in the clinic

Chronic Kidney Disease

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Chronic kidney disease (CKD) is currently defined as either functional or structural kidney damage or a glomerular filtration rate (GFR) less than 60 mL/min per 1.73 m² for at least 3 months (1). CKD affects as many as 25 million people in the United States, and more than 500,000 have end-stage renal disease (2, 3). The most common risk factors for CKD are diabetes and hypertension. Patients with CKD are at increased risk for cardiovascular disease. In fact, the risk for dying of cardiovascular disease in older patients with CKD is often higher than the risk for progression to treated end-stage renal disease (4, 5). Other complications of CKD include anemia, secondary hyperparathyroidism, bone disease, vascular complications, and electrolyte disturbances. The main goals of treatment are to slow the decline in renal function, prevent cardiovascular disease, and treat complications. Collaboration between the primary care physician and nephrologists can improve the care of patients with this challenging condition.

Table 1. Risk Factors for Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Clinical factors</th>
<th>Sociodemographic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Family history of chronic kidney disease</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Older age</td>
</tr>
<tr>
<td>Primary glomerular disease</td>
<td>Black race</td>
</tr>
<tr>
<td>Autoimmune diseases</td>
<td>Smoking</td>
</tr>
<tr>
<td>Systemic infections</td>
<td>Obesity</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>Certain medications (aminoglycosides, cisplatinum, long-term compound analgesic use)</td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td></td>
</tr>
<tr>
<td>Lower urinary tract obstruction</td>
<td></td>
</tr>
<tr>
<td>Hereditary renal disease (autosomal dominant polycystic kidney disease, the Alport syndrome)</td>
<td></td>
</tr>
<tr>
<td>Certain medications (cisplatinum, proton-pump inhibitors)</td>
<td></td>
</tr>
</tbody>
</table>

Kidney Disease Outcomes and Quality Initiative (KDOQI) guidelines of the National Kidney Foundation (NKF) do recommend screening individuals at increased risk for CKD (1). These guidelines were invaluable in writing In the Clinic, but their goal of comprehensive coverage of the topic means that some guidelines are based on clinical consensus rather than solid evidence. For example, evidence about the effect of targeted screening on clinical outcomes is lacking. Individuals at increased risk include those older than 55 years; those with hypertension or diabetes; and specific ancestral groups, such as African Americans, Native Americans, Hispanics, Asians, and Pacific Islanders (7). The Box lists tests recommended for patients at increased risk (5), which include screening patients with diabetes for microalbuminuria (30 to 299 µg/mg creatinine in a spot urine sample) at the time of diagnosis and then annually (8).

In the HUNT II study of a community-based population, 3069 of 65,604 participants (4.7%) had CKD (estimated GFR <60 mL/min per 1.73 m²). Screening only individuals with hypertension, diabetes, or age greater than 55 years identified 93.2% (95% CI, 92.4% to 94.0%) of patients with CKD (number needed to screen to identify 1 person with CKD, 8.7 [CI, 8.5 to 9.0]) (9).
What can clinicians and patients do to prevent CKD?

Primary prevention of CKD means preventing the 2 principal risk factors: diabetes and hypertension. In patients with diabetes or hypertension, secondary prevention of CKD means maintaining good control of blood sugar and blood pressure. In patients with diabetes, hyperglycemia is associated with the development and progression of diabetic nephropathy. Although current KDOQI guidelines recommend maintaining hemoglobin A1c level at less than 7.0%, recent randomized trial evidence suggests that cardiovascular disease (CVD) events increase when the hemoglobin A1c level is below 6.5% (10). Therefore, patients with CKD due to diabetes may wish to maintain a hemoglobin A1c level close to 7.5% but not less than 7.0% while waiting for a consensus about the optimum maintenance level.

Hypertension is the second most common risk factor for CKD in the United States; it hastens loss of renal function regardless of the primary cause of CKD. How often it causes CKD is controversial. According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines, patients with hypertension should maintain blood pressure less than 140/90 mm Hg (less than 130/80 mm Hg if they have diabetes) by using lifestyle modification and antihypertensive drug therapy (11). An angiotensin-converting enzyme (ACE) inhibitor or an angiotensin-receptor blocker (ARB) are the recommended drugs, often with a thiazide diuretic (5).

Screening and Prevention... No high-quality evidence shows that screening for CKD alters clinical outcomes. Practice guidelines do not recommend screening average-risk, healthy individuals but do recommend screening patients with diabetes for proteinuria by measuring the urine albumin level or protein–creatinine ratio. Some guidelines recommend screening patients older than 55 years and those with hypertension and diabetes for CKD by measuring blood pressure, estimating GFR by measuring serum creatinine level, and testing for proteinuria. To prevent CKD in patients with diabetes, maintain strict blood pressure control and glycemic control. In patients with hypertension, maintain strict blood pressure control.

What is the definition of CKD?
The NKF KDOQI guidelines define CKD as kidney damage or a GFR less than 60 mL/min per 1.73 m² for more than 3 months (5). The guidelines define kidney damage as either functional abnormalities of the kidneys (such as proteinuria; albuminuria; or abnormalities of the urinary sediment, such as dysmorphic erythrocytes) or structural abnormalities as noted on imaging studies (Table 2) (5). This definition is controversial because it applies the label “CKD” to older persons whose GFR is less than 60 mL/min per 1.73 m² (which can be in the normal range for older persons) but who have no kidney damage.

Applying the NKF KDOQI definition—which is controversial—to the 1999 to 2004 NHANES data, 13% of the U.S. adult population has CKD (stages 1–5), which represents a 30% increase in prevalence over a 10-year period (1).

How should clinicians classify CKD and construct a differential diagnosis?

According to the NKF KDOQI guidelines, the 3 broad categories of CKD are diabetic kidney disease,
nondiabetic kidney disease (with subcategories of glomerular, tubulo-interstitial, vascular [including hypertension], and cystic), and kidney disease in the transplant recipient (including chronic rejection, drug toxicity, recurrent diseases, or transplant glomerulopathy) (Table 3). Whether hypertension is an important cause of CKD is controversial. Hypertension is far more often a consequence of advancing CKD than it is a cause, although African Americans with hypertension are particularly likely to develop CKD.

