated almost entirely by glomerular filtration, and plasma and renal clearance values are similar to observations with other marker agents: Strong correlations of 0.90 or greater and significant relationships such with iothalamate have been reported. These data support iohexol as a suitable alternative marker for the measurement of GFR. A reported advantage of this agent is that a limited number of plasma samples (as few as two collected at 120 and 300 min after injection) can be used to quantify iohexol plasma clearance. For patients with a reduced GFR more time must be allotted—more than 24 hours if the estimated GFR is less than 20 mL/min (0.33 mL/s).

### Radiolabeled Markers

The GFR has also been quantified using radiolabeled markers, such as 125I-iothalamate (614 Da, radioactive half-life of 60 days), 99mTc-diethylenetriamine pentaacetic acid (99mTc-DPTA; 393 Da, radioactive half-life of 6.03 hours), and 67Cu-ethylenediaminetetraacetic acid (67Cu-EDTA; 292 Da, radioactive half-life of 27 days). These relatively small molecules are minimally bound to plasma proteins and do not undergo tubular secretion or reabsorption to any significant degree. 125I-iothalamate and 99mTc-DPTA are used in the United States, whereas 51Cr-EDTA is used extensively in Europe. The use of radiolabeled markers allows one to determine the individual contribution of each kidney to total renal function. Various protocols exist for the administration of these markers and subsequent measurement of GFR using either plasma or renal clearance calculation methods. The nonrenal clearance of these agents appears to be low (3 to 8 mL/min [0.05 to 0.13 mL/s]), suggesting that plasma clearance is an acceptable technique except in patients with severe renal insufficiency (GFR <30 mL/min [<0.50 mL/s]). Indeed, highly significant correlations between renal clearance among radiolabeled markers have been demonstrated. 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.

### Creatinine

#### Measured Creatinine Clearance

Although the measured (24-hour) CL₆₄ has been used as an approximation of GFR for decades, it has limited clinical utility for a multiplicity of reasons. Short-duration witnessed measured CL₆₄ correlates well with iothalamate clearance performed using the single-injection technique. In a multicenter study of 1.36 patients with type 1 diabetic nephropathy, the correlations of simultaneous measured CL₆₄ and 24-hour CL₆₄ (compared to CLiothalamate) were 0.81 and 0.49, respectively, indicating increased variational with the 24-hour clearance determination. In a selected group of 110 patients, measurement of a 4-hour CL₆₄ during water diuresis provided the best estimate of the GFR as determined by the CLiothalamate. Furthermore, the ratio of CL₆₄ to CLiothalamate did not appear to increase as the GFR decreased. These data suggest that a short collection period with a water diuresis may be the best CL₆₄ method for estimation of GFR.

A 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. If the nonspecific Jaffe reaction is used, which overestimates the serum creatinine concentration by approximately 10% because of the noncreatinine chromogens, then the measurement of CL₆₄ is a very good measure of GFR in patients with normal kidney function. Tubular secretion, however, increases to as much as 100% in patients with renal insufficiency. The result is that measured CL₆₄ markedly overestimates GFR. For example, Bauer et al. reported that the CL₆₄-to-CLiothalamate ratio in subjects with mild impairment was 1.20; for those with moderate impairment, it was 1.87; and in those with severe impairment, it was 2.32. Thus, a measured CL₆₄ is a poor indicator of GFR in patients with moderate to severe renal insufficiency, that is, stages 3 to 5 CKD.

Because cimetidine blocks the tubular secretion of creatinine the potential role of several oral cimetidine regimens to improve the

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eTable 18-4  Sensitivity and Clinical Utility of Renal Function Tests

<table>
<thead>
<tr>
<th></th>
<th>Accuracy</th>
<th>Clinical Utility</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inulin clearance</td>
<td>+++</td>
<td>+</td>
<td>$$$</td>
</tr>
<tr>
<td>Radiolabeled markers</td>
<td>++++</td>
<td>+</td>
<td>$ $$</td>
</tr>
<tr>
<td>Nonisotopic contrast agents</td>
<td>+++</td>
<td>++</td>
<td>$$ $$</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>++</td>
<td>+++</td>
<td>$ $$</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>+</td>
<td>++++</td>
<td>$</td>
</tr>
</tbody>
</table>

+, least acceptable; ++, adequate; ++++, better; +++++, best.
accuracy and precision of measured CL\textsubscript{cr} as an indicator of GFR has been evaluated. The CL\textsubscript{cr}–to–CL\textsubscript{iothalamate} ratio declined from 1.33 with placebo to 1.07 when 400 mg of cimetidine was administered four times a day for 2 days prior to and during the clearance determination.\textsuperscript{90} Similar results were observed when a single 800-mg dose of cimetidine was given 1 hour prior to the simultaneous determination of CL\textsubscript{cr} and CL\textsubscript{iothalamate}; the ratio of CL\textsubscript{cr} to CL\textsubscript{iothalamate} was reduced from a mean of 1.53 to 1.12.\textsuperscript{91} Thus a single oral dose of 800 mg of atinine concentration on CL\textsubscript{cr}, the test is usually performed over a 24-hour period with the plasma creatinine obtained in the morning, as long as the patient has stable kidney function. Collection of urine remains a limiting factor in the 24-hour CL\textsubscript{cr} because of incomplete collections, and interconversion between creatinine and creatine that can occur if the urine is not maintained at a pH < 6.

**Estimation of GFR**

Because of the invasive nature and technical difficulties of directly measuring GFR in clinical settings, many equations for estimating GFR have been proposed over the past 10 years (etabTable 18-5).\textsuperscript{6} A series of related GFR estimating equations (eGFR) have been developed for the primary purpose of identifying and classifying CKD in many patient populations.\textsuperscript{92–99} 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 Study (MDRD) where GFR was measured using the renal clearance of \textsuperscript{125}I-iothalamate methodology. The first regression model yielded a six-variable Modification of Diet in Renal Disease Study (MDRD6) equation.\textsuperscript{99} This equation (r\textsuperscript{2} = 0.902) provided a more precise estimate of the measured GFR in the MDRD population than measured CL\textsubscript{cr} (r\textsuperscript{2} = 0.866) or CL\textsubscript{cr} estimated by the Cockcroft-Gault equation (r\textsuperscript{2} = 0.842). A newer four-variable version of the original MDRD equation (MDRD4), based on plasma creatinine, age, sex, and race, was shown to provide a similar estimate of GFR results compared to the six-variable equation predecessor\textsuperscript{93} and has been subsequently updated according to nationally recognized serum creatinine concentration (IDMS) assay results.\textsuperscript{94} The MDRD4–IDMS equation is recommended by the NKF and the National Kidney Disease Education Program (NKDEP) for calculating the estimated GFR (eGFR) in patients with a history of CKD risk factors and a GFR <60 mL/min/1.73 m\textsuperscript{2} (<0.58 mL/s/m\textsuperscript{2}). The performance of the MDRD4 equations has been assessed in a variety of patient populations with GFR < 60 mL/min/1.73 m\textsuperscript{2} (<0.58 mL/s/m\textsuperscript{2}), including those with diabetic nephropathy and renal transplant patients. However, the MDRD4 equations have been shown to be significantly biased in healthy subjects, diabetic patients with normal GFR (88 to 182 mL/min/1.73 m\textsuperscript{2} [0.85 to 1.75 mL/s/m\textsuperscript{2}]), and healthy potential kidney donors.\textsuperscript{95} In patients with GFR values >60 mL/min/1.73 m\textsuperscript{2} (>0.58 mL/s/m\textsuperscript{2}), the values provided by the MDRD4 equation have been shown to be highly variable and less accurate than other traditional estimation methods, perhaps in part due to the fact that the original study population consisted of only patients with low GFR values (<60 mL/min/1.73 m\textsuperscript{2} [<0.58 mL/s/m\textsuperscript{2}]). The study also included few Asians, elderly patients, and those with diabetes, or ill, hospitalized patients.\textsuperscript{96,97} A recent study conducted by the FDA compared the eGFR estimated by the MDRD4 equation to the CL\textsubscript{cr} estimated by the Cockcroft-Gault equation in 973 subjects enrolled in pharmacokinetic studies conducted for new chemical entities submitted to the FDA from 1998 to 2010.\textsuperscript{98} The MDRD4 equation eGFR consistently overestimated the CL\textsubscript{cr} calculated by the Cockcroft-Gault method. The FDA investigators concluded that “For patients with advanced age, low weight, and modestly elevated serum creatinine concentration values, further work is needed before the MDRD equations can replace the Cockcroft-Gault equation for dose adjustment in approved product information labeling.”

