

Clinical Practice Guidelines for Chronic Kidney Disease in Adults: Part I. Definition, Disease Stages, Evaluation, Treatment, and Risk Factors

CYNDA ANN JOHNSON, M.D., M.B.A., *Brody School of Medicine at East Carolina University, Greenville, North Carolina*

ANDREW S. LEVEY, M.D., *Tufts University School of Medicine, Boston, Massachusetts*

JOSEF CORESH, M.D., PH.D., *Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland*

ADEERA LEVIN, M.D., *University of British Columbia Faculty of Medicine, Vancouver, British Columbia*

JOSEPH LAU, M.D., *Tufts-New England Medical Center, Boston, Massachusetts*

GARABED EKNOYAN, M.D., *Baylor College of Medicine, Houston, Texas*

In February 2002, the Kidney Disease Outcome Quality Initiative of the National Kidney Foundation published clinical practice guidelines on chronic kidney disease. The first six of the 15 guidelines are of the greatest relevance to family physicians. Part I of this two-part article reviews guidelines 1, 2, and 3. Chronic kidney disease is defined by the presence of a marker of kidney damage, such as proteinuria (ratio of greater than 30 mg of albumin to 1 g of creatinine on untimed [spot] urine testing), or a decreased glomerular filtration rate for three or more months. Disease staging is based on the glomerular filtration rate. Evaluation should be directed at determining the type and severity of chronic kidney disease. Treatment goals include preventing disease progression and complications. The guidelines place special emphasis on the prevention and treatment of cardiovascular disease in patients with chronic kidney disease. Risk factors for chronic kidney disease include diabetes mellitus, hypertension, family history of chronic kidney disease, age older than 60 years, and U.S. racial or ethnic minority status. The guidelines recommend testing for proteinuria and estimating the glomerular filtration rate in patients at risk for chronic kidney disease. Family physicians should weigh the value of the National Kidney Foundation guidelines for their clinical practice based on the strength of evidence and perceived cost-effectiveness until additional evidence becomes available on the usefulness of the recommended quality indicators. (*Am Fam Physician* 2004;70:869-76. Copyright© 2004 American Academy of Family Physicians.)



☒ See editorial on page 823.

☒ This is part I of a two-part article on chronic kidney disease. Part II, "Glomerular Filtration Rate, Proteinuria, and Other Markers," will appear in the next issue of *AFP*.

See page 801 for definitions of strength-of-recommendation labels.

ACE This article exemplifies the AAFP Annual Clinical Focus on caring for America's aging population.

Chronic kidney disease is a major public health problem throughout the world. In the United States, kidney failure is becoming increasingly common and is associated with poor health outcomes and high medical expenditures. In this country, the number of patients treated with dialysis or transplantation is projected to increase from 340,000 in 1999 to 651,000 in 2010.¹

The major outcomes of chronic kidney disease, regardless of the specific diagnosis (i.e., type of kidney disease), include progression to kidney failure, complications

from decreased kidney function, and development of cardiovascular disease. Increasing evidence shows that early detection and treatment often can prevent or delay some of these adverse outcomes.² However, opportunities for prevention may be lost because chronic kidney disease is not diagnosed or is treated insufficiently.³⁻⁶ One reason is lack of agreement about the definition of chronic kidney disease, as well as the classification of its stages. Another reason is lack of uniform application of simple tests for the detection and evaluation of the disease.

In February 2002, the Kidney Disease

Early detection and treatment often can prevent or delay some adverse outcomes of chronic kidney disease.

Outcome Quality Initiative (K/DOQI) of the National Kidney Foundation (NKF)^{7,8} published clinical practice guidelines on chronic kidney disease. The goals of the Work Group that developed the guidelines were as follows: to define chronic

kidney disease and classify its stages, regardless of the underlying cause; to evaluate laboratory measurements for clinical assessment of kidney disease; to associate the level of kidney function with the complications

of chronic kidney disease; and to stratify risk for the loss of kidney function and the development of cardiovascular disease.

The leaders of the NKF recognized the role of family physicians in providing medical care for patients with chronic kidney disease (particularly during the early stages when interventions might slow disease progression) and therefore wanted the guidelines to be practical and accessible to primary care physicians. To these ends, a family physician was invited to be an active participant in the guidelines Work Group and a member of the K/DOQI Advisory Board, which oversees all guidelines developed under its auspices. At present, there are only about 5,000 nephrologists in the United States. With the projected increase in the number of patients diagnosed with chronic kidney disease (especially as defined by the NKF guidelines^{7,8}), a strong partnership with family physicians and general internists will be necessary.