What elements of the history and physical examination may be useful in determining the cause of CKD?

CKD is most often an asymptomatic disorder. However, a careful history and physical examination will reveal the likely cause in a majority of cases. The search for a cause should start with diabetes because it is a common cause of CKD. Patients with long-standing, poorly controlled diabetes who have other diabetic complications, such as retinopathy and peripheral neuropathy, are also likely to have diabetic nephropathy. Similarly, patients with long-standing hypertension with hypertensive retinopathy and a family history of hypertension and CKD are likely to have hypertensive nephrosclerosis, especially if they are African American and have minimal proteinuria and no hematuria. Occasionally, hypertension is the first manifestation of CKD, especially with immunoglobulin A nephropathy and autosomal dominant polycystic kidney disease.

If hypertension and diabetes are not present, the search for a cause becomes more challenging. A careful history and physical examination may reveal a history of heart failure or cirrhosis, which suggests decreased renal perfusion from decreased effective intravascular volume as a cause. Persistent proteinuria is a clue to underlying glomerular disease. Hepatitis B and C and HIV infection may cause CKD and proteinuria, so clinicians should ask about intravenous drug use and high-risk sexual behavior. A family history of kidney disease may be a clue to the diagnosis of polycystic kidney disease, the Alport syndrome, or medullary cystic kidney disease. Urinary frequency, hesitancy, incontinence, nocturia, dysuria, or hematuria may reflect underlying urinary tract disease, such as obstruction or infection (12, 13). The presence of a skin rash, arthritis, mononeuropathy, or systemic symptoms suggests vasculitis or a multisystem illness, such as lupus. Clinicians should ask about recent diarrhea, bleeding, and dehydration, because volume loss may decrease renal perfusion and cause a short- or long-term decline in GFR. Finally, a thorough medication history of prescription and over-the-counter drugs may reveal medications that can cause CKD or require dose adjustment because of loss of renal function.

Physical examination should include taking the blood pressure and checking for orthostasis in patients with recent fluid loss. Rashes and petechiae could suggest an underlying vasculitis. Fundoscopic examination may

Table 2. Structural Abnormalities of the Kidney and Their Significance*

<table>
<thead>
<tr>
<th>Finding</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound</td>
<td></td>
</tr>
<tr>
<td>General appearance</td>
<td>Nephrocalcinosis, stones, cysts, masses, hydronephrosis</td>
</tr>
<tr>
<td>Increased echogenicity</td>
<td>Cystic disease</td>
</tr>
<tr>
<td>Small, hyperechoic kidneys</td>
<td>Usually means chronic kidney disease</td>
</tr>
<tr>
<td>Large kidneys</td>
<td>Tumors, infiltrating disease, causes of the nephritic syndrome, cystic disease</td>
</tr>
<tr>
<td>Size difference and scarring</td>
<td>Suggests vascular, urologic, or interstitial disease</td>
</tr>
<tr>
<td>Doppler interrogation</td>
<td>May be useful to detect venous thrombosis</td>
</tr>
<tr>
<td>Intravenous pyelography</td>
<td>May show asymmetry of structure or function, stones, medullary sponge kidney</td>
</tr>
<tr>
<td>Computed tomography</td>
<td>Obstruction, tumors, cysts, ureteral calculi</td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td>Masses, cysts, renal vein thrombosis, renal artery stenosis</td>
</tr>
<tr>
<td>Nuclear scanning</td>
<td>Asymmetry, renal artery stenosis, acute pyelonephritis, scars</td>
</tr>
</tbody>
</table>

*Adapted from reference 5.
reveal diabetic retinopathy (microaneurysms, dot hemorrhages, and cotton wool spots) or hypertensive retinopathy (arteriovenous nicking, silver wiring, tortuosity, hemorrhages, exudates, and papilledema). Volume overload from heart failure may manifest as pulmonary rales,

Table 3. Differential Diagnosis of Chronic Kidney Disease*

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Cause</th>
<th>Prevalence among Incident Dialysis Patients, 2001–2005†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic glomerulosclerosis</td>
<td>Diabetes mellitus (types 1 and 2)</td>
<td>44.9%</td>
</tr>
<tr>
<td>Glomerular diseases</td>
<td></td>
<td>10.4%</td>
</tr>
<tr>
<td>Proliferative glomerulonephritis</td>
<td>Systemic lupus erythematosus, vasculitis, bacterial endocarditis, chronic hepatitis B or C, HIV infection</td>
<td></td>
</tr>
<tr>
<td>Membranoproliferative glomerulonephritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal proliferative glomerulonephritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse proliferative glomerulonephritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crescentic glomerulonephritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noninflammatory glomerular diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal change disease</td>
<td>Hodgkin disease</td>
<td></td>
</tr>
<tr>
<td>Focal glomerular sclerosis</td>
<td>HIV infection, drugs (pamidronate), lithium</td>
<td></td>
</tr>
<tr>
<td>Membranoproliferative disease</td>
<td>Drug toxicity, solid tumors, chronic infections</td>
<td></td>
</tr>
<tr>
<td>Fibrillar glomerular diseases</td>
<td>Amyloidosis, light chain disease</td>
<td></td>
</tr>
<tr>
<td>Vascular diseases</td>
<td></td>
<td>27.6%</td>
</tr>
<tr>
<td>Diseases of large-size vessels</td>
<td>Renal artery stenosis</td>
<td></td>
</tr>
<tr>
<td>Diseases of medium-size vessels (nephrosclerosis)</td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>Diseases of small vessels (microangiopathy)</td>
<td>Sickle cell disease, the hemolytic uremic syndrome (including cyclosporine or tacrolimus toxicity), systemic and renal-limited vasculitis</td>
<td></td>
</tr>
<tr>
<td>Tubulointerstitial diseases</td>
<td></td>
<td>4.6%</td>
</tr>
<tr>
<td>Tubulointerstitial nephritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>Infection, kidney stones</td>
<td></td>
</tr>
<tr>
<td>Analgesic nephropathy</td>
<td>Compound analgesics</td>
<td></td>
</tr>
<tr>
<td>Allergic interstitial nephritis</td>
<td>Antibiotics</td>
<td></td>
</tr>
<tr>
<td>Granulomatous interstitial nephritis</td>
<td>Sarcoidosis</td>
<td></td>
</tr>
<tr>
<td>Autoimmune interstitial nephritis</td>
<td>Uveitis</td>
<td></td>
</tr>
<tr>
<td>Noninflammatory tubulointerstitial diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reflux nephropathy</td>
<td>Vesico-ureteral reflux</td>
<td></td>
</tr>
<tr>
<td>Obstructive nephropathy</td>
<td>Malignancy, BPH, kidney stones</td>
<td></td>
</tr>
<tr>
<td>Myeloma kidney</td>
<td>Multiple myeloma</td>
<td></td>
</tr>
<tr>
<td>Cystic diseases</td>
<td></td>
<td>2.2%</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>Autosomal dominant or recessive</td>
<td></td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Von Hippel Lindau syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medullary cystic disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hereditary renal diseases</td>
<td></td>
<td>not applicable</td>
</tr>
<tr>
<td>The Alport syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fabry disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diseases in the transplant recipient</td>
<td></td>
<td>not applicable</td>
</tr>
<tr>
<td>Chronic rejection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug toxicity</td>
<td>Cyslosporine or tacrolimus</td>
<td></td>
</tr>
<tr>
<td>Recurrent disease</td>
<td>Glomerular diseases</td>
<td></td>
</tr>
<tr>
<td>Transplant glomerulopathy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BPH = benign prostatic hypertrophy; ESRD = end-stage renal disease; NSAIDs = nonsteroidal anti-inflammatory drugs.