**etabTable 18-5** Equations for the Estimation of GFR in Adults with Stable Renal Function

<table>
<thead>
<tr>
<th>Equation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levey et al.\textsuperscript{92} (MDRD6)</td>
<td>GFR = 170 × (S\textsubscript{cr})\textsuperscript{−0.996} × [age]\textsuperscript{−0.018} × [0.762 if patient is female] × [1.180 if patient is black] × [BUN]\textsuperscript{−0.170} × [Alb]\textsuperscript{0.118}</td>
</tr>
<tr>
<td>Levey et al.\textsuperscript{93} (MDRD4)</td>
<td>GFR = 186 × (S\textsubscript{cr})\textsuperscript{−1.114} × [age]\textsuperscript{−0.205} × [0.742 if patient is female] × (1.210 if patient is black)</td>
</tr>
<tr>
<td>Levey et al.\textsuperscript{94} (MDRD4-IDMS)</td>
<td>GFR = 175 × (S\textsubscript{cr})\textsuperscript{−1.154} × [age]\textsuperscript{−0.200} × [0.742 if patient is female] × (1.210 if patient is black)</td>
</tr>
<tr>
<td>Levey et al.\textsuperscript{100} (CKD-EPI)</td>
<td>GFR = 141 × min(S\textsubscript{cr}/k; 1)\textsuperscript{×} max(S\textsubscript{cr}/k; 1)\textsuperscript{−1.209} × 0.993*\textsuperscript{44+} × 1.018 [if female] × 1.159 [if black]</td>
</tr>
<tr>
<td>Rule et al.\textsuperscript{102} (MCQ)</td>
<td>GFR = exp(1.911 + \frac{5.249}{S\textsubscript{cr}} – \frac{2.114}{S\textsubscript{cr}} – 0.00686 × Age – 0.205 [if female])</td>
</tr>
<tr>
<td>Larsson et al.\textsuperscript{109}</td>
<td>GFR = 77.24 × (CysC in mg/L)\textsuperscript{−1.223}</td>
</tr>
<tr>
<td>Macdonald et al.\textsuperscript{106}</td>
<td>Log\textsubscript{10} eGFR = 2.222 + \left[-0.802 × \sqrt{\text{CysC in mg/L}}\right] + (0.009886 × LM)</td>
</tr>
<tr>
<td>CKD-EPI Equation 8\textsuperscript{112}</td>
<td>eGFR = 127.7 × (CysC in mg/L)\textsuperscript{−1.17} × (age in years)\textsuperscript{−0.215} × (0.015 if female) + (0.106 if black)</td>
</tr>
<tr>
<td>CKD-EPI Equation 8*\textsuperscript{112}</td>
<td>eGFR = 127.7 × (–0.105 + 1.13 × standardized SCysC)\textsuperscript{+0.318} × (age in years)\textsuperscript{−0.215} × (0.015 if female) + (0.106 if black)</td>
</tr>
<tr>
<td>CKD-EPI Equation 9\textsuperscript{112}</td>
<td>eGFR (mL/min/1.73 m\textsuperscript{2}) = 76.7 × (CysC in mg/L)\textsuperscript{−1.19}</td>
</tr>
<tr>
<td>CKD-EPI Equation 9*\textsuperscript{112}</td>
<td>eGFR (mL/min/1.73 m\textsuperscript{2}) = 76.7 × (–0.105 + 1.13 × CysC in mg/L)\textsuperscript{−1.19}</td>
</tr>
<tr>
<td>CKD-EPI Equation 10\textsuperscript{112}</td>
<td>eGFR (mL/min/1.73 m\textsuperscript{2}) = 177.6 × (S\textsubscript{cr} in mg/dL)\textsuperscript{−0.445} × (CysC in mg/L)\textsuperscript{−0.557} × (age in years)\textsuperscript{−0.231} × (0.015 if female) + (0.106 if black)</td>
</tr>
<tr>
<td>CKD-EPI Equation 10*\textsuperscript{112}</td>
<td>eGFR (mL/min/1.73 m\textsuperscript{2}) = 177.6 × (S\textsubscript{cr} in mg/dL)\textsuperscript{−0.445} × (CysC in mg/L)\textsuperscript{−0.557} × (age in years)\textsuperscript{−0.231} × (0.015 if female) + (0.106 if black)</td>
</tr>
</tbody>
</table>

Alb, serum albumin concentration (g/dL); BUN, blood/serum urea nitrogen concentration (mg/dL); CL\textsubscript{cr}, creatinine clearance in mL/min; IBW, ideal body weight (kg); S\textsubscript{cr}, serum or plasma creatinine concentration (mg/dL).

x is 0.7 for females and 0.9 for males, a is –0.329 for females and –0.411 for males, min indicates the minimum of Scr/k or 1, and max indicates the maximum of Scr/k or 1. (*If S\textsubscript{cr} < 0.8 mg/dL, use 0.8 for S\textsubscript{cr}.) For SI conversion purposes serum/plasma creatinine is converted from µmol/L to mg/dL by multiplying by 0.0113; BUN is converted from mmol/L to mg/dL by multiplying by 2.80; Alb is converted from g/L to g/dL by multiplying by 0.1.

Conversion from eGFR conventional units of mL/min/1.73 m\textsuperscript{2} to eGFR SI units of mL/s/m\textsuperscript{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 0.0113; Cystatin C in nmol/L can be converted to mg/L by multiplication using 0.01335 as the conversion factor.

The starred equations were developed for use with standardized CysC assays.\textsuperscript{112}
A single GFR equation may not be best suited for all populations, and choice of equation has been shown to impact CKD prevalence estimates. This has led to a revitalized interest in the development of new equations to estimate GFR. The newest equations to be proposed for the estimation of GFR have been derived from wider CKD populations than the MDRD study, and include the Chronic Kidney Disease Epidemiology Study (CKD-EPI) and the Mayo Clinic Quadratic Equation (MCQ). 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 m² (0.65 ± 0.39 mL/s/m²) (range 2 to 190 mL/min/1.73 m² [0.02 to 1.83 mL/s/m²]). It has been reported that the CKD-EPI equation is less biased (2.5 vs. 5.5 mL/min/1.73 m² [0.024 vs. 0.053 mL/s/m²]) but similarly imprecise compared to MDRD4.

