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## Recognizing and Treating Chronic Kidney Disease

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*End-stage renal disease (ESRD) is a devastating condition that, according to the United States Renal Data System (USRDS), plagued approximately 406,000 individuals in the United States in 2001 and is projected to increase to a prevalence of approximately 725,000 by 2010.[1] Furthermore, it is a major public health issue, given the overall poor outcomes and high costs for this chronic condition. Medicare is the major payer for ESRD care, and the cost of ESRD to Medicare has risen 33% during the past 11 years, now comprising 6.4% of the Medicare budget.[1] Given these realities, it is evident that measures need to be taken to help reduce this disease burden. One solution involves improving recognition of and instituting interventions for the illness during its earlier stages, known as chronic kidney disease (CKD). Increasing evidence suggests that early intervention can delay and possibly prevent some of the adverse outcomes associated with kidney failure. Furthermore, while ESRD affects a relatively small proportion of individuals in the United States, CKD affects 11% of the adult population, and the complications, particularly cardiovascular disease (CVD), begin in the early stages of CKD.[2]*

*—The Editor*

### Definition

The National Kidney Foundation (NKF), through its Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines, defines CKD as structural or functional abnormalities of the kidney for three months or more, demonstrated by kidney damage (with abnormal blood, urine, or imaging tests), with or without an impaired glomerular filtration rate (GFR) less than 60 mL/min/1.73m², or an impaired GFR less than 60 mL/min/1.73m² with or without evidence of kidney damage.[3] Those with a normal GFR but evidence of kidney damage are included because GFR can be maintained at normal or increased levels despite significant damage to the kidney. GFR is a better measure of overall kidney function than serum creatinine level. Serum creatinine is affected by muscle mass, and thus, normal values vary by age, race, and gender. It has a high specificity but low sensitivity for detecting CKD, making it a poor screening tool.[3,4] In contrast, estimates of GFR can be calculated using the serum creatinine with equations that take into account many of these variables. These formulas include the Modification of Diet in Renal Disease (MDRD) equation as well as the Cockcroft-Gault equation:[3]

**Modified MDRD:**

GFR = 186 × (Creatinine - 1.154) × (Age - 0.203) × 1.212 (if black) × 0.742 (if female)

**Cockcroft-Gault:**

Creatinine clearance = [(140 - age) × weight (kg)]/(72 × Cr), if female multiply by 0.85

The formulas are readily available on various website calculators and easily can be installed onto personal digital assistant devices. Many clinical laboratories are beginning to provide estimated GFR, in addition to serum creatinine, in their results. Some limitations for the formulas that may lead to an overestimation or underestimation of the true GFR include extremes of body size and age, malnourished and obese patients, those with diseases of the liver and skeletal muscle, and vegetarians. In these situations, a direct measure of GFR or creatinine clearance should be used.

The K/DOQI guidelines further divide individuals with CKD into different stages with an appropriate clinical action plan for each stage.[3] Table 1 outlines the staging and clinical action plans.

## Epidemiology

As noted previously, the prevalence of ESRD is significant; however, the prevalence of CKD is even greater. An analysis of data from the Third National Health and Nutrition Examination Survey (NHANES III) found a prevalence of renal impairment of approximately 3%, or 5.6 million individuals, defined as a creatinine greater than or equal to 1.6 mg/dL in males, and greater than or equal to 1.4 mg/dL in females.[5] A more recent analysis of the NHANES III database revealed a much higher prevalence rate of approximately 11%, or 19.2 million individuals.[2] In this study, CKD was defined as persistent microalbuminuria with a GFR greater than or equal to 60 mL/min/1.73 m² or a GFR less than 60 mL/min/1.73 m². This disparity between the two prevalence rates underscores the importance of identifying patients with CKD using estimated GFR, as the use of serum creatinine alone highly underestimates the prevalence.

To reduce the rate of loss of function as well as the adverse outcomes associated with the illness, early identification of patients at risk for CKD is imperative. Potential risk factors are listed in Table 2.[3] The prevalence of CKD rises with age. While approximately 2% of individuals ages 40-59 have moderate to severe CKD, 25% of those older than 70 years have stage 3-5 CKD.[2] ESRD, but perhaps not CKD prevalence, is higher in African-Americans, suggesting that progression to ESRD is more rapid.[6] The two most common causes of ESRD in the United States are diabetes and hypertension.[1] These two conditions also are highly prevalent in individuals with CKD. With the rising age of the population and the epidemic of obesity, diabetes, and hypertension, the prevalence of CKD likely will increase.