* Adapted from reference 1.
jugular venous distention, an S₂, or peripheral edema. Listen for a renal bruit, which suggests renal artery stenosis (14). Inflamed joints suggest vasculitis and autoimmune processes. Finally, asterixis and encephalopathy on neurologic examination or signs of pericarditis may indicate advanced uremia and the need to start dialysis immediately (15).

What other studies should clinicians obtain in evaluating patients with CKD?

Estimate the GFR (eGFR) in every CKD patient by measuring serum creatinine levels. Measure serum electrolytes (sodium, potassium, chloride, and bicarbonate); complete blood cell count; lipid profile; uric acid; serum albumin; spot urine albumin–creatinine or protein–creatinine ratio; and a urinalysis for dysmorphic erythrocytes and especially erythrocyte casts suggest active glomerular disease. Because patients with CKD are at high risk for cardiovascular disease (3, 4), test for CVD risk factors and estimate CVD risk with the Framingham Risk scoring system.

How should clinicians estimate GFR and the stage of CKD?

To estimate GFR, clinicians should use the simplified Modification of Diet in Renal Disease (MDRD) equation, which gives GFR in mL/min per 1.73 m², or the Cockcroft–Gault equation, which gives the creatinine clearance in mL/min (see Box) (17). Creatinine clearance is usually about 20% higher than true GFR. Estimated GFR or creatinine clearance is a more accurate measure of renal function than serum creatinine alone, particularly in older patients (19), but neither is sufficiently accurate to avoid misclassifying 20% to 25% of patients. The eGFR calculated with the MDRD equation and the true GFR are very close when the GFR is less than 60 mL/min per 1.73 m², whereas the true GFR exceeds the estimated rate by a small amount when the GFR is greater than 60 mL/min per 1.73 m² (20).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (mL/min per 1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or increased GFR</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with decreased GFR</td>
<td>60–89</td>
</tr>
<tr>
<td>3</td>
<td>Moderately decreased GFR</td>
<td>30–59</td>
</tr>
<tr>
<td>4</td>
<td>Severely decreased GFR</td>
<td>15–29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 (or dialysis)</td>
</tr>
</tbody>
</table>

GFR = glomerular filtration rate

**Table 4. Stages of Chronic Kidney Disease**
Estimated GFR has not been validated in vegans or very old, very young, or severely obese or malnourished persons.

Classify the stage of CKD according to the patient’s GFR, as outlined in Table 4 (5). Remember that eGFR cannot reliably distinguish between stage 1 and 2 CKD. Also, GFR declines as people age, so older people with an eGFR of 45 to 59 mL/min per 1.73 m², no proteinuria, and normal renal imaging may have normal kidney function for their age.

When should clinicians ask a nephrologist to evaluate a patient in the early stages of CKD?

Obtain a nephrology consultation in patients with proteinuria greater than 3.5 g per 24 hours, evidence of nephritis (hematuria, proteinuria, and hypertension), an eGFR decline of 50% within a 1-year period, or type 2 diabetes with proteinuria but no retinopathy or neuropathy. The KDOQI guidelines recommend referral for all patients with a GFR less than 30 mL/min per 1.73 m² (5).

**Diagnosis...** The definition of CKD is kidney damage or an eGFR less than 60 mL/min per 1.73 m² for greater than 3 months. The first step in diagnosis is to classify a patient as having diabetic nephropathy, nondiabetic kidney disease, or transplant-related kidney disease. The history and physical examination often point to a cause, but a definitive diagnosis requires a variety of diagnostic tests, renal ultrasonography, and sometimes a renal biopsy.

**CLINICAL BOTTOM LINE**

**Treatment**

Reducing sodium intake from the high to intermediate level reduced the systolic blood pressure by 2.1 mm Hg (P < 0.001) among patients on the control diet and by 1.3 mm Hg (P = 0.03) among patients on the DASH diet. Reducing sodium intake from the intermediate to the low level caused additional reductions of 4.6 mm Hg (P < 0.001) and 1.7 mm Hg (P < 0.01) among participants on the control and DASH diets, respectively. Although lower-sodium content had more effect in participants on the control diet, blood pressure was lower on the DASH diet than on the control diet at all levels of sodium intake (22).