Chronic Kidney Disease–EPI Equation

The CKD-EPI study equation was recently compared to the MDRD equation using pooled data from patients enrolled in research or clinical outcomes studies, where GFR was measured by any exogenous tracer. The findings of the study indicated that the bias of CKD-EPI equation was 61% to 75% lower than the MDRD equation for patients with eGFR of 60 to 119 mL/min/1.73 m² (0.58 to 1.15 mL/s/m²). Based on these findings, the CKD-EPI equation is most appropriate for estimating GFR in individuals with eGFR values >60 mL/min/1.73 m² (>0.58 mL/s/m²). Currently the Australasian Creatinine Consensus Working Group is one of the first to recommend that clinical laboratories switch from the MDRD4 to CKD-EPI for routine automated reporting. If one’s clinical lab does not automatically calculate eGFR using the CKD-EPI, it becomes a bit of a challenge since the equation requires a more complex algorithm than the MDRD equation.

Most labs now use IDMS–calibrated creatinine assays and with the recommendation that a revised “CKD-EPI–IDMS” equation be used based on the estimated 5% lower creatinine values that result from the using the IDMS–calibrated assay are nearly fully implemented.

Limitations of the pooled analysis approach used to develop the MDRD and CKD-EPI equations include the use of different GFR markers between studies (iothalamate, 1/Cr-EDTA, 1/Scr, 1/Scr², age, and sex as the covariates). Using the NHANES database, Snyder et al. reported that MCQ GFR values resulted in 28% fewer patients being categorized as CKD stage 3 or 4 when compared to MDRD4.

Mayo Clinic Quadratic Equation

The MCQ equation was developed by Rule et al. to estimate GFR from a population of CKD (n=320) and healthy individuals (n=580), using 1/S₁₆, 1/S₁,², age, and sex as the covariates. Using the NHANES database, Snyder et al. reported that MCQ GFR values resulted in 28% fewer patients being categorized as CKD stage 3 or 4 when compared to MDRD4.

Combined Serum Creatinine and Cystatin C Equations

Addition of serum cystatin as a covariate in equations to estimate GFR has been employed as a means to improve creatinine-based estimations that historically were limited to lean body mass (LM), age, sex, and race, and serum creatinine concentration (Sₘ₉). Numerous studies have consistently reported that the MDRD4 eGFR equation overestimates CLₘ₉, estimated by the Cockcroft-Gault equation in more than 40,000 patients. For example, Wargo et al. evaluated 409 patients with CKD admitted to a tertiary care clinic. The CKD-EPI equation significantly overestimated the Cockcroft-Gault equation (39.9 mL/min vs. 34.8 mL/min [0.67 mL/s vs. 0.58 mL/s]), respectively; p < 0.001, with 95% of cases ranging from –5.1 mL/min to +15.3 mL/min (0.09 mL/s to +0.26 mL/s). In the largest retrospective study comparing the Cockcroft-Gault and MDRD equation conducted to date, Melloni et al. reported that use of MDRD eGFR 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 their cohort of more than 49,000 patients. The excessive MDRDIND-derived eGFR were also correlated with major bleeding episodes (odds ratio 1.57 [95% CI 1.35–1.84]). Thus, the MDRD equation should not be used in lieu of Cockcroft-Gault for renal dose adjustments for these drugs. Thus, it is important to understand that eGFR equations such as MDRD4 and CKD-EPI were developed for the purpose of identifying and stratifying CKD based on large multicenter epidemiologic studies. Extension of their use for individualized drug dosing has not been fully evaluated and automatic substitution of MDRD4 or CKD-EPI in place of estimated or measured CLcr for drug dose calculations should be avoided.

Serum Cystatin C Equations

A significant limitation of serum cystatin C as a renal biomarker is the influence of body mass on serum concentrations. Studies by MacDonald et al. and Vuppaturi et al. reported that fat-free mass is a significant covariate in GFR determination using cystatin C. Using GFR measured as plasma inulin clearance, lean body mass accounted for at least 16.3% of the variance in GFR values obtained using cystatin C (p < 0.001). When using a cystatin C-based estimate of GFR, which incorporates the CysC, age, race, and sex, a higher prevalence of CKD was reported in obese patients when compared to the MDRD4 equation. In a recent retrospective analysis of over 1,000 elderly individuals (mean age 85 y) enrolled in the Cardiovascular Health Study, GFR was estimated using the CKD-EPI and CKD-EPI-CysC equations. In this population, all-cause mortality rates were significantly different between equations. The CKD-EPI equation yielded a U-shaped association, whereas the CysC equation yielded a linear relationship at eGFR values <60 mL/min/1.73 m² (<1.0 mL/s/m²), suggesting that CysC does not accurately predict mortality risk in patients with low serum creatinine concentration, reduced muscle mass and malnutrition. This further highlights the important relationship between muscle mass and serum CysC concentrations, and cautions against the use of CysC-based equations in the elderly.
Use of CysC-based equations to estimate GFR may also be problematic in patients with autoimmune disorders. It has been reported that cystatin C levels are associated with disease activity in patients with rheumatoid arthritis, which may be due to the presence of C-reactive protein or analytical interference from drugs such as glucocorticoids and infliximab. A single dose of infliximab (3 mg/kg) resulted in a 14% ($p < 0.05$) increase in CysC, whereas no change was observed in serum creatinine concentration or GFR values. In 167 patients with rheumatoid arthritis and 91 controls, CysC levels were significantly higher in RA than controls (15%; $p < 0.001$). Furthermore, CysC levels correlated positively with erythrocyte sedimentation rate ($p < 0.001$), and C-reactive protein ($p = 0.01$), indicating that CysC levels are associated with severity of disease. Thus, CysC-based equations should be used with caution in the obese, elderly and those with inflammatory conditions such as rheumatoid arthritis.

Additional research on the utility of these newer eGFR equations in diverse ethnic groups has resulted in modifications or “correction factors,” such as those for Japanese and Chinese populations.

A variety of online resources provide GFR calculators such as the NKDEP website, which provides aGFR calculator based on the MDRD4-IDMS equation. The NKDEP also recommends that laboratories report eGFR values greater than or equal to 60 as “>60 mL/min/1.73 m² (>1.0 mL/s/m²), not as an exact number,” due to inaccuracies of the MDRD4 equation at higher levels of GFR. It should be noted that one must verify that a given equation is appropriate for the institutional creatinine reporting method.

Clinical Controversy...

Drug-dose individualization is often required in patients with chronic kidney disease (CKD). Approved drug labeling typically includes dose-adjustment information based on the patient’s estimated creatinine clearance ($\text{CL}_{\text{cr}}$) using the Cockcroft-Gault method. Automated estimated glomerular filtration rate (eGFR) reporting by many hospital laboratories has now raised the question if the four-variable Modification of Diet in Renal Disease Study equation (MDRD4)/CKD-EPI or any other GFR estimation equations should be used as a guide for drug-dose adjustments.