The first purpose of this article is to disseminate the simple definition and the five-stage classification system of chronic kidney disease that were developed through an evidence-based process and justified with existing literature. The second purpose is to describe the six guidelines with the most immediate relevance to family physicians. Guidelines on evaluation, treatment, and risk factors are reviewed in part I of this two-part article. Part II⁹ reviews guidelines on estimation of glomerular filtration rate, assessment of proteinuria, and use of markers of chronic kidney disease other than proteinuria.

Background

The NKF Work Group defined two principal outcomes of chronic kidney disease: progressive loss of kidney function and development of complications, particularly cardiovascular disease.

Progressive loss of kidney function over time in most patients with chronic kidney disease is a well-known outcome. Because of the older age at onset for many forms of kidney disease and the slow rate of decline in kidney function, decreased kidney function

The Authors

CYNDA ANN JOHNSON, M.D., M.B.A., is dean of the Brody School of Medicine at East Carolina University, Greenville, N.C. Previously she was professor and head of the Department of Family Medicine at the University of Iowa Roy J. and Lucille A. Carver College of Medicine, Iowa City. Dr. Johnson is a past president of the American Board of Family Practice. She also is the co-author of *Women's Health Care Handbook*.

ANDREW S. LEVEY, M.D., is the Dr. Gerald J. and Dorothy R. Friedman professor of medicine at Tufts University School of Medicine, Boston, and chief of the William B. Schwartz, M.D., Division of Nephrology at Tufts-New England Medical Center, Boston. Dr. Levey is past chair of the National Kidney Foundation (NKF) Task Force on Cardiovascular Disease in Chronic Renal Disease and chair of the NKF Work Group on Hypertension and Antihypertensive Agents in Chronic Kidney Disease.

JOSEF CORESH, M.D., PH.D., is associate professor of epidemiology, medicine, and biostatistics at Johns Hopkins Bloomberg School of Public Health, Baltimore. Dr. Coresh serves on the National Analgesic Nephropathy Advisory Committee and is conducting research on cardiovascular and kidney diseases. He is an American Heart Association established investigator.

ADEERA LEVIN, M.D., is clinical associate professor of nephrology, director of clinical research and education for nephrology, and postgraduate fellowship director at the University of British Columbia Faculty of Medicine, Vancouver. Dr. Levin is a past president of the Canadian Society of Nephrology. She is on the editorial boards of *Nephrology Dialysis Transplantation* and the *American Journal of Kidney Disease*.

JOSEPH LAU, M.D., is professor of medicine and professor of clinical research for the Division of Clinical Care Research at Tufts-New England Medical Center. He currently is director of one of the Agency for Health Care Research and Quality's evidence-based practice centers, as well as director of the Boston branch of the U.S. Cochrane Center. Dr. Lau also serves as methodologic director of the NKF K/DOQI evidence-based clinical practice guidelines program. He is a member of the editorial board of *Clinical Evidence*.

GARABED EKNONYAN, M.D., is professor of medicine at Baylor College of Medicine, Houston, and co-chair of the NKF Kidney Disease Outcomes Quality Initiative. Dr. Eknonyan is a past president of the NKF. He currently serves on the editorial boards of *Clinical Nephrology*, *Advances in Renal Replacement Therapy*, and *Seminars in Nephrology*.

Address correspondence to Cynda Ann Johnson, M.D., M.B.A., Dean, Brody School of Medicine at East Carolina University, 600 Moye Blvd., Suite AD-52, Greenville, NC 27834 (e-mail: johnsoncyn@mail.ecu.edu). Reprints are not available from the authors.

is far more common than kidney failure, for which replacement therapy (dialysis or transplantation) becomes necessary.

Decreased kidney function is associated with complications in virtually all organ systems. Therapeutic interventions in the earlier stages may prevent or ameliorate some of these complications, as well as slow progression to kidney failure. Cardiovascular disease is considered an outcome of chronic kidney disease for several reasons. First, cardiovascular events are more common than kidney failure in patients with chronic kidney disease. In addition, chronic kidney disease appears to be a risk factor for cardiovascular disease.