Finally, although the MDRD randomized trial of a low-protein diet showed only a statistically non-significant trend toward delayed progression of CKD, subsequent analyses, meta-analyses, and guidelines recommend that patients with stage 4 or 5 CKD consider a low-protein diet (0.6 g/kg per day) (23–26). Patients starting a low-protein diet should be well-nourished and under the care of

What dietary modifications delay the progression of CKD?

Patients with prehypertension or stage 1 hypertension should adopt the DASH diet (Dietary Approaches to Stop Hypertension), which is high in fruits, vegetables, and dairy foods containing little total saturated fat and cholesterol. However, the DASH diet is only recommended for patients with a GFR greater than 60 mL/min per 1.73 m² because it contains more protein, potassium, and phosphorus than recommended for patients with stage 3 or 4 CKD (21). Patients with CKD and hypertension should restrict their dietary sodium intake to less than 2.4 g/d.

In the DASH–Sodium study, 412 participants were randomly assigned to either a control diet typical of the United States or the DASH diet. All participants assigned to the DASH diet ate it in 3 forms (high, intermediate, and low levels of sodium) for 30 consecutive days each, in random order.

What drugs and other agents cause acute kidney injury in patients with CKD?

Poor renal function increases the likelihood of acute kidney injury from nephrotoxic agents. Therefore, avoid using known nephrotoxic agents, such as aminoglycoside antibiotics, amphotericin B, nonsteroidal anti-inflammatory drugs (27), and radiocontrast agents. If radiocontrast agents are unavoidable, consider giving sodium bicarbonate, 0.45% normal saline, or N-acetylcysteine intravenously before and after the procedure (28–30). However, whether these agents reduce contrast-induced nephropathy in patients with CKD is controversial.

A recent meta-analysis summarized 41 randomized trials of agents to prevent contrast-induced nephropathy. Most of the trials (n = 34) compared N-acetylcysteine plus volume expansion with saline to saline alone (29). In most of the trials, the patients had impaired renal function and were undergoing an intravascular procedure. The trial results varied considerably: Most trials were inconclusive, including several large trials; however, N-acetylcysteine was effective in a few large trials. The summary measure of effect showed a substantial reduction in the risk for contrast-induced nephropathy. However, the heterogeneity of the study results leaves considerable uncertainty about whether N-acetylcysteine prevents contrast-induced nephropathy.

Avoid exposure to high doses of gadolinium contrast in patients with CKD stages 4 and 5 because it increases the risk for nephrogenic systemic fibrosis (31). Finally, avoid metformin in patients with diabetes and CKD because it increases the risk for lactic acidosis.

What is the role of blood-pressure management in patients with CKD?

Treatment of hypertension reduces the risk for cardiovascular disease in patients with CKD (21). The goal blood pressure should be less than 130/80 mm Hg.

The MDRD study enrolled 840 patients with a GFR between 13 and 55 mL/min per 1.73 m². Patients were randomly assigned to either a low-target blood pressure—approximately 125/75 mm Hg—or a usual-target blood pressure of 140/90 mm Hg and treated for a mean of 2.2 years. The outcomes—kidney failure and all-cause mortality—were determined from the U.S. Renal Data System and the National Death Index. After a mean follow-up of 6.2 years, the hazard ratio for low-target blood pressure compared with usual-target blood pressure was 0.68 (CI, 0.57 to 0.82) for kidney failure and 0.77 (CI, 0.65 to 0.91) for a composite outcome of kidney failure and all-cause mortality (32).

The choice of antihypertensive agents depends on the patient’s comorbid conditions. In patients with diabetic CKD or nondiabetic CKD with proteinuria, strong evidence favors use of an ACE inhibitor or an ARB. For cardiovascular risk reduction, diuretics may be the preferred agent, particularly in patients without diabetes and without proteinuria (11). Patients with CKD and hypertension will often require combination therapy to achieve goal blood pressures. Diuretics are often the foundation of combination therapy because they reduce extracellular fluid volume, lower blood pressure, and reduce the risk for cardiovascular disease in CKD. In addition, thiazides potentiate the effects of ACE inhibitors, ARBs, and other antihypertensive agents. However, the recent ACCOMPLISH (Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension) randomized trial has prompted a reassessment of thiazides. This trial showed that in patients with hypertension taking an ACE inhibitor, coronary heart disease (CHD) outcomes were fewer on amlodipine than on hydrochlorothiazide (33).
The level of GFR informs the choice of diuretic: Use a thiazide-type diuretic in patients with an eGFR greater than or equal to 30 mL/min per 1.73 m². Use a loop diuretic, such as furosemide, when the GFR is less than 30 mL/min per 1.73 m².

In the ALLHAT (Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial) study, 33,357 participants age 55 years or older with hypertension and at least 1 other CHD risk factor were randomly assigned to receive chlorthalidone (n = 15,255), amlodipine (n = 9,048), or lisinopril (n = 9,054) for a mean of 4.9 years. The rates of end-stage renal disease or a 50% or greater decline in GFR were the same in the 3 groups (34).

In ALLHAT, if the baseline GFR was less than 60 mL/min per 1.73 m², patients assigned to chlorthalidone had similar rates of fatal CHD or nonfatal myocardial infarction compared with amlodipine and lisinopril (6-year rates per 100 of 15.2, 16.0, and 15.1, respectively; P > 0.50). In these patients with CKD, the rate of the composite outcome of CHD, stroke, treated angina, heart failure, and peripheral arterial disease was the same with chlorthalidone and amlodipine and lower with chlorthalidone than lisinopril (6-year rates per 100 of 38.7, 41.1, and 41.3, respectively; P = 0.175 for the comparison between chlorthalidone and amlodipine, and P = 0.038 for the comparison between chlorthalidone and lisinopril) (34, 35).

What is the role of glycemic control in patients with diabetes and CKD?