Estimation of Creatinine Clearance

Many equations describing the mathematical relationships between various patient factors and measured $\text{CL}_{\text{cr}}$, the most widely recognized surrogate for GFR in clinical settings. Most equations incorporate factors such as age, gender, weight, and serum creatinine concentration, without the need for urine collection. The most widely used of these estimators is the Cockcroft-Gault equation, which identified age and body mass as factors, which significantly contribute to the estimate of $\text{CL}_{\text{cr}}$. This relationship was based on...
observations from 249 male patients with stable kidney function in whom the creatinine production rates were estimated. Estimated creatinine clearance (eClcr), using the Cockcroft-Gault equation, is one of the methods endorsed by the FDA for stratifying patients in drug development pharmacokinetic studies, and has been reported most often in FDA-approved package inserts for new drug entities since the 1990s.7,26

One of the key considerations with the use of this equation is whether or not a modified weight index should replace 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/m² but less than 40 kg/m², it is generally recommended that total or actual body weight be used. This is based on a recent analysis by the FDA indicating that the Cockcroft-Gault equation had <10% bias in nearly 600 normal weight, overweight, and obese individuals enrolled in drug pharmacokinetic studies.220 In morbidly obese individuals (BMI ≥ 40 kg/m² obesity class III) an alternate measure of body weight such as lean body weight was shown to significantly reduce bias in the Cockcroft-Gault equation, where lean body weight (LBW) is calculated as:

\[
\text{LBW (kg, males)} = (9270 \times \text{weight}) / (6680 + 216 \times \text{BMI}) \\
\text{LBW (kg, females)} = (9270 \times \text{weight}) / (8780 + 244 \times \text{BMI})
\]

And BMI is calculated as:

\[
\text{BMI (kg/m}^2) = \text{weight (kg)} / \text{height (m)}^2
\]

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

### Clinical Controversy...

The use of ideal or lean body weight for estimating creatinine clearance (Clcr) in obese patients is controversial. Some clinicians recommend using a weight adjustment in patients that are greater than 30% above ideal body weight (IBW), such as using an adjusted body weight. However, recent studies by the FDA indicate that use of IBW should be avoided. Further research evaluating weight-based adjustments and drug pharmacokinetic outcomes is needed.

Luke et al.211 evaluated the ability of the Cockcroft-Gault method and four other methods to determine eClcr, with inulin clearance being considered the standard measure of GFR. The simultaneously determined inulin and measured creatinine clearances correlated best, \( r^2 = 0.85 \), and the measured Clcr overestimated Clin by approximately 15% due to tubular secretion of creatinine. Of the five estimated creatinine clearances, the ones calculated by the Cockcroft-Gault and Mawer et al. methods212 correlated the best with GFR. Other methods, such as Jelliffe213 and Hull et al.,214 consistently underestimated the measured Clcr (eTable 18-6).

Patients undergoing screening for participation in the African American Study of Kidney Disease (AASK) were evaluated for kidney function based on eClcr, simultaneous 125I-iothalamate and measured 24-hour Clcr.215 The simultaneous measured Clcr provided the best estimate of GFR. The Cockcroft-Gault method was the preferred method for eGFR, based on performance and ease of use. This method was noted to underestimate the GFR by 9%, perhaps because of the increased excretion rate of creatinine by black patients.216

Administration of cimetidine has also resulted in improved performance of the Cockcroft-Gault equation as means to calculate eGFR. Ixkes et al.217 gave patients three 800-mg doses of cimetidine in 24 hours, and measured creatinine plasma levels from 3 to 7 hours following the first dose. During this 4-hour period, the Cliothalamate was determined as the measure of GFR. The Cockcroft-Gault calculations were performed with the plasma creatinine measurement 3 hours after the last dose of cimetidine. The ratio of the Cockcroft-Gault eClcr-to-Cliothalamate decreased from 1.28 ± 0.21 to 0.98 ± 0.11 in the presence of cimetidine. This cimetidine dosing schedule also improved the accuracy of Cockcroft-Gault eClcr relative to GFR in renal transplant patients with GFR values ranging from 20 to 80 mL/min/1.73 m² (0.19 to 0.77 mL/s/m²).218,219

### Liver Disease

The estimation of Clcr or GFR is particularly problematic in patients with preexisting liver disease and renal impairment. Lower-than-expected serum creatinine concentration values may result from reduced muscle mass, protein-poor diet, diminished hepatic synthesis of creatine (a precursor of creatinine), and fluid overload leading to significant overestimation of Clcr. Orlando et al.220 evaluated 10 healthy subjects, 10 patients with mild liver disease, and 10 with severe liver disease, and observed a measured Clcr-to-Cliothalamate ratio of 1.05, 1.03, and 1.04 for each group, respectively. When the Clcr of patients with severe liver disease was estimated using the Cockcroft-Gault equation, the resultant ratio (eClcr-to-Cliothalamate) was 1.23. Lam et al.221 likewise noted an overestimation by Cockcroft-Gault of the measured Clcr in patients with severe disease, by 40% to 100%.

Studies of renal function in patients with severe hepatic disease confirm the earlier observations of Hull et al.222 and Caregaro et al.223 who reported that measured Clcr overestimated GFR by up to 50% in hepatic patients with a GFR of 56 ± 19 mL/min/1.73 m² (0.54 ± 0.18 mL/s/m²) because of increased tubular secretion of creatinine. The effect of cimetidine administration on measured Clcr was evaluated in a small study by Sansoe et al.224 In 12 patients with compensated cirrhosis, serum creatinine concentration values increased from 0.68 ± 0.11 to 0.94 ± 0.14 mg/dL (69 ± 10 µmol/L to 83 ± 12 µmol/L) during coadministration of cimetidine (1.000 mg given as 400 mg x 1 then 200 mg every 3 hours) during a 9-hour clearance period. The measured Clcr declined from 138 ± 20 prior to cimetidine administration to 89 ± 13 mL/min (2.30 ± 0.33 to 1.49 ± 0.22 mL/s), with no change in measured GFR.
In cirrhotic patients being evaluated for liver transplant (GFR 58 ± 5.1 mL/min/1.73 m² [0.56 ± 0.049 mL/s/m²]) the eGFR by the MDRD4 and MDRD6, and the eCLₘₜ by Cockcroft-Gault significantly overestimated measured GFR by 30% to 50%, and all three were considered unacceptable methods for renal function assessment in liver transplant patients.134,135

Recently, Gerhart et al.136 evaluated the performance of the CKD-EPI and MDRD4–IDMS equations in patients with liver disease following transplantation (group 1, n = 59) and those with cirrhosis (group 2; n = 44). When compared to measured GFR, both equations yielded positively biased estimates of GFR (4 to 9 mL/min/1.73 m² [0.04 to 0.09 mL/s/m²]) in transplanted patients. However, in patients with hepatic cirrhosis, both equations were more significantly positively biased (40 to 42 mL/min/1.73 m² [0.39 to 0.40 mL/s/m²]), with low precision (21 to 26 mL/min/1.73 m² [0.20 to 0.25 mL/s/m²]) and low accuracy with only 7% of patients having eGFR values within 30% of the measured GFR.

Thus, renal function assessment in patients with hepatic disease should be performed by measuring glomerular filtration, and estimation equations for GFR or eCLₘₜ should be avoided.

