Chronic Kidney Disease: A Brief Review for the Primary Care Physician

Rasheed A. Balogun, MD, and W. Kline Bolton, MD

Abstract

Objective: To review clinical guideline recommendations for the identification and management of chronic kidney disease (CKD).

Methods: Qualitative assessment of the literature and review of current management guidelines.

Results: The incidence and prevalence of CKD is rising rapidly. Mortality rates are still unacceptably high despite improved technical and medical knowledge in the care of patients with end-stage renal disease (CKD stage 5). Efforts to decrease the morbidity and mortality observed with end-stage renal disease have focused on improving care in the earlier stages of kidney disease. These efforts seek greater involvement from primary care physicians, who have a critical role to play in early identification, treatment, and appropriate referral of patients with CKD. Multiple clinical practice guidelines are available to guide primary care physicians in identifying patients with CKD and in initiating therapy, which includes treatment of the primary disease and comorbid conditions, interventions to prevent progression of kidney disease and complications of CKD, and interventions to maintain a good quality of life. Collaboration with a nephrologist is best initiated no later than stage 3 of CKD.

Conclusion: Early recognition of CKD along with timely initiation of comprehensive treatment and collaboration with a nephrologist will provide optimal care for patients with CKD.

The prevalence of chronic kidney disease (CKD) in the United States has reached epidemic proportions [1–4]. Data presented in the National Kidney Foundation’s (NKF’s) Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines estimate that over 20 million adult Americans have some degree of CKD and an additional 20 million have risk factors for developing CKD [5].

End-stage renal disease (ESRD) is the final stage in the continuum of CKD. According to the U.S. Renal Data Systems, more than 412,215 patients were receiving renal replacement therapy for ESRD as of December 2001 [6]. This number is projected to increase to more than 660,000 by 2010 [6]. Incident rates adjusted for age show that patients over age 65 years are the fastest growing cohort of new ESRD patients [6]. In 2000, the average yearly cost of treatment for each patient with ESRD was approximately $68,000 [7]. Despite improvements in dialysis and transplantation medicine over the past 40 years, mortality rates in ESRD remain in the 20% to 25% range [6]. Recent efforts to decrease ESRD morbidity and mortality have focused on identifying patients at earlier stages of CKD and providing interventions to delay the progression of kidney disease [5,8–14]. These efforts require greater involvement from the primary care physician, who can play a critical role through early recognition and treatment of patients with CKD as well as informed collaboration with a nephrologist once a referral is made.

Current treatment guidelines that support the primary care physician in providing care to patients with CKD are available from the NKF and the Renal Physicians Association (RPA). NKF and RPA guidelines are the most widely used in the United States, and more than a dozen sets of guidelines from these organizations provide extensive information in multiple areas. However, the application of these guidelines in clinical practice can be limited by their length (each approximately 200 pages) and complexity. In this article, we present a distillation of NKF and RPA guideline recommendations on the identification and management of CKD.

Screening and Classification

The K/DOQI guidelines define chronic kidney disease as a persistent reduction in kidney function (ie, glomerular filtration rate [GFR] \(< 60\) mL/min/1.73 m²) for more than 3 months or evidence of kidney damage with or without reduction in GFR for more than 3 months [5]. Kidney damage is identified as structural or functional abnormalities of the kidneys (eg, with radiologic imaging) or abnormal composition of blood or urine. It has been suggested that all patients with CKD be
diagnosed as such and terms like “insufficiency,” “chronic renal failure,” and “renal dysfunction” be avoided [5].

Screening for CKD is done with measurement of blood pressure and serum glucose, urinalysis (including microscopy), measurement of albumin-to-creatinine ratio in a spot urine sample (proteinuria), and estimation of the GFR. These tests are readily available, relatively inexpensive, and already performed widely in primary care physicians’ offices. Patients with one or more risk factors for CKD (Table 1) should be screened at least once every year. Diabetics, patients with family history of kidney disease, African Americans, and hypertensive patients are at particularly high risk [15].

Timely identification of CKD is inevitably linked to the clinical methods of measuring or monitoring renal function. Despite its widespread use for the past decades, serum creatinine concentration alone is an inadequate indicator of renal function, especially in the elderly. Inulin clearance is the gold standard for measuring GFR, but this method is seldom used in clinical practice because it is cumbersome and costly [16]. Clearance of endogenous creatinine (24-hour urine collection) has been used, but this method frequently overestimates GFR and is becoming obsolete based on studies that have shown that various prediction equations are convenient and more accurate for assessing GFR [17,18]. The most popular prediction equations are the MDRD formula (adults < 70 years) (from the Modification of Diet in Renal Disease trial), the Cockcroft-Gault formula (all adults), and the Schwartz formula (children) [19–21] (Figure 1). The prediction equations are readily available on personal digital assistant software and on various sites on the internet [22,23]. A national effort is underway to have clinical laboratories routinely report estimated GFRs [22]. This improvement has been implemented successfully at our center.