Poor glycemic control is associated with development and progression of diabetic nephropathy via alterations in tubuloglomerular feedback, abnormalities in polyol metabolism, and formation of advanced glycation endproducts. To slow progression, management guidelines until recently advocated intensive control of glycemia to a target hemoglobin A₁c level of less than 7.0%, based on the landmark U.K. Prospective Diabetes Study (36) in type 2 diabetes and the equally influential Diabetes Control and Complications Trial in type 1 diabetes (37). These studies showed that intensive control reduced microvascular events (including microalbuminuria) but did not reach firm conclusions about the effect of intensive control on macrovascular events because they enrolled only 3867 and 1441 patients, respectively. The more recent, much larger ACCORD (Action to Control Cardiovascular Risk in Diabetes) (10) and ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) (38) trials showed that intensive control (to a hemoglobin A₁c level of 6.5%) did not reduce the incidence of macrovascular events and, in the ACCORD study, increased mortality from macrovascular disease as well as causing more hypoglycemia. On the basis of these 2 studies, managing to a target hemoglobin A₁c level of about 7.5% seems to be optimal.

The ACCORD trial evaluated the effects of intensive control of CVD risk factors on the incidence of CVD in 10,251 patients with type 2 diabetes. The trial compared patients managed to an average hemoglobin A₁c level of 6.4% with patients managed to an average hemoglobin A₁c level of 7.5%. The trial was stopped early because the relative risk for death was 1.22 in the intensive control group (CI, 1.01 to 1.46; P = 0.04). Hypoglycemia and weight gain were also more common in the intensive care group. The incidence of CVD events did not decrease in the intensive management group (hazard ratio, 0.90 [CI, 0.78 to 1.04; P = 0.16]) (10).

The ADVANCE trial, performed in Australia, had slightly different results. The trial evaluated the effects of intensive control of CVD risk factors on the incidence of CVD in 11,140 patients with type 2 diabetes. It compared patients managed to an average hemoglobin A₁c level of 6.5% with patients managed to an average hemoglobin A₁c level of 7.3%. After 5 years of follow-up, intensive management reduced the incidence of a combined primary end point of microvascular and macrovascular events (hazard ratio, 0.90 [CI, 0.82 to 0.98; P = 0.01]). Macrovascular events did not decrease with intensive control (hazard ratio, 0.93 [CI, 0.81 to 1.08; P = 0.28]).


ACE inhibitors or ARBs to patients with CKD?

Diabetes and proteinuria are the 2 main indications for ACE inhibitors or ARBs in patients with CKD. An ACE inhibitor or an ARB is the preferred initial anti-hypertensive agent in patients with hypertension and either diabetic kidney disease or a spot urine total protein–creatinine ratio greater than 200 mg/g (regardless of the underlying cause) (37). ACE inhibitors and ARBs decrease the progression of diabetic nephropathy even in patients without hypertension (39–41). In patients with non-diabetic proteinuria, ACE inhibitors or ARBs decrease proteinuria and reduce the risk for a doubling of serum creatinine or end-stage renal disease, regardless of their effect on blood pressure (42). Combination therapy with an ACE inhibitor and an ARB reduces proteinuria over the short-term, more than either alone (43, 44). However, recent data from the ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) study suggest an increased risk for major renal outcomes with combination therapy without a reduction in major cardiovascular events (45, 46). The evidence that ACE inhibitor–ARB combination therapy is better than high-dose monotherapy is still uncertain at best.

In a prospective trial of patients with diabetic nephropathy, 207 patients received captopril and 202 received placebo. Over a median follow-up of approximately 2.5 years, serum creatinine concentrations doubled in 25 patients in the captopril group and 43 patients in the placebo group (P = 0.007). Captopril treatment reduced by 50% the risk for the combined end point of death, dialysis, and transplantation (41).

The ONTARGET (Irbesartan Diabetic Nephropathy Trial) was a randomized, double-blind, placebo-controlled study that compared irbesartan with amlodipine and irbesartan with placebo in hypertensive patients with type 2 diabetes. Irbesartan reduced proteinuria more than amlodipine and placebo (44). Compared with amlodipine, irbesartan reduced by 23% the risk for a composite outcome of doubling of serum creatinine, end-stage renal disease, and death (P = 0.02). Compared with placebo, irbesartan reduced the risk for the composite outcome by 20% (P = 0.006) (47).

ACE inhibitors and ARBs have substantial adverse effects. Fetal malformations have occurred. ACE inhibitors frequently cause dry cough, which resolves quickly after stopping the drug or switching to an ARB. Monitor salt-depleted patients treated with ACE inhibitors or ARBs closely for hypotension, decline in GFR, and hyperkalemia. Measure blood pressure, GFR, and potassium within 4 weeks of starting treatment and adjust the dose if any of the following are present: systolic blood pressure less than 120 mm Hg or greater than 140 mm Hg, GFR less than 60 mL/min per 1.73 m², greater than 140 mm Hg, GFR greater than 140 mm Hg, GFR less than 60 mL/min per 1.73 m², or a serum potassium level greater than 4.5 mEq/L. Otherwise, check these parameters within 12 weeks of starting therapy or altering the dose. In patients with CKD, GFR may transiently decline when starting an ACE inhibitor or ARB. It is usually safe to continue the medication if GFR decreases less than 30% from baseline over 4 months and the serum potassium is less than 5.5 mEq/L (21).

What metabolic complications occur in patients with CKD and how should clinicians manage them?

Patients with CKD develop metabolic abnormalities as the kidney fails to maintain its role in normal homeostasis because of declining
GFR and synthesis of renal hormones. The main metabolic complications of concern are hyperphosphatemia and vitamin D deficiency, which lead to secondary hyperparathyroidism. Hyperkalemia and metabolic acidosis may also develop.

**Vitamin D and phosphorous metabolism**

Vitamin D metabolism and phosphate balance are disordered in mild CKD, but significant derangements usually occur only after the GFR falls below 30 to 40 mL/min per 1.73 m² (48, 49). Hyperphosphatemia and vitamin D deficiency cause hypocalcemia, and this induces secondary hyperparathyroidism, which is associated with renal osteodystrophy and increased mortality in patients on hemodialysis. Although we lack evidence for long-term benefit (50), KDOQI guidelines recommend a combination of dietary phosphorous restriction, phosphate binders, and vitamin D supplementation to maintain serum calcium, phosphorous, and intact parathyroid hormone levels within target ranges (Table 5) (51).