The U.S. Preventive Services Task Force does not recommend screening of asymptomatic adults for proteinuria or hematuria.[7] However, screening in high-risk groups may be of benefit. The American Diabetes Association and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) recommend screening for CKD in all adults with diabetes mellitus (DM) or hypertension.[8,9] The K/DOQI Work Group recommends testing these same individuals as well as those with a family history of CKD, age older than 60 years, or U.S. minority status.[3] A program recently instituted by the NKF attempted to identify individuals at risk for or in the early stages of kidney disease. This program, known as the Kidney Early Evaluation Program (KEEP), specifically targeted individuals with DM or hypertension, and/or those with a family history of DM, hypertension, or kidney disease.[10] Results from the program demonstrated that 2.3% of individuals reported a history of kidney disease, but 47.4% of those with laboratory data actually had evidence of CKD based on the criteria of an estimated GFR less than 60 mL/min/1.73 m² or an estimated GFR of greater than or equal to 60 mL/min/1.73 m² with microalbuminuria. Furthermore, 56.4% of diabetic patients who also had a measured blood pressure had readings greater than 140/90 mmHg, well above the recommended target for blood pressure control in diabetic patients. In a study from London, elderly individuals with hypertension or diabetes ages 50-75 years and for whom there was no data on serum creatinine in the past year were invited for screening.[11] Researchers found that 12.6% of people with diabetes, 6.1% of people with hypertension, and 16.9% of individuals with both conditions had a creatinine level greater than 120 mmol/L (1.35 mg/dL). Of those screened, 44.5% had inadequately controlled

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**Table 1. NKF/DOQI Staging of CKD and Clinical Action Plans**

| STAGE | DESCRIPTION | GFR, (ML/MIN/1.73 M²) | ACTION* |
|---|---|---|---|
| 1 | Kidney damage with normal or increased GFR | ≥ 90 | Diagnosis and treatment; treatment of comorbid conditions; slowing progression; cardiovascular disease reduction |
| 2 | Kidney damage with mildly decreased GFR | 60-89 | Estimating progression |
| 3 | Moderately decreased GFR | 30-59 | Evaluating and treating complications |
| 4 | Severely decreased GFR | 15-29 | Preparation for kidney replacement therapy |
| 5 | Kidney failure | < 15 (or dialysis) | Kidney replacement (if uremia present) |

*Includes actions from previous stages

Kidney damage is defined as pathologic abnormalities, abnormalities in the composition of urine (e.g., proteinuria, hematuria), or abnormalities on imaging tests.
Reprinted with permission from: National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. *Am J Kidney Dis* 2002;39:S1-S246.

blood pressure. These studies illustrate the benefits of targeted screening and the lack of control of important risk factors for CKD.

## Significance of CKD: Cardiovascular Disease

Though ESRD typically is considered the major risk of CKD, CVD probably is the main risk. When facing a person with CKD, a physician needs to be aware of the high likelihood that the patient has significant atherosclerosis and multiple cardiovascular risk factors.[12] CVD is the major cause of death in ESRD patients.[1] Dialysis patients have a cardiovascular mortality rate that is 10-20 times higher than the general population.[13] The difference in mortality rates is greatest for young adults. Approximately 50% of patients have a history of CVD at the start of dialysis, and 30% have a history of congestive heart failure.[1] Furthermore, several studies now have shown that earlier stages of CKD also are associated with an increased risk of cardiovascular events and mortality.[14-18] CKD predicts the development of heart failure, in addition to predicting CVD. The risk of CVD is seen with estimated GFR less than 60 and with normal GFR but in the presence of significant levels of proteinuria. Because of the high CVD burden, the risk of dying from CVD may be greater than the risk of progressing to ESRD. A study of Medicare beneficiaries found that 5.9% of patients with codes or both diabetes and CKD, and 2.3% of patients with CKD without diabetes, developed ESRD after one-year of follow-up.[19] In contrast, 29% and 24.6%, respectively, died.