Other Special Populations
Davis and Chandler137 confirmed the accuracy of the Cockcroft-Gault eCLₘₜ method in trauma patients with stable kidney function, and Thakur et al.138 demonstrated its acceptable performance in 42 paraplegic patients. Renal transplant recipients are frequently monitored for renal function, as numerous complications may occur during the life of the allograft. Ruiz-Esteban et al.139 evaluated the bias and precision of the MDRD4 and CKD-EPI relative to Cockcroft-Gault in 153 postrenal transplant patients. Here, the mean bias for MDRD4 was –10.6 ± 12.7 compared to –9.8 ± 11.3 mL/min/1.73 m² (–0.10 ± 0.12 compared to –0.09 ± 0.11 mL/s/m²) for CKD-EPI (p = 0.006), with the CKD-EPI having a higher percentage of patients within 30% of the Cockcroft-Gault value than the MDRD equation (86.9% vs. 81.7%), p < .001). Huang et al.140 reported the inability of several CLₘₜ equations to predict renal function in hospitalized patients with advanced human immunodeficiency virus (HIV) disease. All of the prediction methods overestimated the measured 24-hour CLₘₜ. The reasons for the poor predictability of these methods are unclear, although 24-hour collection methods result in increased variability, often because of inadequate collection of urine.

Renal function assessment during pregnancy is usually performed using a 24-hour CLₘₜ determination, and estimation equations have been shown to perform poorly particularly in the preeclampsia population. For example, Alper et al.141 recently evaluated the Cockcroft-Gault, MDRD4 and CKD-EPI equations in 543 women, aged 16 to 49 years, with preeclampsia after the 20th week of gestation. When compared to 24-hour measured CLₘₜ (mean 133 ± 43 mL/min [2.22 ± 0.72 mL/s]), the Cockcroft-Gault equation was positively biased (36 ± 2 mL/min [0.60 ± 0.03 mL/s]) whereas both the MDRD4 and CKD-EPI were negatively biased (–20 ± 1.5 mL/min [–0.33 ± 0.025 mL/s]). Thus, kidney function estimating equations should not be used during pregnancy.

Unstable Renal Function
Patients with unstable kidney function or AKI present a unique situation because serum creatinine concentration values are changing, and steady state cannot be assumed, which is one of the assumptions of all the above-mentioned eCLₘₜ methods. It is now widely accepted that a change in the serum creatinine concentration of more than 50% over a period of 7 days, or an increase in serum creatinine concentration by at least 0.3 mg/dL (227 μmol/L) over a 24- to 48-hour period indicates the presence of AKI.141 Methods to measure GFR in this population, such as 123I-iothalamate clearance, are cumbersome and costly especially in the acute care setting. Although several equations have been proposed the calculate eCLₘₜ in AKI patients or those with rapidly progressive renal disease,142–144 a rigorous evaluation of the accuracy and precision of each of these proposed methods is lacking and none of them is currently recommended for clinical use. Use of semiquantitative approaches is preferred for the purpose of estimating severity of disease using RIFLE and AKIN criteria (see Chap. 28 for more details).

Use of abbreviated CLₘₜ measurements (<24 h) may be valuable for detecting early evidence of AKI in critically ill patients. Pickering et al.145 recently reported that 4-hour CLₘₜ measurements were significantly better at predicting AKI events than serum creatinine concentration alone in 484 patients. However, the lack of true measured GFR in these patients prevented assessment of the accuracy and precision of the CLₘₜ values. Hoste et al.146 used 1-hour CLₘₜ measurements to evaluate the Cockcroft-Gault and MDRD equations in critically ill patients within 1 week of ICU admission. Both equations were poorly correlated with CL¢ₘₜ (R < 0.5), and they were similarly imprecise with Bland-Altman 95% confidence intervals ranging from –77 to 64 mL/min (–1.29 to 1.07 mL/s) for Cockcroft-Gault and –77 to 58 mL/min/1.73 m² (–0.74 to 0.56 mL/s/m²) for MDRD. Changes in serum creatinine concentration have also been shown to be more sensitive than cystatin C in early AKI.

It is thus, ultimately, most important to recognize that renal function in patients with AKI is generally markedly lower than one would estimate using steady-state methods, and dose adjustments should be made if necessary to avoid drug toxicity (see Chaps. 28 and 33).

Kidney Function in Children
Kidney function in the neonate is difficult to assess because of difficulty in urine and blood collection, the frequent presence of a non–steady-state serum creatinine concentration, and apparent disparity between development of glomerular and tubular function. Preterm infants demonstrate significantly reduced GFR prior to 34 weeks, which rapidly increases and becomes similar to term infants within the first week of life.147 Evaluation of GFR in preterm infants on day 3 of life, using an infusium infusion, failed to identify a relationship between patient weight and GFR. Gestational age, which ranged from 23.4 to 36.9 weeks (mean: 30.2 weeks), however, correlated with both GFR and reciprocal of serum creatinine concentration (Sₜ). The inulin clearance increased from 0.67 to 0.85 mL/min (0.011 to 0.014 mL/s) in those with gestational age <28 weeks versus those of 32 to 37 weeks of age, while Sₜ decreased from 1.05 to 0.73 mg/dL (93 to 65 μmol/L), respectively. Creatinine was measured using a specific enzymatic method to avoid interference from bilirubin or drugs.148 Creatinine clearance has also been evaluated in infants younger than 1 week of age, and values of 17.8 mL/min/1.73 m² (0.351 mL/s/m²) by day 6.149 In light of these rapid changes in GFR, estimation of GFR is not recommended for infants younger than 1 week of age. Kidney function expressed as GFR standardized to body surface area 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 123I-iothalamate has been effectively used to measure GFR in children ranging in age from 1 to 20 years.150 The original equation to estimate GFR as described by Schwartz et al.151 is dependent on the child’s age and length:

\[
GFR = \left[ \text{length (cm)} \times k \right] / \left( Sₜ \text{ in mg/dL} \right)
\]

where \( k \) is defined by age group: infant (1 to 52 weeks) = 0.45; child (1 to 13 years) = 0.55; adolescent male = 0.7; and adolescent female = 0.55. Serum creatinine in mmol/L can be converted to mg/dL by multiplication using 0.0113 as the conversion factor.

A newer version of the Schwartz equation152 was developed from a population of 349 children (age 1 to 19 y) with mild-to-moderate
from over 600 pediatric patients enrolled the CKiD study\textsuperscript{155}: creatinine concentration (in mg/dL) and demographic data derived from pediatric patients. Peirrat et al.\textsuperscript{154} compared the MDRD, Schwartz, and Cockcroft-Gault equations in children 3 to 19 years of age. In children <12 years, the Schwartz and MDRD equations were significantly more biased than Cockcroft-Gault, and Cockcroft-Gault provided the best prediction of GFR in children >12 years. The results of these investigations suggest that further studies will be needed to clarify the value of any of these predictive methods in children. Most recently, an equation for GFR based on beta-trace protein was shown to yield similar values of GFR compared to the Schwartz equation in 387 pediatric patients (age 10.7 ± 7.1 y) who underwent a \textsuperscript{99m}TC-DTPA GFR scan.\textsuperscript{70} The most recent GFR equation evaluated in pediatrics includes use of cystatin C, BUN, serum creatinine concentration (in mg/dL) and demographic data derived from over 600 pediatric patients enrolled the CKiD study\textsuperscript{155}.

\begin{equation}
\text{GFR} = 0.41 \times \left(\frac{\text{length (cm)}}{S_{\text{cr}} \text{ in mg/dL}}\right)
\end{equation}

Lee et al.\textsuperscript{155} recently reported that this new Bedside Schwartz equation performed better than the original Schwartz equation for patients with mild-moderate CKD, but was less accurate in patients with mild CKD. Thus, the appropriate use of the Bedside Schwartz equation and accuracy in subpopulations of CKD is yet to be fully determined.