**Hyperkalemia**

Hyperkalemia is a late manifestation of CKD. Mild elevations occur in stage 3, but substantial, dangerous elevations usually only occur in stages 4 and 5 (49). Maintain normal potassium levels through dietary restriction of potassium and pre-existing elevations usually only occur in stage 3, but substantial, dangerous elevations seldom occur until the GFR is below 30 mL/min per 1.73 m² (49). Chronic metabolic acidosis alters bone metabolism and renal synthesis of 1,25-vitamin D and decreases the effectiveness of vitamin D therapy for osteodystrophy. Despite a weak evidence base, KDOQI guidelines recommend alkali therapy to maintain serum bicarbonate levels greater than 22 mmol/L.

**Metabolic acidosis**

CKD is associated with metabolic acidosis but, like hyperkalemia, substantial acidosis seldom occurs until the GFR is below 30 mL/min per 1.73 m² (49). Chronic metabolic acidosis alters bone metabolism and renal synthesis of 1,25-vitamin D and decreases the effectiveness of vitamin D therapy for osteodystrophy. Despite a weak evidence base, KDOQI guidelines recommend alkali therapy to maintain serum bicarbonate levels greater than 22 mmol/L.

**Should clinicians treat anemia in patients with CKD?**

Anemia accompanies worsening CKD as synthesis of erythropoietin declines. Anemia is associated with decreased quality of life, left-ventricular hypertrophy, and cardiovascular complications in patients with CKD. Although patients with normocytic, normochromic anemia and a low reticulocyte count are likely to have anemia of CKD, do not assume that CKD is the sole cause of anemia. The evaluation of patients with anemia and CKD should include measurement of hemoglobin and hematocrit, erythrocyte indices, reticulocyte count, serum iron levels, total iron-binding capacity, percent hyperkalemic electrocardiographic changes require urgent action. Emergency treatment includes intravenous calcium gluconate initially, intravenous glucose and insulin, intravenous bicarbonate if acidosis is present, and sodium polystyrene sulfonate. If these measures fail, hemodialysis is the next step.

**Table 5. Target Levels of Intact Parathyroid Hormone (iPTH), Corrected Total Calcium, Phosphorous, and Calcium–Phosphorous Product by Stage of Chronic Kidney Disease (CKD)**

<table>
<thead>
<tr>
<th>CKD Stage (GFR)</th>
<th>iPTH, pg/mL</th>
<th>Corrected Calcium, mg/dL</th>
<th>Phosphorous, mg/dL</th>
<th>Calcium–Phosphorous Product, mg²/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 (30–59)</td>
<td>35 to 70</td>
<td>Within the &quot;normal&quot; range for the lab</td>
<td>2.7–4.6</td>
<td>&lt;55</td>
</tr>
<tr>
<td>4 (15–29)</td>
<td>70 to 110</td>
<td>Within the &quot;normal&quot; range for the lab</td>
<td>2.7–4.6</td>
<td>&lt;55</td>
</tr>
</tbody>
</table>

* From reference 51.
† Corrected calcium = total calcium (mg/dL) + 0.0704 × (34 – serum albumin (g/L)).
transferrin levels (52). Patients with iron deficiency should receive tests to detect a source of gastrointestinal bleeding.

On the basis of randomized trial evidence that CVD mortality is worse—or at least no better—after a dose of erythropoetin sufficient to maintain a normal-range hemoglobin (53, 54), current guidelines recommend that clinicians treat patients with anemia of CKD with erythropoetin to correct anemia and maintain target hemoglobin levels of 11 to 12 g/dL (52). Therefore, do not try to “normalize” hemoglobin levels (53). Adequate iron stores are necessary for successful treatment of anemia of CKD, because iron is essential for hemoglobin formation and erythropoiesis. Prescribe oral or intravenous iron as needed to maintain adequate iron stores (transferrin saturation >20% and serum ferritin levels >100 ng/mL).

In the open-label CHOR (Correction of Hemoglobin and Outcomes in Renal Insufficiency) trial, 715 patients with CKD were randomly assigned to receive a dose of epoetin alfa to achieve a target hemoglobin level of 13.5 g/dL, and 717 were assigned to receive a dose of epoetin alfa to achieve a target hemoglobin level of 11.3 g/dL. Both groups had significant improvement in quality of life. However, the risk for the primary end point of death, myocardial infarction, hospitalization for congestive heart failure (without renal replacement therapy), and stroke was higher in the high-target hemoglobin group than in the low-target hemoglobin group (hazard ratio, 1.34 [CI, 1.03 to 1.74; P = 0.03]) (53).

In a very similar contemporaneous trial, the rates of a composite CVD outcome were the same in a low hemoglobin group and a normal hemoglobin group (54).

In addition, measure cardiovascular risk factors and treat them as aggressively as if the patient had CHD. Measure blood pressure and screen for diabetes and treat hypertension and diabetes as previously outlined. Unfortunately, no one has performed randomized, controlled intervention trials of treating dyslipidemia in patients with CKD, so we lack evidence that treatment reduces their incidence of acute CVD. In the absence of strong evidence, KDOQI expert panels have recommended using the guidelines of the Adult Treatment Panel III for treating dyslipidemia in patients with stage 1 to 4 CKD (55, 56). Obtain a lipid profile annually or if kidney function worsens, and prescribe medications to reduce low-density lipoprotein cholesterol level if it is greater than 100 mg/dL. The hemoglobin level; and serum potassium, calcium, phosphorous, parathyroid hormone, and albumin levels (5). Monitor more frequently in patients with an eGFR less than 60 mL/min per 1.73 m²; a rapid decline in kidney function in the past (>4 mL/min per 1.73 m² per year); risk factors for faster progression (smoking, poorly controlled hypertension or diabetes, older age, and proteinuria); exposure to a known cause of acute kidney injury (such as radiocontrast agents); or