Cardiovascular disease in patients with chronic kidney disease is treatable, as well as potentially preventable. A 1998 report from the NKF Task Force on Cardiovascular Disease¹⁰ recommended that patients with chronic kidney disease be considered in the “highest risk” group for subsequent cardiovascular events, and that most interventions that are effective in the general population should be applied to patients with chronic kidney disease.^{11,12}

The NKF guidelines^{7,8} are based on a systematic literature review using an approach adapted from the one used by the Agency for Healthcare Research and Quality. A uniform format for summarizing strength of evidence was developed based on an evaluation of study size, applicability, results, and methodologic quality. Guideline statements were prepared from the analysis of this review. Each rationale statement was graded according to the supporting level of evidence (*Table 1*).⁷ Note that the evidence grading system differs from the system used in *American Family Physician*: only AFP’s evidence level C (consensus/expert opinion) compares with the NKF grade O (opinion).

In preparing the guidelines, 18,153 abstracts were screened, 1,045 articles were reviewed, and results were extracted from 367 articles. Many rationale statements are based on a structured review of evidence specifically for the guidelines (NKF grade S or C)⁷; however, most guidelines are based in part on unstructured review or opinion.

TABLE 1

Grading of Rationale Statements in the NKF Clinical Practice Guidelines for Chronic Kidney Disease

Grade	Level of evidence
S	Analysis of individual patient data from a single, large, generalizable study of high methodologic quality (e.g., NHANES III)
C	Compilation of original articles (using evidence tables)
R	Review of reviews and selected original articles
O	Opinion

NKF = National Kidney Foundation; NHANES III = Third National Health and Nutrition Examination Survey.

Adapted with permission from National Kidney Foundation. KIDDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;39(2 suppl 1):S231.

Guideline 1: Definition and Stages of Chronic Kidney Disease

Early detection and treatment often can prevent or delay adverse outcomes in patients with chronic kidney disease. Routine laboratory tests can detect the disease in its earlier stages (NKF grades R and O).⁷

A definition of chronic kidney disease is provided in *Table 2*.⁷ The presence of the disease should be established based on the occurrence of kidney damage and the level of kidney function (i.e., glomerular filtration rate [GFR]), regardless of the specific diagnosis. Disease stage should be assigned based on the level of kidney

TABLE 2

NKF Definition of Chronic Kidney Disease

Kidney damage for three or more months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifested by pathologic abnormalities or markers of kidney damage, including abnormalities in the composition of the blood or urine or abnormalities in imaging tests

GFR < 60 mL per minute per 1.73 m² for three months or more, with or without kidney damage

NKF = National Kidney Foundation; GFR = glomerular filtration rate.

Adapted with permission from National Kidney Foundation. KIDDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;39(2 suppl 1):S18.

function, also regardless of the specific diagnosis.⁷

Kidney damage usually is ascertained by the presence or absence of certain markers, rather than by kidney biopsy. The NKF guidelines^{7,8} emphasize persistent proteinuria as a marker of kidney damage, because proteinuria has been studied most thoroughly¹³ and is identified readily using a simple office procedure. A ratio of greater than 30 mg of albumin to 1 g of creatinine in an untimed (spot) urine sample usually is considered abnormal.

Other markers of kidney damage include abnormalities in urine sediment, blood, and urine chemistries, and abnormal findings on imaging studies. Patients who have normal kidney function but have markers of kidney damage are at increased risk for adverse outcomes of chronic kidney disease.

The GFR is considered the best measure of overall kidney function.¹⁴ Normal GFR varies according to patient age, sex, and body size. In young adults, the normal GFR is approximately 120 to 130 mL per minute per 1.73 m² and declines with age.¹⁴⁻¹⁷ A GFR level below 60 mL per minute per 1.73 m² represents loss of one half or more of the adult level of normal kidney function. Traditionally, an age-related decline in GFR has been considered “normal.” However, a decreased GFR in an elderly patient requires adjustment of drug dosages¹⁸ and appears to be an independent predictor of adverse outcomes such as mortality and cardiovascular disease.¹⁹⁻²¹

The definition of chronic kidney disease is not modified based on patient age. The situation is analogous to the situation with blood pressure levels and the definition and prevalence of hypertension. Blood pressure rises with age, but hypertension in elderly persons is associated with adverse outcomes; however, the definition of hypertension is not age dependent, and the majority of elderly persons are classified as having hypertension.²² Similarly, because of the age-related decline in GFR, the prevalence

of chronic kidney disease increases with age; approximately 17 percent of persons older than 60 years have an estimated GFR of less than 60 mL per minute per 1.73 m².⁶

