Evidence-based treatment of chronic kidney disease

Abstract: Chronic kidney disease is prevalent among adults in the United States. To aid in diagnosis and treatment, the Kidney Disease: Improving Global Outcomes 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease provides an evidence-based approach. This article reviews the major recommendations of this guideline.

By Cynthia Ann Smith, DNP, APRN, FNP-BC, CNN-NP

It is estimated that 14% of adults in the United States have some stage of chronic kidney disease (CKD), with the majority being undiagnosed.1 For adults over age 70, approximately half have a glomerular filtration rate (GFR) under 60 mL/min/1.73 m2.2 Multiple factors can increase an individual’s risk for developing CKD, including diabetes mellitus, hypertension, cardiovascular disease, family history of kidney disease, autoimmune diseases, and older age. Pacific Islanders, Asians, Hispanics, American Indians, and Blacks have an increased risk of developing CKD.1

Prior to 2002, there was no clear definition of CKD or any defining guidelines to aid in its diagnosis, evaluation, and management. A review of the medical literature from 2000 found 23 different designations for kidney disease.3 In 2002, the National Kidney Foundation’s (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) published the first guideline, which offered both a definition of CKD and standards of care for patients with the disease.4

The organization Kidney Disease: Improving Global Outcomes (KDIGO) was founded in 2003 to develop and implement guidelines regarding kidney disease care and outcomes.5 In 2013, KDIGO published a new evidence-based guideline, Kidney Disease: Improving Global Outcomes 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease, with international standards for CKD management.6 This article will review the major recommendations of this guideline along with commentary by the NKF-KDOQI work group and the NKF Primary Care Initiative (PCI)-CKD panel.6-8

Defining and classifying CKD
CKD is defined as an abnormality in kidney function or structure for more than 3 months. The new guideline includes the stage of albuminuria in the definition and classification in addition to the GFR (see Prognosis of CKD by GFR and albuminuria categories). The NKF-KDOQI work group disagreed with including the cause of CKD in the definition.7 The PCI-CKD panel noted that inclusion of the cause of CKD could impact disease management by differentiating a localized kidney disorder from a systemic cause. When the cause of CKD is not apparent, such as from diabetes mellitus or hypertension, the panel recommends consultation with a nephrologist.8

Keywords: chronic kidney disease, chronic kidney disease clinical practice guideline, CKD management, CKD patient care, KDIGO, Kidney Disease: Improving Global Outcomes
GFR is recommended over the use of serum creatinine measurement alone for CKD classification and evaluation. Although GFR can be determined through several different equations, the CKD-Epidemiology Collaboration (CKD-EPI) equation is preferred. This equation uses serum creatinine, race, age, and gender but in a different mathematical relationship than the previously recommended Modification of Diet in Renal Disease (CKD-MDRD) equation. Comparison of the CKD-EPI to the CKD-MDRD found CKD-EPI to be more accurate with less bias, especially in patients with higher GFRs. However, the use of any GFR equation is acceptable, and many labs use the CKD-MDRD formula.

GFR may not be accurate in patients with unusual diets, those at extremes of muscle mass (the very frail, amputees, paraplegics, or body builders), and those with unstable creatinine levels. Pregnancy, acute kidney injury (AKI), and serious comorbid conditions, such as cirrhosis, heart failure, and protein-calorie malnutrition, can also impact a patient’s GFR. The NKF-KDOQI work group does not recommend using cystatin C to estimate GFR because there are multiple assays for cystatin C without a clear consensus on best practice.

There are three important nuances and changes in the new guideline for categorizing CKD:

• Stages 1 (G1) and 2 (G2) must show evidence of kidney damage as before. This requirement was emphasized in response to criticisms that decreased GFR associated with normal aging was being misclassified as CKD.
• Stage 3 has been divided into G3a and G3b. Dividing stage 3 was needed for medication dosing guidelines and more precise prognostication.
• Albuminuria, a vital prognostic factor, has been added to the classifications.

In order of preference for random or spot testing of urine, suggested options include the urine albumin-to-creatinine ratio (UACR), the urine protein-to-creatinine ratio (UPCR), and the reagent strip urinalysis for total protein (automated preferred over manual), with early morning urine sampling preferred. If using a reagent strip urinalysis, confirmatory testing is suggested, preferably obtaining a UACR or UPCR measurement.

While the KDIGO guideline recommends a 24-hour timed urine sample for albumin or protein when more accuracy is needed, it is recognized that these tests can be inaccurate if not all of the urine produced during testing is collected. In situations of significant albumin or proteinuria (nonalbumin in nature), the patient should be referred to a nephrologist. Testing for urine albumin should be avoided in patients who are menstruating, have strenuously exercised within 24 hours of testing, have a fever, or have a urinary tract infection. Samples should be collected under standard lab protocols.