There are many reasons why CKD is associated with CVD. The phenomenon may be due to the increased presence of established risk factors for cardiovascular disease in the CKD population, including older age, hypertension, hyperlipidemia, DM, and decreased physical activity. In cross-sectional studies, individuals with CKD have more severe atherosclerosis.[12] However, studies have adjusted for several of these factors and continue to demonstrate that renal impairment is an independent risk factor for CVD.[14,15,17,18]

This suggests that other factors are important and CKD is associated with many nontraditional risk factors, including proteinuria, electrolyte abnormalities, anemia, increased inflammatory and thrombogenic mediators, oxidative stress, and elevated homocysteine levels.[20] These risk factors cluster together, and most patients with CKD have multiple CVD risk factors, both traditional and nontraditional.

It has been recommended by the National Kidney Foundation Task Force on Cardiovascular Disease that patients with CKD be considered as part of the highest risk group for CVD.[20] A recent American Heart Association position statement similarly stated that CKD should be considered in the highest risk group for recommendations for prevention and treatment of CVD.[21] In other words, in a similar fashion to diabetes, CKD should be considered a CVD risk equivalent. Goals for blood pressure control (< 130/80 mmHg) and low density lipoprotein (LDL) cholesterol (< 100 mg/dL) are lower than for the general population. See sections below for further treatment of risk factors.

In a related area, CKD is a risk factor for adverse outcomes after cardiac and non-cardiac surgery. The American College of Cardiology/American Heart Association, in their guidelines for cardiac risk stratification during major non-cardiac surgery, has recognized renal insufficiency as an intermediate clinical predictor of increased perioperative cardiovascular risk.[22] In addition, a recent, large prospective study demonstrated that a preoperative serum creatinine level greater than 2 mg/dL was a major independent risk factor for perioperative cardiac events.[23] Other studies have used a cutoff of 1.5 mg/dL and have found an increased risk of mortality.[24,25] CKD also is associated with increased surgical bleeding and need for blood products.[25]

Overall, it is evident that a definite association exists between CKD and CVD, and that the adverse outcomes can be of far-reaching proportions. This link only further emphasizes the importance of early identification and treatment of CKD and its associated risk factors to potentially reduce the negative outcomes associated with such disease.

**Table 2. Risk Factors for Chronic Kidney Disease**

- Age
- Minorities (African-American, Native American, Hispanic)
- Lower socioeconomic status
- Diabetes
- Hypertension
- Lower urinary tract obstruction
- Family history of chronic kidney disease
- Autoimmune diseases (e.g., lupus)
- Reduction in kidney mass
- Peripheral vascular and renovascular disease

**Table 3. Indications for Referral to Nephrology**

- Etiology of CKD not clear
- Nephrotic range proteinuria, especially if no history of diabetes
- Hematuria with decreased GFR or hematuria with proteinuria
- Acute worsening of CKD
- Estimated GFR ≤ 30 mL/min/1.73 $m^2$ .

## Complications of Chronic Kidney Disease

CKD is associated with many complications, especially as GFR declines. The goals of treatment are to slow the progression of renal disease, prevent and treat complications, make preparations for renal replacement therapy as disease progresses, and, once uremia develops, to initiate renal replacement therapy. Much of the care is provided by primary care physicians, but as renal disease worsens, treatment of complications is performed by nephrologists in conjunction with primary care. Table 3 summarizes indications for referral to a nephrologist. Late referral of advanced kidney disease has been associated with increased mortality, decreased treatment of complications, and poorer preparations for renal replacement therapy with increased catheter use and decreased transplant referral.[26] Though the majority of patients with CKD have diabetes or hypertension as the underlying etiology, many people have a primary renal disease. In general, late treatment of glomerular disease is not as beneficial, making early diagnosis important. Nephrotic range proteinuria or hematuria that does not have a urologic etiology should be evaluated for underlying cause. Isolated hematuria is typically urologic and, unless it is associated with proteinuria or a decreased GFR, should be evaluated first by a urologist. An initial evaluation of CKD includes urinalysis, serum chemistries, estimation of GFR, renal ultrasound, and quantification of proteinuria, which can be performed with a spot urine for albumin and creatinine. Further evaluation depends upon the results of these tests, but may involve serologic tests for hepatitis B and C, HIV, rheumatologic disorders, or a renal biopsy. Treatment of specific glomerular diseases is beyond the scope of this review.

The areas that generally are addressed during nephrology visits are shown in Table 4. Further details on these areas are summarized in the sections below.