Kidney failure is defined as a GFR below 15 mL per minute per 1.73 m², usually accompanied by signs and symptoms of uremia, or as the need for initiation of kidney replacement therapy for management of the complications of a decreased GFR. In the United States, approximately 98 percent of patients begin dialysis when their GFR falls below 15 mL per minute per 1.73 m².²³

Kidney failure is not synonymous with end-stage renal disease (ESRD). In the United States, “end-stage renal disease” is an administrative term based on the conditions for health care payment by the Medicare ESRD Program for patients treated with dialysis or transplantation. However, the term does not include patients with kidney failure who are not treated with dialysis or transplantation. Thus, although the term “end-stage renal disease” is in widespread use and provides a simple operational classification of patients according to treatment, it does not precisely define a stage of severity in kidney disease.

As demonstrated in *Table 3*,^{6,7,24-26} more than 20 million adults in the United States have chronic kidney disease, and millions more are at risk of developing the disease. Patients who have diabetes mellitus and hypertension are at highest risk. As the number of patients with diabetes and hypertension continues to increase, the number of patients with chronic kidney disease also will increase. Consequently, clear definition and classification of the stages of disease severity are needed to assess patients for the development and progression of chronic kidney disease.

The NKF classification of the stages of chronic kidney disease supports communication between physicians. The classification system helps clear up the ambiguities caused by vague terms such as “chronic renal insufficiency” and “chronic renal failure.” Using the NKF system, family physicians can ask nephrologist consultants more precise questions and can expect more precise

The stage of chronic kidney disease should be assigned based on the level of kidney function, regardless of the specific diagnosis.

answers. For example, at what stage does the nephrologist want to see a potential kidney transplant recipient? What interventions should be used at each stage to give a patient the best chance of preserving kidney function?

Staging of chronic kidney disease also allows physicians to talk more clearly with patients. For example, use of the word “kidney” rather than “renal” facilitates communication. In addition, patients are becoming accustomed to dealing with numbers (cholesterol levels, blood pressure measurements, blood sugar levels). Knowing their GFR and the type of personal interventions that may slow the decline in GFR allows patients to take greater control of their disease.

Guideline 2: Evaluation and Treatment of Chronic Kidney Disease

Patients with chronic kidney disease should be evaluated to determine the following: specific diagnosis (type of kidney disease), comorbid conditions, disease severity (assessed by the level of kidney function), complications (related to the level of kidney function), risk for loss of kidney function, and risk for development of cardiovascular disease (NKF grades R and O).⁷

Treatment of patients with chronic kidney disease includes the following: therapy based on the specific diagnosis, evaluation, and management of comorbid conditions; measures to slow loss of kidney function; measures to prevent and treat cardiovascu-

TABLE 3
NKF Classification of Chronic Kidney Disease*

Stage	Description†	GFR (mL per minute per 1.73 m ²)	U.S. prevalence, number of affected patients (%)‡	Action plan§
—	At increased risk for chronic kidney disease	> 60 (with risk factors for chronic kidney disease)		Screening, reduction of risk factors for chronic kidney disease
1	Kidney damage with normal or elevated GFR	≥ 90	5.9 million (3.3)	Diagnosis and treatment, treatment of comorbid conditions, interventions to slow disease progression, reduction of risk factors for cardiovascular disease
2	Kidney damage with mildly decreased GFR	60 to 89	5.3 million (3.0)	Estimation of disease progression
3	Moderately decreased GFR	30 to 59	7.6 million (4.3)	Evaluation and treatment of disease complications
4	Severely decreased GFR	15 to 29	400,000 (0.2)	Preparation for kidney replacement therapy (dialysis, transplantation)
5	Kidney failure	< 15 (or dialysis)	300,000 (0.1)	Kidney replacement therapy if uremia is present

NKF = National Kidney Foundation; GFR = glomerular filtration rate.

*—Chronic kidney disease is defined as either kidney damage or a GFR below 60 mL per minute per 1.73 m² for three months or more. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

†—For stages 1 and 2, kidney damage was estimated by a ratio of greater than 17 mg of albumin to 1 g of creatinine in men or greater than 25 mg of albumin to 1 g of creatinine in women on two untimed (spot) urine tests.