### Progression of CKD

CKD progression is associated with GFR and albuminuria. With deterioration of kidney function and/or elevation of albuminuria, the risk of progression of CKD to kidney failure increases. For the young adult, normal GFR is typically 120 to 130 mL/min/1.73 m². Multiple studies assessing healthy adults without albuminuria or comorbidities have found a yearly GFR decline from 0.3 to 1.00 mL/min/1.73 m² typically starting in one’s 30s. Although a few studies showed lower rates of progression in those with CKD (thought primarily due to statistical issues), the majority of studies found an association between lower GFR levels and faster progression.
of kidney deterioration (yearly losses from 0.35 to 4.9 mL/min/1.73 m²).6

Patients in CKD stages 3 to 5 (G3 to G5) and/or with albuminuria (UACR 30 mg/g or greater and urine albumin excretion rate 30 mg/24 hours or greater) should be assessed often, and the guideline leaves the timing to the practitioner’s discretion.7 Slight fluctuations in GFR are common, but a decline from the baseline GFR by 25% is a cause for concern. Rapid progression of CKD is a persistent decrease in a GFR over 5 mL/min/1.73 m²/year.6

Managing CKD progression and complications

Patient age, risk of CKD progression, presence of diabetes mellitus, and concurrent cardiovascular disease are considered when setting BP goals and the need for antihypertensive therapy (see KDIGO BP goals in adults relative to diabetes mellitus: Status and level of albuminuria)6,12 Additional information can be found in the KDIGO Clinical Practice Guideline for the Management of BP in CKD.11 Essential hypertension is the second most prevalent cause for CKD and kidney failure.1

Optimal BP goals for those with CKD with or without albuminuria has been debated. Upon reviewing the KDIGO’s guideline of BP management in CKD, the NKF’s KDOQI expert panel concluded the recommendations were evidence-based with a BP goal equal to or less than 140/90 mm Hg in the presence of normal-to-mild albuminuria, irrespective of diabetes status. However, the panel noted it was reasonable to select a BP goal equal to or less than 140/90 mm Hg in those with moderate-to-severe albuminuria, regardless of concurrent diabetes status.13 The Eighth Joint National Committee’s (JNC8) 2014 guideline regarding management of high BP in adults made similar recommendations.

Antihypertensive therapy should be initiated with systolic BP equal to or greater than 140 mm Hg or diastolic BP of equal to or greater than 90 mm Hg in those ages 18 to 69 with CKD and anyone with a UACR greater than 30 mg/g. The use of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) therapy in the management of hypertension in those 18 years old or older with concurrent CKD, irrespective of diabetes status or racial background, was recommended.14

The KDIGO guideline for CKD evaluation and management recommends the adult patient who has CKD with concurrent diabetes mellitus and hypertension with a UACR of 30 to 300 mg/g or the equivalent should be treated with an ARB or ACEI.7 In all adult patients with CKD, hypertension, and significant albuminuria (UACR greater than 300 mg/g), use of an ACEI or ARB is also recommended.6

Due to limited evidence, the JNC8 panel did not make a recommendation regarding BP goals for those age 70 or older with GFR less than 60 mL/min/1.73 m².16 The KDIGO CKD evaluation and management guideline recommended careful management of older adults with concurrent CKD and hypertension. When indicated, gradual increases in antihypertensive medications with close monitoring for associated adverse reactions are advised.6 Common adverse reactions in older adults include orthostatic hypotension, an acute decline in kidney function, and electrolyte disturbances.6

The renin-angiotensin-aldosterone system (RAAS) aids in regulating fluid balance and BP. Blockade of this system with use of ACEIs and ARBs can both lower BP and decrease glomerular hypertension.11 Because these medications increase the risk of hyperkalemia and/or decreased GFR, especially in patients with CKD, GFR and serum potassium should be reassessed 1 or 2 weeks after initiation or with dosage changes. With the development of hyperkalemia, before discontinuing these medications, the PCI-CKD panel recommends treating metabolic acidosis, the use of loop or thiazide diuretics, potassium-binding exchange resins, and/or restricting dietary potassium.8

If the GFR decreases more than 25% within 3 months, evaluation for renal artery stenosis and overdiuresis should be considered.4 The KDIGO guideline does not recommend combination ARB and ACEI therapy.4 The NKF-KDOQI work group also highlighted the risks of hyperkalemia and AKI for those on dual RAAS therapy.7

For the pediatric patient with CKD, when the BP is found to be consistently above the 90th percentile for the child’s age, height, and gender, BP-lowering treatment is recommended. Use of an ACEI or ARB is recommended in these patients regardless of albuminuria status. Unless there is development of hypotension, the suggested goal for pediatric patients with CKD is BP less than or equal to the appropriate 50th percentile for the child’s age, height, and gender.6