How should clinicians monitor the progression of CKD?
Monitor progression of CKD and its complications (anemia, hyperphosphatemia, secondary hyperparathyroidism, and malnutrition) with an annual assessment of blood pressure; measurement of eGFR; hemoglobin level; and serum potassium, calcium, phosphorous, parathyroid hormone, and albumin levels (5). Monitor more frequently in patients with an eGFR less than 60 mL/min per 1.73 m²; a rapid decline in kidney function in the past (>4 mL/min per 1.73 m² per year); risk factors for faster progression (smoking, poorly controlled hypertension or diabetes, older age, and proteinuria); exposure to a known cause of acute kidney injury (such as radiocontrast agents); or

How should clinicians treat cardiovascular risk factors in patients with CKD?
Patients with CKD—especially those with proteinuria—are at higher risk for CVD than progressing to end-stage renal disease (17, 18). Aggressively

active treatment of CKD, hypertension, or proteinuria (5).

What are the indications for renal replacement therapy in patients with CKD?
The absolute indications are volume overload unresponsive to diuretics, pericarditis, uremic encephalopathy, major bleeding secondary to uremic platelet dysfunction, and hypertension that does not respond to treatment. Renal replacement therapy is the only treatment for these conditions (15).

Relative indications for renal replacement therapy include hyperkalemia, moderate metabolic acidosis, hyperphosphatemia, hypercalcemia or hypocalcemia, and anemia. Renal replacement is effective in these conditions, but other less costly, less invasive therapies may also be effective. More subjective relative indications for renal replacement therapy include fatigue, nausea and vomiting, loss of appetite, evidence of malnutrition, and insomnia (15, 57).

When should clinicians refer patients with CKD to a nephrologist?
A substantial body of observational evidence shows a strong association between care by a nephrologist and survival in the months before dialysis (58, 59). Clinicians should consult a nephrologist for advanced or complex renal disease or for assistance in formulating or implementing a care plan for CKD. Nephrologists are accustomed to managing complications of advanced CKD, such as anemia, bone disease, and hypertension. Nephrologists should be involved in therapeutic decision making about complex acute or chronic glomerular diseases, which often require immunosuppressive therapy.

In a prospective cohort study of 2195 incident dialysis patients, 730 patients were referred to a nephrologist less than 4 months before initiation of dialysis. This late-referral group had a 44% higher risk for death at 1 year after initiation of dialysis than patients referred earlier than 4 months before starting renal replacement therapy (hazard ratio, 1.44 [CI, 1.15 to 1.80]) (58).

A retrospective analysis of 39,021 Veterans Health Administration clinic users with diabetes and stage 3 or 4 CKD evaluated the association between care by a nephrologist and survival over a median of 19.3 months. Compared with patients with no nephrology visits, patients with 2, 3, and 5 nephrology visits had adjusted hazard ratios for mortality of 0.80 (CI, 0.67 to 0.97), 0.68 (CI, 0.55 to 0.86), and 0.45 (CI, 0.32 to 0.63), respectively (59).

As CKD progresses, consult a nephrologist no later than when the eGFR first falls below 30 mL/min per 1.73 m². As the GFR falls below 30 mL/min per 1.73 m², a nephrologist who is well-versed in the technical aspects of renal replacement therapy can discuss treatment modalities for end-stage renal disease (peritoneal dialysis, hemodialysis, and renal transplantation); prepare patients by providing counseling, psychoeducational interventions, and referral for dialysis access (peritoneal or hemodialysis); and initiate dialysis when appropriate (57).

References:
Practice Improvement

What do professional organizations recommend with regard to prevention, screening, diagnosis, and treatment of CKD?

Many of the recommendations included in this review come from guidelines developed by the National Kidney Foundation (NKF) as part of their Kidney Disease Outcomes and Quality Initiative (KDOQI) (1).

What measures do stakeholders use to evaluate the quality of care for patients with CKD?

The Centers for Medicare & Medicaid Services through the Physician Quality Reporting Initiative (PQRI) has established 134 eligible quality measures (www.cms.hhs.gov/PQRI/). Five of these measures apply to the care of adult patients with CKD (see Box).

Quality Measures for the Care of Adult Patients with CKD

- Percentage of patients younger than 75 years of age with diabetes who received urine protein screening or treatment for nephropathy

In patients with stage 4 or 5 CKD not on dialysis:

- Percentage of patients with hypertension and proteinuria who were prescribed an ACE inhibitor or ARB
- Percentage of patients who had serum levels of calcium, phosphorous, intact parathyroid hormone, and lipids checked at least once in the past 12 months
- Percentage of patients with a blood pressure less than 130/80 mm Hg or a blood pressure of 130/80 mm Hg or greater and a documented plan to achieve better blood-pressure control
- Percentage of patients who are receiving erythropoietin who have a hemoglobin level less than 13 g/dL or a hemoglobin level of 13 g/dL or greater and a documented plan to achieve a goal hemoglobin level less than 13 g/dL.
Healthy kidneys do many things to help the body work well. They get rid of waste from the body. They keep a good balance between water and electrolytes. The kidneys also make hormones that help make red blood cells. Chronic kidney disease is often caused by diabetes. But many other diseases can harm your kidneys. Ask your doctor if you should be tested for chronic kidney disease if you:

- are older than 55 years
- have diabetes or high blood pressure
- have a relative with kidney failure

How to keep from getting kidney disease

- Don’t smoke
- Exercise regularly
- If you have high blood pressure or diabetes, work with your doctor to keep your blood pressure and blood sugar at healthy levels

Symptoms of chronic kidney disease

You may not know you have chronic kidney disease until the kidneys are already badly damaged. Symptoms may include:

- Tiredness
- Confusion
- Trouble sleeping
- Feeling sick to your stomach or throwing up
- Having no appetite
- Swelling in your feet, ankles, or around your eyes

Treatment of chronic kidney disease

Your doctor will decide how to treat your disease on the basis of what is causing it. If it is found early and treated, chronic kidney disease can be controlled so that your kidneys will keep working. If your kidneys do fail, kidney dialysis and kidney transplantation are effective treatments.