Once patients with CKD are identified, the extent of their disease is classified based on estimated GFRs using the K/DOQI staging system (Table 2) [5]. The clinical course of CKD is variable and dependent on concurrent comorbidities and the stage of CKD. Across all stages, patients are more likely to die of cardiovascular disease than to progress to ESRD [24]. For patients who survive, those in stages 4 and 5 are very likely to progress to ESRD [19]. Presently, there is less information available in the literature about the clinical course of patients in earlier stages (stage 3 and below). The ongoing Chronic Renal Insufficiency Cohort study is likely to provide valuable information about the course of early CKD and the relationship with cardiovascular disease in the near future [25].

**Treatment**

Optimal therapy of CKD focuses on treatment of the primary disease and comorbid conditions, attempts to prevent progression of CKD and complications of CKD, and maintenance of a good quality of life [5,14]. Without optimal therapy, the GFR declines at a much higher rate. The complications of CKD involve multiple organ systems and usually begin in stage 3. An algorithmic approach to intervention in CKD patients is shown in Figure 2.

---

**Cockcroft-Gault formula:**

Creatinine clearance = \[ \frac{(140 - \text{age in years}) \times \text{(body weight in kg)}}{72 \times \text{serum creatinine in mg/dL}} \]

To determine the GFR in a woman, multiply the result by 0.85.

**MDRD formula:**

\[ \text{GFR} = 170 \times (\text{serum creatinine concentration}^{0.99}) \times \left( \frac{1}{\text{age}^{0.176}} \right) \times 0.762 \text{ if female} \times 1.180 \text{ if black} \times \text{blood urea nitrogen concentration}^{0.17} \times \text{serum albumin concentration}^{0.318} \]

**Table 1. Risk Factors for Chronic Kidney Disease**

<table>
<thead>
<tr>
<th>Modifiable</th>
<th>Nonmodifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerosis</td>
<td>Age</td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>Congenital renal disease</td>
</tr>
<tr>
<td>Anatomic abnormalities of the urogenital system</td>
<td>Family history of any process that can lead to CKD</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Glomerular disease</td>
</tr>
<tr>
<td>Exposure to nephrotoxic agents (eg, NSAIDS, IV contrast, drugs)</td>
<td>Male gender</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>Non-Caucasian race</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Other causes of decreased kidney mass</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Renal allograft</td>
</tr>
<tr>
<td>Obesity</td>
<td>Renal calculi</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Tubulointerstitial disease</td>
</tr>
<tr>
<td>Renal calculi</td>
<td>Tobacco use</td>
</tr>
</tbody>
</table>

CKD = chronic kidney disease; IV = intravenous; NSAID = non-steroidal anti-inflammatory drug.
CHRONIC KIDNEY DISEASE

Table 2. Stages of Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR, mL/min/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 mild decrease in GFR</td>
<td>60–89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate decrease in GFR</td>
<td>30–59</td>
</tr>
<tr>
<td>4</td>
<td>Severe decrease in GFR</td>
<td>15–29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt; 15 or renal replace-ment therapy</td>
</tr>
</tbody>
</table>


Management of Comorbid Conditions

High blood pressure control must be addressed in the CKD patient. CKD patients are considered to be at high risk for cardiovascular disease. The current recommended blood pressure goal in CKD patients is below 130/80 mm Hg [8,26]. Blood pressure should be checked at every clinic visit even after it has been brought down to goal. Most hypertensive patients with CKD will require multiple drug therapy. The angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are the preferred agents for blood pressure control in patients with CKD (especially with any evidence of proteinuria), heart failure, or diabetes as they not only effectively lower blood pressure but also have renoprotective effects [8]. Addition of a diuretic agent like hydrochlorothiazide can also be considered. If additional blood pressure control is needed, second- and third-generation β blockers are preferred for blood pressure control in patients with CKD (especially with any evidence of proteinuria), heart failure, or diabetes as they not only effectively lower blood pressure but also have renoprotective effects [8].

Because of its high prevalence, diabetes is the leading underlying cause of ESRD. Effective glycemic control is imperative in CKD patients to reduce the renal complications of diabetes.

Treatment of CKD Complications

Anemia. Anemia of CKD from absolute or relative deficiency of erythropoietin usually begins when the GFR falls below 60 mL/min/1.73 m² (stage 3). In patients with CKD, lower hematocrit values are associated with increased odds of death. For every 3% increase in hematocrit up to normal (men, 41%–50%; women, 35%–45%), there is a 10% decrease in risk of death [27–33].