## Hypertension and CKD

The ultimate goals of treating hypertension in patients with CKD are to prevent cardiovascular events and to slow progression to ESRD. Table 5 summarizes maneuvers that may slow the progression of kidney disease. As mentioned previously, blood pressure is controlled inadequately in the majority of the CKD population. In the Modification of Diet in Renal Disease (MDRD) study, 91% of patients were found to be on an antihypertensive agent, yet only 54% of those patients had a blood pressure less than 140/90 mmHg.[27] Furthermore, numerous studies of patients with renal disease or DM now show the goal blood pressure in these populations should be less than 130/80 mmHg, as this level has demonstrated significantly lower rates of cardiovascular events (e.g., fatal and non-fatal myocardial infarction, strokes, sudden death) and slower declines in renal function compared with higher levels of blood pressure control.[28-31] Recommendations from the JNC VII and American Diabetes Association concur with these guidelines.[9,32] A recent report reviewing several clinical trials randomizing patients with either diabetes or renal disease to similar blood pressure goals showed an average of 3.2 different antihypertensive agents daily were required to achieve this level of blood pressure control.[33] Overall, these data emphasize the importance of adequate blood pressure control in the CKD population as well as the intensity of therapy that typically is necessary to achieve this level of control.

With the understanding that hypertension in CKD may require multiple antihypertensive agents, the question arises as to which class of antihypertensives is ideal for the treatment of the CKD patient. Several studies have shown that angiotensin-converting enzyme inhibitors (ACEI) are the class of choice for treatement of both diabetic and non-diabetic renal disease patients due to their ability to slow progression of renal disease independent of their ability to decrease blood pressure.[34-36] Concerns that often arise with the initiation of ACEI therapy include an increase in serum creatinine; however, a small elevation in serum creatinine after initiation of an ACEI or angiotensin II receptor blocker (ARB) is not sufficient reason for discontinuation of the medication given the long-term renoprotective effects of these medications. In fact, only when the serum creatinine increases by more than 30% above baseline in 2-4 weeks after initiation or change in dose (in patients with a baseline creatinine less than 3 mg/dL) should one consider removal of the medication.[37] In many cases, reversible causes, particularly prerenal factors (e.g., volume depletion or non-steroidal anti-inflammatory medications) are present, and the correction of these factors will improve the creatinine and allow continuation of the ACEI. A significant increase in creatinine with ACEI also should raise the possibility of renal artery stenosis. In contrast, development of significant hyperkalemia or other adverse effects (e.g., angioedema) will necessitate discontinuation of the medication. If ACEIs are not tolerated secondary to cough, ARBs can be used. ARBs have been shown to slow the progression of diabetic nephropathy in individuals with Type 2 diabetes and microalbuminuria or

**Table 4. Areas Addressed During Nephrology Follow-up Visits**

- Follow-up of disease-specific therapies
- Hypertension
- Volume status
- Assessment of proteinuria
- Cardiovascular risk factors
- Potassium control
- Acid-base—treatment of acidosis
- Calcium, phosphorus, parathyroid hormone levels
- Anemia
- Nutrition
- Adjustment of doses of medications for declining GFR
- Preparations for renal replacement therapy
  - Education
  - Modality selection
  - Referral and evaluation for transplantation
  - Permanent access placement

**Table 5. Maneuvers to Slow the Progression of Kidney Disease**

- Hypertension control
- Use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and possibly the combination of ACEI/ARB
- Lipid control
- Cessation of smoking
- Glucose control
- Restriction of protein and phosphorus

overt nephropathy.[38-40] In these studies, ARBs were more effective than calcium channel blockers despite similar blood pressure control. An ACEI has been shown to be of cardiovascular benefit in CKD in subgroup analyses of the Heart Outcomes and Prevention Evaluation (HOPE) study.[14] There are no published studies directly comparing ACEIs or ARBs in progression of diabetic nephropathy, so it is not possible to recommend one rather than the other.