Equations derived from adult populations have also been evaluated in pediatric patients. Peirrat et al.\textsuperscript{154} compared the MDRD, Schwartz, and Cockcroft-Gault equations in children 3 to 19 years of age. In children <12 years, the Schwartz and MDRD equations were significantly more biased than Cockcroft-Gault, and Cockcroft-Gault provided the best prediction of GFR in children >12 years. The results of these investigations suggest that further studies will be needed to clarify the value of any of these predictive methods in children. Most recently, an equation for GFR based on beta-trace protein was shown to yield similar values of GFR compared to the Schwartz equation in 387 pediatric patients (age 10.7 ± 7.1 y) who underwent a \textsuperscript{99m}TC-DTPA GFR scan.\textsuperscript{70} The most recent GFR equation evaluated in pediatrics includes use of cystatin C, BUN, serum creatinine concentration (in mg/dL) and demographic data derived from over 600 pediatric patients enrolled the CKiD study\textsuperscript{155}.

\begin{equation}
\text{eGFR} = 39.9 \times \left(\frac{\text{ht(m)}}{1.4}\right)^{0.179} \times (1.8/\text{cystatin C})^{0.418} \times (30/\text{BUN})^{0.79} \times 1.076^{\text{male}} \times \left(\frac{\text{ht(m)}}{1.4}\right)^{0.179}
\end{equation}

This equation had the lowest root-mean square error (0.147), highest \( R^2 \) (0.863) and highest frequency of values within 30% of iohecol-measured GFR (91.3%) when compared to seven other GFR equations.

### Kidney Function in the Elderly

Cross-sectional studies have historically shown that GFR declines as a function of age.\textsuperscript{156,157} The largest prospective study conducted in healthy elderly individuals is the Baltimore Longitudinal Study on Aging (BLSA).\textsuperscript{157} In an initial analysis of 254 BLSA participants without kidney disease, it was reported that measured CL\textsubscript{cr} decreases at the rate of approximately 0.75 mL/min/1.73 m\textsuperscript{2} (0.0072 mL/s/m\textsuperscript{2}/y) beginning at the fourth decade of life. These subjects were then evaluated prospectively for up to 23 years. Importantly, approximately one-third of the subjects showed no change in renal function from their baseline value, and a small number showed an increased clearance. 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 renal function. Fliser et al.\textsuperscript{158} studied renal functional reserve in healthy young (23 to 32 years) and elderly (61 to 82 years) volunteers using an amino acid infusion technique. Measured GFR increased by 16% in young and 17% in elderly subjects following the infusion. Renal functional reserve thus appears to be maintained in healthy elderly individuals.

Interpretation of the serum creatinine concentration alone is difficult in the elderly patient primarily because of the decreased muscle mass and resultant lower production rate of creatinine. Thus, the serum creatinine concentration often remains within the normal range despite a reduction in the number of functional nephrons. As renal function declines, the kidneys excrete a larger fraction of creatinine. This perpetuates the “normal” serum creatinine concentration. Recent recommendations such as the adoption of standardized creatinine assays by clinical laboratories and reporting of serum creatinine concentration values to two decimal places will likely improve the accuracy of renal function estimation in the elderly population.\textsuperscript{154}

### Clinical Controversy...

**Estimation of creatinine clearance in elderly with low serum creatinine values is controversial.** Some clinicians advocate correction of serum creatinine to 1.0 mg/dL (88 \( \mu \)mol/L) to account for reduced muscle mass. This practice should be avoided, and the impact of this correction factor on glomerular filtration rate (GFR) estimates using the four-variable Modification of Diet in Renal Disease Study equation (MDRD4) or other equations has yet to be evaluated in this population.

The Cockcroft-Gault formula\textsuperscript{119} continues to provide a valid estimate of the CL\textsubscript{cr} of elderly patients. Smythe et al.\textsuperscript{159} estimated CL\textsubscript{cr} in 23 patients >60 years of age using seven different methods, and compared the results to a measured 24-hour CL\textsubscript{cr} determination. Estimations were performed with the actual serum creatinine concentration and also with the serum creatinine concentration rounded up to 1.0 mg/dL (88 \( \mu \)mol/L) if the actual value was <1.0 mg/dL (<88 \( \mu \)mol/L). Rounding the serum creatinine concentration to 1.0 mg/dL (88 \( \mu \)mol/L) resulted in a significantly lower eCL\textsubscript{cr} (-28.8 mL/min [-0.481 mL/s]) compared to the unadjusted serum creatinine concentration (+2.3 mL/min [+0.038 mL/s]). In patients >60 years of age with serum creatinine concentration <1.0 mg/dL (<88 \( \mu \)mol/L), rounding the serum creatinine concentration value up to 1.0 mg/dL (85 \( \mu \)mol/L) resulted in dose estimates for gentamicin that were significantly lower (-90 ± 67 mg/day) than doses calculated based on the actual serum creatinine concentration value.\textsuperscript{160} Until further data are available, fixing or rounding serum creatinine concentration to an arbitrary value in elderly patients is not recommended.

An alternative to the estimation of GFR or a 24-hour measured CL\textsubscript{cr} is a 4-hour measured clearance performed during water diuresis. This approach correlated with the inulin clearance as well as with an observed inpatient 24-hour measured CL\textsubscript{cr}.\textsuperscript{161} However, one must be aware of the potential risk of hyponatremia in the geriatric patient who is unable to tolerate an oral water load, as well as the need for complete bladder emptying to ensure accurate results. O’Connell et al.\textsuperscript{161} assessed the accuracy of 2- and 8-hour urine collections compared with 24-hour CL\textsubscript{cr} determinations in 45 hospitalized patients >65 years old with indwelling urethral catheters. The 8-hour timed urine collection for CL\textsubscript{cr} showed minimal bias (2.2 mL/min [0.037 mL/s]) as compared with the 24-hour value, whereas the 2-hour determination was both positively biased (11 mL/min [0.18 mL/s]) and less precise (25 mL/min [0.42 mL/s]).

### 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 CL\textsubscript{cr} for renal dose adjustments. Concerns with this approach, particularly in the elderly, include the uncertainty of applying eGFR values to CL\textsubscript{cr}-based dosage adjustment algorithms in package inserts, which may result in dosing errors and toxicity especially for drugs with narrow therapeutic indices.\textsuperscript{162–169} Roberts et al.\textsuperscript{162} reported that the MDRD eGFR values overestimated gentamicin clearance by 29% (\( p < 0.001 \)), whereas the Cockcroft-Gault yielded only 10% overestimation (\( p < 0.01 \)), and MDRD overestimated renal function as age increased. Retrospective studies in more than 1,200 patients with renal disease have shown that overestimation of renal function using the MDRD4 with or without IDMS creatinine equation results in up to 30% to 60% higher doses for digoxin, amantadine
and various antimicrobials compared to doses calculated using eCLcr. A recent study by Stevens et al.170 reported that use of a back-corrected value of eGFR, based on a calculated body surface area (BSA), yields dose calculations that are similar to those calculated using a measured GFR. This back-correction approach has not been validated and calculating BSA in clinical settings is inconvenient and unlikely to occur. A more detailed discussion of application of renal function estimates and renal dosing approaches is provided in Chapter 33.