Initial evaluation of anemia includes a blood smear and assessment of iron stores, reticulocyte count, mean corpuscular volume, serum folate, and serum vitamin B₁₂ levels. Iron deficiency is common in CKD patients due to poor nutrition and increased need of iron for erythropoiesis. If indicated, other reasons for anemia should be sought, including blood loss, malignancies, dysplastic disorders, chronic inflammatory diseases, and HIV infection. Low iron stores (transferrin saturation < 20% and ferritin < 100–200 ng/mL) should be treated with oral or intravenous iron supplements. Intravenous iron supplementation is often preferred because up to 1 g of iron is needed to raise the hematocrit from 25% to 35% [34,35]. Oral iron has low bioavailability, especially in patients with CKD. In addition, patient compliance with oral iron therapy is poor. Improved anemia of CKD has been reported in patients who were switched to intravenous iron after failure of oral iron therapy [36].

Treatment with recombinant erythropoietin should be started only after a thorough evaluation has been conducted (as noted above) and the patient has been adequately treated for other treatable causes of anemia. There are 2 commercially available preparations approved for use in CKD by the U.S. Food and Drug Administration: epoetin alfa and darbepoetin alfa. In CKD stages 3 and 4 (but not 5), epoetin is administered subcutaneously on a weekly schedule, with a starting dose between 50 and 100 U/kg that is increased incrementally; darbepoetin is administered subcutaneously at a starting dose of 0.45 mg/kg. The rate at which the hematocrit rises should be monitored weekly until the patient’s condition is stable; hypertension, seizures, and venous thrombosis can occur when hematocrit rises too rapidly.

The target hemoglobin level for anemia management in CKD is 11 to 12 g/dL (hematocrit, 33%–36%) [37–39]. Improved hemoglobin concentration in anemia of CKD has been associated with improved quality of life, including decreased hospitalizations, decreased length of stay in hospitals, and decreased costs [15]. Other positive effects of higher hemoglobin levels include improved energy, appetite, mood, and sex life. In addition, there may be stabilization and possibly regression of left ventricular hypertrophy [15].

Renal osteodystrophy and acid-base control. Deficiency of vitamin D, retention of phosphorus, and elevation of the calcium-phosphorus product and parathyroid hormone (PTH) levels (secondary hyperparathyroidism) are common as CKD progresses to stage 3 and beyond. The target value for serum phosphorus is 2.7 to 4.6 mg/dL; the target value for serum calcium is 8.5 to 9.6 mg/dL; and the target value for calcium-phosphorus product is less than 55. Phosphorus retention should be treated with dietary phosphorus restriction (0.8 g/day) and, when serum phosphorus exceeds 5 mg/dL, with phosphate binders to be taken with meals.
Phosphate binders available in the United States include the calcium-based binders calcium carbonate and calcium acetate (Calphron, PhosLo); aluminum-based binders such as aluminum hydroxide (Amphojel, ALternaGEL); and the non-metal-based binder, sevelamer hydrochloride (Renagel). Currently, the calcium-based binders are used most commonly. Aluminum hydroxide is best used only for short periods (no more than 4–6 weeks) because of the potential of aluminum toxicity. Sevelamer is a relatively new binder that does not contribute to metal accumulation and has a desirable effect of lowering low-density lipoprotein cholesterol [40]. Currently, sevelamer costs considerably more than other binders. Typical oral doses for these binders are as follows: calcium acetate, 2 to 4 667-mg tablets with meals 3 or 4 times daily; aluminum hydroxide, 500 to 1500 mg with meals 3 to 4 times daily; and sevelamer, 2 to 6 400-mg capsules with meals 3 to 4 times daily. Dosage should be adjusted based on the serum phosphorus concentration. Dietitians are an invaluable resource in providing patient education and recommendations about phosphorus binders.

Poor control of secondary hyperparathyroidism is associated with many clinical problems (Table 3) and increased mortality [41]. Vitamin D supplements are recommended to prevent hypocalcemia and decrease PTH, provided

Figure 2. Treatment of chronic kidney disease (CKD). ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.
Table 3. Long-Term Consequences of Secondary Hyperparathyroidism

<table>
<thead>
<tr>
<th>Condition</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calciphylaxis</td>
<td>Erythropoietin resistance, Need for parathyroidectomy, Osteitis fibrosa, Resistance to vitamin D therapy, Soft tissue calcification, Vascular calcification</td>
</tr>
</tbody>
</table>

Phosphorus levels are normal. The target PTH value is 35 to 70 pg/mL in stage 3 and 70 to 110 pg/mL in stage 4 (or more simply, 1 to 1.5 × upper limit of normal for the respective laboratory PTH assay for stages 3 and 4, and 2 to 3 × upper limit of normal for stage 5) [41]. With mild elevations of PTH, 25-OH vitamin D levels should be measured; if this level is less than 30 ng/mL, replacement therapy with oral ergocalciferol (vitamin D2) should be initiated at a typical dose of 50,000 U once a month for 6 months. For patients with higher PTH levels (> 3 times the upper limit of normal PTH), oral cholecalciferol (vitamin D3) is initiated at typical starting doses of calcitriol 0.25 µg/day or doxercalciferol 2.5 µg/day 3 to 7 days per week.