If blood pressure is not controlled adequately with ACEIs or ARBs alone, then thiazide diuretics may be synergistic, especially if patients eat a high salt diet. Combination medications with an ACEI or ARB and a thiazide also might improve compliance. Though often ignored as a therapy, salt restriction is beneficial for both blood pressure control and for the volume overload often associated with CKD. Hypertension in CKD often is volume-mediated.[41,42] Salt restriction potentiates the antihypertensive and antiproteinuric effects of ACEIs and ARBs.[43] Most individuals with CKD will need a diuretic for blood pressure and volume management.[41] Loop diuretics often become necessary in CKD from a management standpoint for volume-mediated hypertension, especially once GFR falls to less than 30 mL/min/1.73 $m^2$.[41] However, aside from ACEIs, no other class of antihypertensives consistently has shown renoprotective effects in the literature; therefore, other antihypertensive medications should be utilized based on related medical conditions (i.e., beta-blockers in the setting of associated coronary artery disease).

Another issue that arises with the use of ACEIs is their efficacy in African-American patients with hypertension. In a recent major trial evaluating the effects of amlodipine, metoprolol, and lisinopril in African-American patients with hypertensive renal disease with reduced GFR, ACEI therapy was found to be superior to both beta-blockers and dihydropyridine calcium channel blockers in slowing disease progression.[44] Approximately three-quarters of the patients in the ACEI arm were on diuretics, so they should be considered part of the regimen. The benefit of ACEIs was most marked in individuals with proteinuria levels greater than 1 gram/day. The calcium channel blocker arm was stopped early because, after an initial improvement in GFR secondary to vasodilatation, it led to a faster decline in GFR. Accordingly, ACEI therapy strongly should be considered as primary therapy in this population as well. However, most individuals with CKD will require multiple medications, and there are no data showing that the addition of calcium channel blockers to ACEIs is harmful. The control of blood pressure is as important as, if not more than, the use of ACEIs/ARBs.

In conclusion, attaining blood pressure levels less than 130/80 mmHG, via monotherapy or combination therapy, is desirable in patients with CKD to delay progression of the disease and minimize cardiovascular events. Furthermore, ACEI or ARB therapy should be considered first-line therapy unless significant contraindications are present. Most patients will need multiple medications to obtain adequate blood pressure control.

## Lipid Control

CKD is associated with a number of lipid abnormalities that increase the risk for CVD. Typically, HDL levels are low and triglycerides levels are elevated.[45] Typically, low-density lipoprotein (LDL) cholesterol levels are not very elevated, except in the setting of proteinuria. However, though LDL levels may be normal, there is a shift to small dense LDL, which is more atherogenic.[45] The recently published NKF guidelines recommend that CKD be considered a coronary heart disease risk equivalent, similar to diabetes.[46] Therefore, the goal LDL level is less than 100 mg/dL. If triglycerides levels are greater than or equal to 500, they should be treated first with lifestyle measures and either a fibrate or niacin; otherwise, LDL is the initial target. Except for gemfibrozil, the fibrates need to be dose adjusted in individuals with low GFR. If the LDL level is more than 130 mg/dL, therapeutic lifestyle and therapy with a statin should be prescribed. Non-HDL cholesterol (total cholesterol minus HDL) is an additional target and should be less than 130 mg/dL if triglyceride levels are greater than or equal to 200. Non-HDL cholesterol has the additional benefit that it can be measured using non-fasting blood specimens. Treatment trials that examine cardiovascular outcomes in CKD are sparse, but there have been a number of subgroup analyses of larger studies that suggest that lipid-lowering therapy with statins in CKD is associated with a similar benefit as in the general population.[47-49] In ESRD, the association of hyperlipidemia with outcomes is complicated by the inflammato-

ry state of uremia. Inflammation is associated with mortality in ESRD, but it lowers cholesterol levels. A recent study in dialysis patients found that in those with evidence of inflammation, lower cholesterol levels were associated with mortality, but in those individuals who did not have evidence of inflammation, higher cholesterol levels were associated with increased cardiovascular mortality.[50] There are two treatment trials in CKD that now are on-going: the 4D trial and the Study of Heart and Renal Protection (SHARP).