Dietary education is essential and should include information on protein, sodium, phosphate, and potassium intake. Adult patients with CKD should decrease their daily sodium intake to less than 2 g.6 Pediatric patients with CKD with prehypertension or hypertension should follow the appropriate age-based Recommended Daily Intake guideline regarding

<table>
<thead>
<tr>
<th>Albuminuria</th>
<th>BP goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>UACR &lt;30 mg/g = diabetes mellitus</td>
<td>140/90 mm Hg or less</td>
</tr>
<tr>
<td>UACR ≥30 mg/g = diabetes mellitus</td>
<td>130/80 mm Hg or less</td>
</tr>
</tbody>
</table>
sodium intake. A high protein intake (greater than 1.3 g/kg/day) is suggested for adult patients with CKD at risk for disease progression. A protein intake of 0.8 g/kg/day in the adult patient with CKD with GFR less than 30 mL/min/1.73 m² is suggested regardless of diabetes status.

Exercise, with a goal of 30 minutes five times a week, should be encouraged, as well as obtaining optimal body mass. Regardless of symptom status of hyperuricemia or gout, insufficient evidence has been found regarding serum uric acid–lowering agents in slowing the progression of CKD. Patients with a serum bicarbonate concentration less than 22 mmol/L should be treated to restore the levels to normal. The PCI-CKD panel recommends the use of sodium bicarbonate 650 mg three times a day, or sodium citrate 30 mL once a day, with consideration for referral to a nephrologist if the level is not restored to within normal limits. Smoking cessation is recommended.

Diabetes mellitus is the most prevalent cause for CKD and for kidney failure. A target hemoglobin A1c (A1c) of 7.0% is recommended for patients with diabetes mellitus. Alternatively, the A1c target can be increased above 7% for those patients at risk for hypoglycemia or with reduced life expectancies or comorbidities.

Metabolic bone disease is of concern for patients with CKD, but how best to evaluate, monitor, and treat the non-dialysis patient for metabolic bone disease is not as straightforward as it is for those on dialysis. Until further evidence is available, the KDIGO guideline recommends consideration for baseline values of alkaline phosphatase, calcium, phosphate, 25-hydroxyvitamin D, and intact parathyroid hormone (IPTH) in adults with a GFR less than 45 mL/min/1.73 m². Maintaining a normal serum phosphate level is suggested.

While the optimal IPTH is not determined in patients with CKD with a GFR less than 45 mL/min/1.73 m², evaluation for hypocalcemia, vitamin D deficiency, and hyperphosphatemia is recommended along with an IPTH. The guideline suggests using the upper limits of the lab’s assay as a point of reference. For patients with CKD not on dialysis and with an elevated IPTH, routinely prescribing vitamin D supplements or using vitamin D analogues without known or suspected vitamin D deficiency is not suggested.

Anemia is a common complication of CKD and is more prevalent with decreasing GFR. Anemia in adult patients with CKD is defined as a hemoglobin level less than 12.0 g/dL in females and less than 13.0 g/dL in males. The definition for pediatric patients with CKD varies depending on age. For patients with a GFR of 30 to 59 mL/min/1.73 m², hemoglobin should be checked at least annually and every 6 months in patients with a GFR less than 30 mL/min/1.73 m².

All patients with CKD are at increased risk for cardiovascular disease. Treatment of patients with heart failure and CKD requires increased monitoring of both serum potassium and GFR. Investigation and evaluation of the patient with CKD with chest pain is the same as for those without CKD. However, troponin levels can be inaccurate in the patient with CKD, and CKD stage should be considered in the interpretation.

Troponins are renally excreted and are often seen elevated in patients with CKD, especially those with lower GFRs, without symptoms of acute coronary syndrome (ACS) or ECG changes. While cautious evaluation of traditional cardiac markers is needed for the patient with cardiac disease and CKD, an elevation in cardiac troponins with concurrent signs and symptoms of ACS is suggestive for ACS. Patients with CKD and ischemic heart disease are treated the same as for those without CKD. Antiplatelet agents for atherosclerotic events should be offered to patients with CKD as indicated and appropriate.

Peripheral artery disease (PAD) is common in adult patients with CKD, and evaluation via ankle-brachial index testing is advised. Patients with CKD and PAD have higher rates of mortality and loss of limb when compared with the general population and are at higher risk for AKI and ACS. Treatment of PAD is the same as for the patient without CKD. For patients with diabetes mellitus, regular podiatric assessments are suggested. Evaluation for PAD in patients with CKD was recommended by the NKF-KDOQI work group only for patients with signs and symptoms of ischemia.