Metabolic acidosis occurs in most patients with CKD, beginning as early as stage 3 and usually when GFR falls below 30 mL/min (stage 4 CKD) with consequences of increased muscle catabolism and potentiation of renal osteodystrophy. Metabolic acidosis is treated with sodium citrate, with a treatment goal of serum bicarbonate concentration greater than 22 mmol/L. Citrate treatment should never be used with aluminum phosphate binders as citrate increases enteral absorption of aluminum and can contribute to aluminum toxicity.

Dyslipidemia. According to the RPA and K/DOQI guidelines, a full lipid evaluation should be performed at initial diagnosis of CKD, after any change in medication status, and at least yearly thereafter [9,14]. Dyslipidemias in CKD are defined in the Adult Treatment Panel III guidelines [42]. Target levels for lipids in CKD are as follows: low-density lipoprotein cholesterol, < 100 mg/dL; triglycerides, < 500 mg/dL; total cholesterol, < 200 mg/dL; and high-density lipoprotein cholesterol, > 40 mg/dL [9]. The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, are the initial drug of choice for treatment of elevated low-density lipoprotein cholesterol.

Nutrition Support
The lower the serum albumin level at initiation of dialysis, the greater the risk of increased length of hospital stay, cost, and mortality rate [5]. Malnutrition, proteinuria, and chronic inflammation are common causes of hypoalbuminemia in CKD patients. The nutritional status of CKD patients should be monitored by measuring and keeping a record of serum albumin (ideally, > 4 g/dL) and edema-free body weight at least every 3 months. A fall in edema-free body weight of greater than 5% or a fall in serum albumin greater than 0.3 g/dL due to no other obvious cause should trigger a dietary assessment and treatment by qualified personnel (registered dietitians or physicians with appropriate training) [14]. Edema-free body weight is the weight at which there is no significant peripheral edema on physical examination and there is no clinical or laboratory evidence of dehydration (eg, orthostasis or prerenal azotemia).

Treatment of Proteinuria
Overt proteinuria and even microalbuminuria are risk factors for CKD and kidney disease progression. Treatment includes lowering blood pressure to a target below 130/80 mm Hg, preferably with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, either alone or in combination. Treatment of any underlying causes (eg, diabetes) and a low sodium diet (< 100 mEq/day) are also necessary.

Referral to a Nephrologist
The various clinical practice guidelines provide evidence-based direction for treating patients with CKD. They are applicable in the primary care setting but are time-consuming and complex to implement. Optimal timing of initiation of collaboration thus remains a decision of the primary care physician. The initial consultation is best done no later than stage 3 of CKD based on accumulating evidence that shows that initiating the collaboration later is associated with more metabolic abnormalities, prolonged hospitalizations with higher costs, and increased mortality [4,43–49]. All patients who have reached stage 4 should be seen by a nephrologist and a team approach to care should be taken [7,50]. Timely initiation of collaboration with a nephrologist will facilitate early counseling about modalities of renal replacement therapy and appropriate evaluation for hemodialysis vascular access placement or renal transplantation.

Conclusion
There is a high and increasing prevalence of CKD. Efforts to reduce morbidity and mortality in CKD patients have focused on improving care in the earlier stages of disease. Thus, primary care physicians can play a critical role in achieving better outcomes in this group of patients. Optimal care of CKD patients includes appropriate screening and early recognition and management of CKD by primary care physicians along with informed collaboration with a...
nephrologist. Evidence-based guidelines available from the NKF and RPA can guide care across the continuum of CKD.

Corresponding author: W. Kline Bolton, MD, Division of Nephrology, Box 800133, University of Virginia Health System, Charlottesville, VA 22908, wkbl5v@virginia.edu.

Financial disclosures: None.

Author contributions: conception and design, RAB, WKB; drafting of the article, RAB, WKB; critical revision of the article for important intellectual content, RAB, WKB.

References


www.turner-white.com

Copyright 2004 by Turner White Communications Inc., Wayne, PA. All rights reserved.