For More Information

National Kidney Foundation
www.kidney.org/atoz/atozItem.cfm?id=134

National Kidney Disease Education Program
www.nkdep.nih.gov

American Association of Kidney Patients
www.aakp.org
CME Questions

1. A 52-year-old woman with type 2 diabetes mellitus and hypertension comes for a routine office visit. She has a 30-pack-year history of cigarette smoking. Her mother had diabetes and was on hemodialysis. Medications are insulin; metoprolol, 100 mg/d; fosinopril, 40 mg/d; hydrochlorothiazide, 50 mg/d; atorvastatin, 40 mg/d; and aspirin, 81 mg/d.

On physical examination, blood pressure is 165/95 mm Hg. There are retinal microaneurysms. Cardiac examination reveals a regular rhythm with an S4. The lungs are clear to auscultation. There is no jugular venous distention. There is 1+ pedal edema. The distal pulses are absent in both feet. Hemoglobin A1c level is 7.2%, glucose level is 180 mg/dL (9.99 mmol/L), creatinine level is 1.2 mg/dL (106.1 µmol/L), and 24-hour urinary protein excretion is 1.8 g/24 h.

Which of the following factors is most likely to cause this patient's chronic kidney disease to rapidly progress to end-stage renal disease?

A. Poorly controlled diabetes
B. Family history
C. Poorly controlled hypertension
D. Proteinuria
E. Cigarette smoking

2. A 42-year-old man is evaluated for intermittent claudication. He has hypertension, type 2 diabetes mellitus, chronic kidney disease, and peripheral arterial disease. Medications are metformin, 1000 mg twice daily; rosiglitazone, 8 mg/d; fosinopril, 80 mg/d; furosemide, 40 mg/d; and atorvastatin, 40 mg/d.

On physical examination, pulse rate is 72/min and blood pressure is 148/68 mm Hg. Cardiac examination reveals a normal S1 and S2 and a grade 2/6 systolic ejection murmur at the base but no S3 or rub. Bowel sounds are normal. The peripheral pulses are absent in both feet. There is 1+ pedal edema. The creatinine level is 1.6 mg/dL (141.47 µmol/L), sodium level is 140 mEq/L (140 mmol/L), potassium level is 4.0 mEq/L (4.0 mmol/L), chloride level is 106 mEq/L (106 mmol/L), and bicarbonate level is 24 mEq/L (24 mmol/L).

Angiography of the legs is scheduled.

In addition to initiating therapy with amoxicillin–clavulanate.

Which of the following is recommended before a planned débridement of his left great toe for a chronic nonhealing diabetic foot ulcer. His creatinine level is 2.4 mg/dL (212.21 µmol/L). Medications are lisinopril, atenolol, furosemide, and glyburide. In addition, he is currently taking a 14-day course of amoxicillin–clavulanate.

On physical examination, pulse rate is 72/min and blood pressure is 148/68 mm Hg. Cardiac examination reveals a normal S1 and S2 and a grade 2/6 systolic murmur radiating to his axilla. Pulmonary examination is normal. There is a 7-mm ulcer extending across the left great toe with purulent drainage.

Which of the following is true?

A. Measurement of serum creatinine is the best predictor of glomerular filtration rate, independent of the patient’s age, body weight, and sex
B. Calculation of the timed 24-hour creatinine clearance is the clinical gold standard for estimating glomerular filtration rate, as it is simple and reproducible
C. Measurement of the clearance of 125I-iothalamate or inulin is the most accurate measurement of glomerular filtration rate and should be applied to all patients
D. The glomerular filtration rate should be estimated by using prediction equations (Cockcroft–Gault or Modification of Diet in Renal Disease) that take into account serum creatinine concentration, age, body weight, and sex

3. A 55-year-old man with chronic kidney disease presumed secondary to diabetic nephropathy comes for an evaluation before a planned débridement of his left great toe for a chronic nonhealing diabetic foot ulcer. His creatinine level is 2.4 mg/dL (212.21 µmol/L). Medications are lisinopril, atenolol, furosemide, and glyburide. In addition, he is currently taking a 14-day course of amoxicillin–clavulanate.

On physical examination, pulse rate is 72/min and blood pressure is 148/68 mm Hg. Cardiac examination reveals a normal S1 and S2 and a grade 2/6 systolic murmur radiating to his axilla. Pulmonary examination is normal. There is a 7-mm ulcer extending across the left great toe with purulent drainage.

Which of the following is recommended to determine the stage of this patient’s chronic kidney disease?

A. 24-hour urine for creatinine clearance
B. 125I-iothalamate radionuclide scanning
C. Cystatin C measurement
D. Renal ultrasonography
E. Mathematical formula for estimation of the glomerular filtration rate

4. A frail, 73-year-old white woman is seen for preoperative assessment of kidney function before aortic valve replacement. Body weight is 46 kg (101 lb). The serum creatinine concentration is 1.6 mg/dL, and results of urinalysis are normal.

In evaluating and classifying patients with chronic kidney disease, the National Kidney Foundation recommends estimating the patient’s glomerular filtration rate. Which of the following statements is true?

A. Measurement of serum creatinine is the best predictor of glomerular filtration rate, independent of the patient’s age, body weight, and sex
B. Calculation of the timed 24-hour creatinine clearance is the clinical gold standard for estimating glomerular filtration rate, as it is simple and reproducible
C. Measurement of the clearance of 125I-iothalamate or inulin is the most accurate measurement of glomerular filtration rate and should be applied to all patients
D. The glomerular filtration rate should be estimated by using prediction equations (Cockcroft–Gault or Modification of Diet in Renal Disease) that take into account serum creatinine concentration, age, body weight, and sex

Questions are largely from the ACP’s Medical Knowledge Self-Assessment Program (MKSAP). Go to www.annals.org/intheclinic/ to obtain up to 1.5 CME credits, to view explanations for correct answers, or to purchase the complete MKSAP program.