The risk of AKI must be balanced against the benefits of exposure to contrast agents for imaging exams. For patients requiring bowel preparation with a GFR less than 60 mL/min/1.73 m², avoid use of an oral phosphate-containing bowel preparation. Although not consistent with the FDA’s Black Box Warning regarding gadolinium-containing contrast media agents in patients with CKD, the KDIGO guideline recommends avoiding use of these agents with a GFR less than 15 mL/min/1.73 m² unless no other viable alternatives are available.

For patients with a GFR less than 30 mL/min/1.73 m² requiring gadolinium, a macrocyclic chelate preparation...
should be offered. Patients with a GFR less than 60 mL/min/1.73 m² requiring intravascular iodinated radiocontrast media should discontinue any potentially nephrotoxic agent(s) before, during, and after the procedure. Adequate hydration with 1.5% or 0.9% sodium chloride and the lowest possible radiocontrast dose avoiding high osmolar agents is recommended. The PCI-CKD panel noted that most studies have suggested using intravenous fluids given at a rate of 1 mL/kg/h starting 1 hour before and 3 to 6 hours after the procedure. GFR should be assessed to 96 hours after the procedure. The NKF-KDOQI work group agreed with the KDIGO recommendations regarding use of imaging exam contrast agents, including avoiding use of gadolinium for those with a GFR less than 15 mL/min/1.73 m².7

When AKI is of concern, renally excreted drugs and those that are potentially nephrotoxic should be temporarily discontinued; examples include direct renin inhibitors, ARBs, ACEIs, aldosterone inhibitors, metformin hydrochloride, nonsteroidal anti-inflammatory drugs, digoxin, calcineurin inhibitors, and lithium.8

Calcineurin inhibitors and lithium require regular evaluation of drug levels, GFR, and electrolytes. The KDIGO guideline recommends metformin if the patient’s GFR remains over or equal to 45 mL/min/1.73 m².6 Metformin use should be reassessed when the GFR is 30 to 44 mL/min/1.73 m², with discontinuation at a GFR less than 30 mL/min/1.73 m².5

The NKF-KDOQI work group supported the KDIGO recommendations regarding metformin use due to evolving evidence suggesting a low risk for lactic acidosis and to aid appropriate use of this medication.7 The FDA recently made labeling changes regarding metformin use. Similar to the KDIGO guideline, initial use of metformin is not advised in those with a GFR between 30 and 45 mL/min/1.73 m². Current metformin use should be reassessed with a GFR below 45 mL/min/1.73 m² with metformin use contraindicated with a GFR below 30 mL/min/1.73 m².5

The pediatric vaccination schedule recommendation is unchanged for those with CKD.6 Adult patients with CKD should have an annual influenza vaccine, and those with a GFR less than 30 mL/min/1.73 m² should have a pneumococcal vaccine and offered revaccination within 5 years.6 Hepatitis B vaccination should be considered for those with a GFR less than 30 mL/min/1.73 m². Because patients with CKD are often immunocompromised, use of live vaccinations should be considered on an individual basis.6

When to refer to a nephrologist

The KDIGO guideline recommends referral to a nephrologist when there is a decrease in GFR, progression of CKD, when the GFR decreases to less than 30 mL/min/1.73 m², and/or significant albuminuria.6 The NKF-KDOQI work group stated that all patients with nephrotic range proteinuria (UACR greater than 300 mg/g) should be seen by a nephrologist, as should those whose albuminuria is not improved despite addition of an ACEI or ARB or when the etiology is unclear.7

The presence of hereditary kidney disease, nephrolithiasis, chronic abnormal serum potassium, unexplained hematuria, and refractory hypertension in patients with CKD requires referral to a nephrologist.6 Additional considerations for referral include secondary hyperparathyroidism, noniron deficiency anemia, and chronic anion gap acidosis.8

If available, care in a multidisciplinary team setting for those with advanced CKD is suggested in the KDIGO guideline.6,24 There are several recommendations for the multidisciplinary team, including the ability to counsel on available renal replacement therapy options as well as transplant and vascular surgery options.6 Two studies on the effects of initiating multidisciplinary teams caring for pediatric patients with CKD found reduced kidney deterioration, improved hemoglobin levels, and improvement in some aspect of bone mineral metabolism.25,26

An evidence-based approach

The KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease provides an updated, evidence-based approach to diagnosing and caring for patients with CKD. CKD is prevalent across several patient populations, and NPs are in an ideal position to facilitate evidence-based care regarding these patients. The complete guideline is available online at www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf.

REFERENCES

Evidence-based treatment of chronic kidney disease


Cynthia Ann Smith is a nephrology and family NP at Renal Consultants, PLLC, South Charleston, WV.

The author and planners have disclosed that they have no financial relationships related to this article.

DOI: 10.1097/01.NPR.0000502790.65984.61