Treatments directed at decreasing proteinuria also improve hyperlipidemia. In a study of non-diabetic proteinuric kidney disease, Ruggenti et al found that titrating lisinopril from 10 mg to 40 mg led to a decline in total cholesterol, LDL, and triglyceride levels.[51] Though the main reason to treat hyperlipidemia is prevention of CVD, lipid lowering may slow the progression of kidney disease as well.[52-54] Small studies in CKD have found that statins decrease proteinuria.[52,54] In the Heart Protection Study, treatment with simvastatin was associated with a smaller rise in creatinine during follow-up.[47]

## Anemia

Anemia is common in CKD. Erythropoietin is produced in the kidney and as GFR declines, anemia develops. The anemia of CKD thus can be treated with the administration of erythropoietin or darbepoetin. Anemia in CKD is associated with left ventricular hypertrophy and adverse outcomes.[55,56] Treatment with erythropoietin improves energy levels and quality of life.[57] Response to erythropoietin requires adequate iron stores, which in ESRD means a ferritin level greater than 100 mcg/dL and an iron saturation greater than 20%.[58] In the setting of chronic loss in hemodialysis, this is difficult to obtain with oral iron, and intravenous iron typically is used if iron stores are low. In studies, the use of intravenous iron decreased the required dose of erythropoietin.[59] Whether higher iron stores are necessary in stage III-IV CKD is not clear, but they generally are recommended. Oral iron can be tried first in individuals who are not on dialysis, but these patients may require treatment with intravenous iron.

With the use of erythropoietin, the treatment target for hemoglobin is 11-12 g/L.[60] Some investigators argue for higher hemoglobin levels, based on analyses of cohort studies showing better outcomes in those with higher hematocrits and better quality of life in randomized studies.[61] Early treatment of anemia also might decrease left ventricular hypertrophy. However, randomized trials have not been as convincing.[62] In fact, results of one study showed increased cardiovascular risk, perhaps because blood pressure increased.[63] The initial dose of erythropoietin is 50-100 units subcutaneously three times per week, though it often can be given once per week.The initial dose for darbepoetin is 25 mcg/week, though some people can be managed with every-other-week dosing. It is important to avoid a too-rapid correction of hemoglobin with either medication, as this has been associated with exacerbation of hypertension or seizures. Adjustment in dosing generally is done every 2-4 weeks. The adjustment in dosing of erythropoietin and darbepoetin is beyond this review, though clinical practice guidelines exist.[60] Some patients exhibit a poor response to erythropoietin. If iron stores are adequate or there is a rapid decline in hemoglobin, acute blood loss should be considered. Checking a reticulocyte count can be helpful, as it would be elevated with acute blood loss, but would be low in the setting of poor responsiveness due to inflammation or a bone marrow process. In the elderly, anemia in the setting of CKD should raise the possibility of myeloma.

## Calcium, Phosphate, and Renal Osteodystrophy

Renal osteodystrophy is due to secondary hyperparathyroidism. In contrast to the use of parathyroid hormone to treat osteoporosis in the general population,[64] the continuously high parathyroid hormone level in CKD causes bone loss. The high parathyroid hormone level is due to phosphate retention, hypocalcemia, and decreased conversion of 25 vitamin D to 1,25 vitamin D. Though the treatment guidelines are somewhat controversial,[65] treatment of renal osteodystrophy involves phosphate restriction in food (800-1000 mg/day), use of phosphate binders (i.e., calcium carbonate, calcium acetate, and/or sevelamer) and use of calcitriol (1,25 vitamin D). Prescription and adjustment of these medications generally are done by nephrologists.

As GFR declines and phosphate rises, the calcium and phosphorus product rises. This also may contribute to vascular calcification. The goal for the calcium x phosphorus product is less than 55.[65] Its level is most dependent upon the phosphorus level as calcium levels are maintained in a narrower range. Patients with ESRD have extremely high coronary artery calcification scores on electron beam computerized tomography (EBCT), and they have an increased prevalence of valvular calcification.[66,67] Appropriate treatment of the calcium and phosphorus product might decrease the risk of cardiovascular events; however, this has not yet been shown in clinical trials.

## Other Metabolic Complications

As GFR worsens, patients with CKD develop other metabolic complications. Non-anion gap acidosis is common as the kidney loses its ability to generate bicarbonate. It is in late stages that an anion-gap acidosis is present. Acidosis can contribute to muscle wasting, bone disease, and nausea.[3] Acidosis in CKD is readily treatable with bicarbonate therapy. The initial starting dose generally is 650 mg tid or 1300 mg bid. Citrate generally is avoided as it increases the absorption of aluminum.[68] Hypermagnesemia can occur if magnesium intake is increased. Therefore, magnesium-containing antacids and laxatives should be avoided in advanced CKD.