ASSESSMENT OF PROGRESSION

Chronic kidney disease (see Chap. 29) will eventually lead to ESRD, necessitating dialysis (see Chap. 30) or transplantation for survival (see Chap. 70). The rate of progression can be slowed and in some cases halted through dietary modification, strict blood pressure control, initiation of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy to reduce urinary protein excretion, and improved glucose control in patients with diabetes mellitus (see Chap. 29). The efficacy of these interventions is optimally assessed with the sequential measurement of an accurate and sensitive index of GFR such as iohexol, iothalamate, or radioisotope clearance.

Alternatively, use of newer methods to estimate GFR, such as cystatin C and the CKD-EPI equation or traditional methods, such as the linear decline in the reciprocal of the Scr as a function of time, can be used to evaluate the rate of progression of renal disease and to predict the time when dialysis will be needed.128

eFigure 18-4 depicts the change in estimated GFR or CLcr over time in a typical patient with progressive CKD. Clinicians can use the GFR or CLcr plotted as a function of time as a prognostic tool, to predict when dialysis may be needed (eCLcr <15 mL/min [<0.25 mL/s]) or as a marker for evaluating the success of therapeutic interventions to alter the rate of decline in renal function. Several factors, such as changes in dietary intake of creatinine and decreased muscle mass, which are associated with a reduction in the production of creatinine, may alter the utility of the relationship. Microalbuminuria has been identified as an early marker of renal disease in patients with diabetic nephropathy173 and numerous other conditions, such as hypertension and obesity.174–177 Albuminuria is a more sensitive marker than total protein for monitoring CKD progression, as well as a modifiable risk factor for renal disease progression and cardiovascular disease.61

Thus patients with microalbuminuria (30 to 300 mg/day) on at least two occasions or overt albuminuria (>300 mg/day) should begin to receive pharmacotherapy. For children, microalbuminuria is considered present if albumin excretion exceeds 0.36 mg/kg/day, and overt albuminuria has been defined as an excretion rate that exceeds 4 mg/kg/day. The urinary albumin-to-creatinine ratio is also an accurate predictor of 24-hour proteinuria, a marker of renal disease. Guidelines for monitoring indicate that a urine albumin to creatinine ratio of >30 mg/g (>3.4 mg/mmol) places the patient at increased risk of developing diabetic nephropathy, mortality, and ESRD and is an indication for the initiation of pharmacotherapeutic intervention.4,23 Microalbuminuria has also been suggested as a risk factor for renal dysfunction among patients with essential hypertension.175

Based on the established link between albuminuria and adverse clinical outcomes in more than 1.5 million individuals with varying levels of eGFR, the albumin-to-creatinine ratio is now included with eGFR as part of an updated approach for staging CKD recommended by KDIGO.5

MEASUREMENT OF RENAL PLASMA AND BLOOD FLOW

Measurement of renal plasma and blood flow is rarely if ever determined in the clinical setting; and it is only occasionally used in research settings to evaluate hemodynamic changes related to disease or drug therapy. The kidneys receive approximately 20% of cardiac output and representative values of renal blood flow in men and women of about 1,200 ± 250 and 1,000 ± 180 mL/min/1.73 m2 (11.6 ± 2.4 and 9.6 ± 1.7 mL/s/m2) have been reported, respectively.176 Renal plasma flow (RPF) is estimated to be 60% of blood flow if it is assumed that the average hematocrit is 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. Because only 20% of the plasma is filtered at the glomerulus, the compound must undergo active tubular secretion and minimal to no reabsorption to be completely eliminated. To accurately reflect RPF, the extraction through the kidney must be nearly 100%. PAH is an organic anion that has been used extensively for the quantification of renal plasma flow. 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. Furthermore, PAH is also metabolized, possibly within the kidney, to N-acetyl-PAH, and it is important for the analytical method to differentiate the parent compound from the metabolite.80,177 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 extraction ratio or if it is assumed to be 1.8 Normal values are about 650 ± 160 mL/min (10.9 ± 2.7 mL/s) for men and 600 ± 150 mL/min (10.0 ± 2.5 mL/s) for women.176 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 of age. The method for calculation of ERPF is based on the relationship between organ clearance, ER, and flow:

\[ \text{ERPF} = \text{renal PAH CL} = \text{RPF} \times \text{ER} \]
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 (hematocrit (HCT)):

\[
ERBF = \frac{ERPF}{1 – HCT}
\]

ERPF can also be measured using the radioisotopes\(^{132}\) I-orthoiodohippurate (\(^{131}\)I-OIH) or \(^{99m}\)Tc-mercaptoacetyltriglycine (\(^{99m}\)Tc-MAG3).\(^{78}\) One important advantage of this method is its ability to measure ERPF in total or for each kidney independently, as well as its ability to produce renal images. Russell and Dubovsky,\(^{79}\) using a single-injection technique, compared clearance methods with and without urine collection and showed similar results with each method.

### Quantitative Assessment of Tubular Function

Although GFR is the best overall indicator of renal function, it may not provide an accurate measure of tubular function, either secretory capacity or cellular function, suitable for use in the research environment.\(^{180}\) Tubular secretory function can be assessed by measuring PAH transport as the prototype marker of the organic anion secretory system. \(N\)-methylnicotinamide (NMN) and tetraethylammonium are prototype compounds secreted by the cationic transport system and may be used as markers of cationic secretory capacity. Edwards et al.\(^{181}\) demonstrated delayed recovery of NMN clearance among patients with psoriasis treated with low-dose cyclosporine, as compared with the recovery of GFR and renal blood flow Dowling et al.\(^{177}\) explored the usefulness of famotidine as a marker for dose-dependent cationic transport, but was unable to demonstrate saturation at doses up to ten times clinically indicated values, likely due to the contribution from other parallel secretory pathways such as P-glycoprotein.\(^{182}\)

Furthermore, Karyekar et al.\(^{183}\) demonstrated that itraconazole, a P-glycoprotein inhibitor, significantly reduced the renal tubular secretion of cimetidine in healthy individuals, suggesting that cimetidine may be used as an in vivo probe of renal P-glycoprotein function. It should also be recognized that these transport systems are not necessarily mutually exclusive. Indeed, probenecid, which is secreted by the anionic pathway, inhibits the secretion of cationic compounds. Quantitative measures of tubular transport capacity are currently limited primarily to the research setting.

Other measures of tubular function are less specific and are regarded primarily as indices of damage within the nephron. Low-molecular weight proteins located in the proximal tubule, such as \(\beta_2\)-microglobulin, can be used as urinary biomarkers to detect early tubular toxicity of drugs such as carboplatin, ifosfamide and etoposide.\(^{184}\) Other low-molecular-weight proteins used as markers of tubular function include retinol-binding protein (21 kDa), protein HC (also known as \(\alpha_1\)-microglobulin, 27 kDa), KIM-1, NGAL, interleukin-18, and fatty-acid binding proteins (FABPs).\(^{65,185,186}\) These proteins are normally freely filtered at the glomerulus and then completely reabsorbed by the proximal tubule. Increases in their excretion are thus suggestive of tubular dysfunction but are not diagnostic. In each case, the maximal reabsorptive capacity may be exceeded, leading to net excretion of the protein.