Hyperkalemia also can develop in CKD. Diabetics are more prone to hyperkalemia at earlier stages of CKD. Other common contributing factors are urinary retention and medications (e.g., ACEI/ARBs, non-steroidal anti-inflammatory medications or Cox-2 inhibitors, potassium sparing diuretics, and potassium supplements). Hyperkalemia can be prevented with a low potassium diet, use of bicarbonate and diuretics (if volume depletion is avoided), and avoidance of contributing medications (though ACEIs or ARBs should be continued if possible). Patients with CKD should avoid salt substitutes as they generally contain potassium.

**Table 6. Indications for Renal Replacement Therapy**

- Uremic symptoms (e.g. ,nausea, vomiting, or anorexia)
- Volume overload, not responsive to diuretics
- Uremic pericarditis
- Uremic encephalopathy
- Hyperkalemia, not responsive to conservative measures
- Acidosis, not responsive to conservative measures
- Neuropathy due to uremia
- Malnutrition in setting of low GFR

CKD is associated with high homocysteine levels. In contrast to the general population, this generally is not due to low folate intake but may be due to decreased proximal tubule metabolism.[69] Multivitamins for renal failure contain 1 mg of folate, and most patients with ESRD are receiving them. Pharmacologic doses of B vitamins may decrease homocysteine, and there are two trials on-going in CKD to see if this improves outcomes: one in stage IV-V and one in transplant patients. Other risk factors for CVD also are elevated (e.g., inflammatory markers), but at this time there is not a therapy to decrease them.[70]

## Medications

Many medications require dose adjustment for decreased GFR. A good reference for dose adjustment is *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults*, available from the American College of Physicians. Certain medications should be avoided in individuals with decreased GFR (e.g., metformin). Cox-2 inhibitors and nonsteroidal anti-inflammatory medications can worsen hypertension and volume control and can cause hyperkalemia, especially when combined with ACEI/ARBs and generally should be avoided. As most individuals with CKD will be taking an ACEI, care needs to be taken with the use of aldosterone antagonists and other potassium sparing diuretics to avoid significant hyperkalemia. In general, procedures with iodinated contrast should be avoided, unless they are necessary and the clinical answer cannot be obtained with other approaches. Gadolinium used for magnetic resonance imaging (MRI) is safe in kidney disease. If iodinated dye is necessary, pretreatment with saline and possibly N-acetylcysteine (600 mg bid for 48 hours) may decrease the risk of acute renal failure.[71-73]

## Nutrition

The diet in CKD can be complicated with restrictions in sodium, potassium, phosphate, and fat. Referral should be made to a nutritionist with expertise in renal disease. This is especially true if protein restriction is planned to slow the progression of renal disease. Protein malnutrition is associated with decreased survival on dialysis,[74] and careful follow-up of individuals who are on protein-restricted diets is necessary.

## Renal Replacement Therapy

When GFR is less than 30 mL/min/1.73 $m^2$, preparations for renal replacement therapy are begun. (*See Table 6.*) Initially, there is a process of education that can begin at higher GFRs to help the patient decide on modality as well as to decrease anxiety and improve acceptance of ESRD. Pre-renal replacement therapy education has been shown to improve patient satisfaction and confidence with modality selection.[75,76] The three modalities for ESRD are hemodialysis, peritoneal dialysis, and renal transplant. Each modality has its benefits and complications. Unless specific contraindications are present, modality selection is based upon patient preference. Whether one therapy is better than the other with regards to patient survival in certain subgroups (e.g., diabetics) is controversial.

If the patient chooses hemodialysis, then referral should be made to a surgeon for hemodialysis vascular access. Ideally, the access would be via a primary arteriovenous fistula (patient's artery to native vein), as these accesses have a longer life span and are associated with decreased access complications (i.e., thromboses or infection).[77] For this to occur, the patient should preserve the veins in his/her nondominant arm (i.e., no blood draws or intravenous lines). The least desirable access for dialysis is a dialysis catheter as it has a high infection rate with bacteremia.[77,78] Early referral for access when the GFR is less than 30 allows time for access placement and maturation.

If the patient is a suitable surgical risk and does not have contraindications to transplantation, renal transplant evaluation can begin when GFR is less than 25-30 mL/min/1.73 $m^2$. Most patients will need a cardiac evaluation, including stress testing. Other tests include age appropriate cancer screening, abdominal imaging, evaluation for infections, and, if indicated by history, pulmonary function testing and evaluation for peripheral vascular disease. Unless the patient has a suitable donor, preparations for dialysis will need to be done in parallel to transplant evaluation.