Numerous urinary enzymes such as \(N\)-acetylglucosaminidase, alanine aminopeptidase, alkaline phosphatase, \(\gamma\)-glutamyltransferase, pyruvate kinase, glutathione transferase, lysozyme, and pancreatic ribonuclease have been used as diagnostic markers for renal disease. Jung et al.\(^{187}\) compared the ability of five enzymes (\(N\)-acetylglucosaminidase, alanine aminopeptidase, alkaline phosphatase, \(\gamma\)-glutamyltransferase, and lysozyme) to detect early rejection episodes in kidney transplant patients. Only \(N\)-acetylglucosaminidase and alanine aminopeptidase were early predictors of rejection. \(N\)-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 were increased approximately 2 days earlier than serum creatinine concentration in patients with transplant rejection.

### Qualitative Diagnostic Procedures

#### Radiologic Studies

1. The etiology of kidney disease can be evaluated using several qualitative diagnostic techniques, including radiography, ultrasonography, magnetic resonance imaging, and biopsy. The standard radiograph of the kidneys, ureters, and bladder (the KUB) provides a gross estimate of kidney size and identifies the presence of calcifications.\(^{66}\) 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.\(^{188}\) Computed tomography is a cross-sectional anatomic imaging procedure. The procedure is frequently performed with contrast to enhance imaging. Spiral, or helical, computed tomography, a more recent technique, 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.

2. Renal Ultrasonography

Ultrasonography uses sound waves to generate a two-dimensional image. 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.

3. 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. The relative advantages and limitations of these procedures are discussed in more detail in recent reviews.86,189

**Biopsy**

Renal biopsy is used in several conditions to facilitate diagnosis when clinical, laboratory, and imaging findings prove inconclusiVe. 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.23

**CLINICAL BOTTOM LINE**

Comprehensive approaches to evaluate renal function in CKD patients include the Cockcroft-Gault equation for estimating Clcr, and drug dosing, the CKD-EPI equation for estimation of GFR and staging of CKD, and measurement of urinary protein excretion or albumin-to-creatinine ratio as a marker of the integrity of the glomerular basement membrane. Measurement of GFR using exogenous administration of iohexol, iothalamate, or radioisotope techniques such as 99mTc-DPTA is increasingly being employed to assess progression of disease or acceptability 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 investigate the underlying cause of kidney disease.

**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADP</td>
<td>adenosine diphosphate</td>
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<tr>
<td>AKI</td>
<td>acute kidney injury</td>
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<td>AASK</td>
<td>African American Study of Kidney Disease</td>
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<td>ATP</td>
<td>adenosine triphosphate</td>
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<tr>
<td>AUC</td>
<td>area under the plasma concentration versus time curve</td>
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<tr>
<td>BLSA</td>
<td>Baltimore Longitudinal Study on Aging</td>
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<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>BSA</td>
<td>body surface area</td>
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<tr>
<td>BTP</td>
<td>β-trace protein</td>
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<tr>
<td>BUN</td>
<td>blood urea nitrogen</td>
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<tr>
<td>CIAKI</td>
<td>contrast-induced acute kidney injury</td>
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<tr>
<td>CKD</td>
<td>chronic kidney disease</td>
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<tr>
<td>CKD-EPI</td>
<td>Chronic kidney disease epidemiology collaboration</td>
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<tr>
<td>CKiD</td>
<td>Chronic Kidney Disease in Children</td>
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<tr>
<td>CL</td>
<td>clearance</td>
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<tr>
<td>Clcr</td>
<td>creatinine clearance</td>
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<tr>
<td>51Cr-EDTA</td>
<td>51Cr-ethylenediaminetetraacetic acid</td>
</tr>
<tr>
<td>Ccr</td>
<td>concentration of a substance in plasma under steady-state conditions</td>
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<tr>
<td>CYP</td>
<td>cytochrome P450</td>
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<tr>
<td>eClcr</td>
<td>estimated creatinine clearance</td>
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<tr>
<td>cGFR</td>
<td>estimated glomerular filtration rate</td>
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<tr>
<td>ER</td>
<td>extraction ratio</td>
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<tr>
<td>ERBF</td>
<td>effective renal blood flow</td>
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<tr>
<td>ERPF</td>
<td>effective renal plasma flow</td>
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<td>ESRD</td>
<td>end-stage renal disease</td>
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<tr>
<td>FABP</td>
<td>fatty-acid binding protein</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GFR</td>
<td>glomerular filtration rate</td>
</tr>
<tr>
<td>GPI</td>
<td>glycoprotein IIb/IIIa inhibitor</td>
</tr>
<tr>
<td>HCT</td>
<td>hematocrit</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>ICU</td>
<td>intensive care unit</td>
</tr>
<tr>
<td>IDMS</td>
<td>isotope dilution-mass spectrometry</td>
</tr>
<tr>
<td>131I-OIH</td>
<td>131I-orthoiodohippurate</td>
</tr>
<tr>
<td>KDIGO</td>
<td>Kidney Disease: Improving Global Outcomes</td>
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<tr>
<td>KUB</td>
<td>kidneys, ureters, and bladder</td>
</tr>
<tr>
<td>MCQ</td>
<td>Mayo Clinic Quadratic Equation</td>
</tr>
<tr>
<td>MDRD</td>
<td>Modification of Diet in Renal Disease study</td>
</tr>
<tr>
<td>MDRD4</td>
<td>four-variable Modification of Diet in Renal Disease Study equation</td>
</tr>
<tr>
<td>MDRD6</td>
<td>six-variable Modification of Diet in Renal Disease Study equation</td>
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<tr>
<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
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<tr>
<td>NKDEP</td>
<td>National Kidney Disease Education Program</td>
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<tr>
<td>NKF</td>
<td>National Kidney Foundation</td>
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<tr>
<td>NMN</td>
<td>N-methylnicotinamide</td>
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<tr>
<td>PAH</td>
<td>para-aminohippuric acid</td>
</tr>
<tr>
<td>RPF</td>
<td>renal plasma flow</td>
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<tr>
<td>Sccr</td>
<td>serum creatinine concentration</td>
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<tr>
<td>SUN</td>
<td>serum urea nitrogen</td>
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<tr>
<td>99mTc-DTPA</td>
<td>technetium-99m diethylenetriamine pentaacetic acid</td>
</tr>
<tr>
<td>99mTc-MAG3</td>
<td>99mTc-mercaptoacetyltriglycine</td>
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**REFERENCES**

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Organ-Specific Function Tests and Drug-Induced Diseases

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61. Brosius FC, Hostetter TH, Kelępours E, et al. Detection of chronic kidney disease in patients with or at increased risk of cardiovascular disease: A science advisory from the American Heart Association Kidney and Cardiovascular Disease Council; the Councils on High Blood Pressure Research, Cardiovascular Disease in the Young, and Epidemiology and Prevention; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: Developed in collaboration with the National Kidney Foundation. Circulation 2006;114(10):1083–1087.