## Summary

The prevalence of kidney disease is rising and, with the aging of the population and the increase in the number of people with diabetes, it is expected to be a growing public health concern. Individuals with CKD have an increased risk of CVD, which is greater than their risk of developing ESRD. They have multiple cardiovascular risk factors, and aggressive risk factor control should slow the progression of both CVD and renal disease. As GFR declines, other CKD complications such as anemia and bone disease develop. Preparations for renal replacement therapy should begin once GFR is less than 30 mL/min/1.73$m^2$.

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## Physician CME Questions

8. The target low density lipoprotein (LDL) cholesterol level in patients with chronic kidney disease is:
   a. less than 130 mg/dL.
   b. less than 100 mg/dL.
   c. less than 160 mg/dL.
   d. less than 100 if the patient has diabetes or coronary heart disease, otherwise less than 130 mg/dL.
   e. less than 100 if the patient has diabetes or coronary heart disease, otherwise target is determined from the Framingham risk score.

9. Angiotensin converting enzyme inhibitors or angiotensin receptor blockers should:
   a. be stopped if the serum creatinine increases from 1.4 to 1.7 mg/dL
   b. be the second-line agent for hypertension in African-Americans with kidney disease.
   c. be stopped once the creatinine increases to more than 3 mg/dL.
   d. not be used because of the increased risk of acute renal failure in chronic kidney disease patients.
   e. be used as a first-line agent in chronic kidney disease patients for both renal and cardiac protection.

## *Primary Care Reports*

## CME Objectives

*To help physicians:*

• summarize the most recent significant primary care medicine-related studies;

• discuss up-to-date information on all aspects of primary care, including new drugs, techniques, equipment, trials, studies, books, teaching aids, and other information pertinent to primary care;

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• describe the pros and cons of new testing procedures.

## CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to evaluate their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. *After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a certificate of completion.* When your evaluation is received, a certificate will be mailed to you.

10. Which of the following patients has chronic kidney disease?
    a. A 23-year-old male with type 1 diabetes, estimated GFR (from MDRD formula) 95 mL/min/1.73 $m^2$, urine protein 20 g albumin/mg creatinine, normal urinalysis
    b. A 68-year-old white woman with creatinine 1.1 mg/dL, estimated GFR 52 mL/min/1.73 $m^2$, urine protein 5 g albumin/mg creatinine, normal urinalysis
    c. A 50-year-old white male with newly diagnosed hypertension, creatinine 0.9 mg/dL, estimated GFR 95 mL/min/1.73 $m^2$, normal urinalysis and renal ultrasound
    d. A 75- year-old white male with creatinine 1.0, estimated GFR 79 mL/min/1.73 $m^2$, urine protein 5 g albumin/mg creatinine, normal urinalysis
    e. A 75-year-old African-American woman with creatinine 1.0, estimated GFR 70 mL/min/1.73 $m^2$, urine protein 5 g albumin/mg creatinine, normal urinalysis

11. With the use of erythropoietin in chronic kidney disease, the current recommended target for hemoglobin is:
    a. 10-11 g/L.
    b. 11-12 g/L.
    c. 12-13 g/L.
    d. 12.5-13.5 g/L.
    e. 13-14 g/L.

12. A patient who has chosen hemodialysis as the modality for renal replacement therapy should be referred for placement of a primary arteriovenous fistula:
    a. once he/she starts dialysis.
    b. when GFR is less than 15 mlLmin/1.73 $m^2$.
    c. when GFR is less than 30 mL/min/1.73 $m^2$.
    d. when GFR is less than 10 mL/min/1.73 $m^2$.
    e. when GFR is less than 45 mL/min/1.73 $m^2$.

13. Which of the following classes of medications should be avoided in CKD?
    a. HMG-CoA reductase inhibitors (statins)
    b. Cox-2 inhibitors
    c. Angiotensin receptor blockers
    d. Beta-blockers
    e. Glitizones (thiazolidinediones)

14. The average number of antihypertensive medications necessary for a person with CKD to achieve blood pressure goal is:
    a. 1.
    b. 1.7.
    c. 2.4.
    d. 3.2.
    e. 4.1.

## CME Answers

8. b
9. e
10. b
11. b
12. c
13. b
14. d

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