‡—Prevalence for stage 5, from the United States Renal Data Survey (1998),²⁴ includes approximately 230,000 patients treated with dialysis and assumes 70,000 other patients who were not on dialysis. Prevalences for stages 1 through 4 are based on data obtained from the Third National Health and Nutrition Examination Survey (1988–1994)⁶: population of 177 million adults 20 years of age and older. GFR was estimated from serum creatinine using an equation based on age, sex, race, and calibration for the serum creatinine level.^{25,26}

§—Includes actions from preceding stages.

||—Prevalence of persons at increased risk for chronic kidney disease has not been estimated accurately.

Adapted with permission from National Kidney Foundation. KIDOO clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;39(2 suppl 1):S19.

lar disease; measures to prevent and treat complications of decreased kidney function; preparation for kidney failure and kidney replacement therapy; and replacement of kidney function by dialysis or transplantation if signs and symptoms of uremia are present.

Medications should be reviewed at all visits. Dosage adjustments should be based on the level of kidney function. It is important to detect drug interactions, as well as potentially adverse effects of medications on kidney function or complications of chronic kidney disease. If possible, therapeutic drug monitoring should be performed.

A clinical action plan should be developed for each patient, with the plan based on the disease stage (Table 3).^{6,7,24-26} Self-management behaviors should be incorporated into the treatment plan at all stages of the disease.

Patients with chronic kidney disease should be referred to a nephrologist for consultation and co-management if a clinical action plan cannot be prepared, the appropriate evaluation cannot be performed, or the recommended treatment cannot be implemented. In most cases, patients with a GFR below 30 mL per minute per 1.73 m² should be referred to a nephrologist (NKF grade O).⁷

Diagnosis of chronic kidney disease traditionally is based on pathology and etiology. A simplified classification emphasizes diseases in the native kidneys (broadly divided into those that are diabetic or nondiabetic in origin) and kidney disease in the transplant patient. In the United States, diabetic kidney disease is the most common cause of kidney failure; its earliest manifestation is microalbuminuria with a normal or elevated GFR. Of note, the NKF guidelines⁷ classify patients who have diabetes and microalbuminuria with a normal GFR as having stage 1 chronic kidney disease. Nondiabetic kidney disease includes glomerular, vascular, tubulointerstitial, and cystic kidney diseases.

Specific treatment depends on the diagnosis, and a thorough search for “reversible causes” of kidney disease should be conducted. The remainder of the action plan is based on the stage of chronic kidney disease, irrespective of the diagnosis (Table 3).^{6,7,24-26}

Guideline 3: Risk Factors for Chronic Kidney Disease

The risk of developing chronic kidney disease is increased in some patients without kidney damage and with a normal or elevated GFR (NKF grade R).⁷ During the routine health care visit, all patients should be assessed for increased risk based on clinical and sociodemographic factors (Table 4).⁷

Patients determined to be at increased risk for kidney disease should undergo testing for markers of kidney damage and an estimation of their GFR. Patients found to have chronic kidney disease should be evaluated and treated as specified in NKF guideline 2. Patients at increased risk who are found not to have chronic kidney disease should be advised to follow a program

TABLE 4
Risk Factors for Chronic Kidney Disease and Its Outcomes

Type	Definition	Examples
Susceptibility factors	Factors that increase susceptibility to kidney damage	Older age, family history of chronic kidney disease, reduction in kidney mass, low birth weight, U.S. racial or ethnic minority status, low income or educational level
Initiation factors	Factors that directly initiate kidney damage	Diabetes mellitus, high blood pressure, autoimmune diseases, systemic infections, urinary tract infections, urinary stones, obstruction of lower urinary tract, drug toxicity
Progression factors	Factors that cause worsening kidney damage and faster decline in kidney function after kidney damage has started	Higher level of proteinuria, higher blood pressure level, poor glycemic control in diabetes, smoking
End-stage factors	Factors that increase morbidity and mortality in kidney failure	Lower dialysis dose (Kt/V),* temporary vascular access, anemia, low serum albumin level, late referral for dialysis

*—In Kt/V (accepted nomenclature for dialysis dose), “K” represents urea clearance, “t” represents time, and “V” represents volume of distribution for urea.

Adapted with permission from National Kidney Foundation. KIDOOI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;39(2 suppl 1):S73.

Strength of Recommendations

Key clinical recommendations	Label	References
The definition of chronic kidney disease is kidney damage or a GFR below 60 mL per minute per 1.73 m ² for three months or more.	C	7,8
A clinical action plan should be developed for each patient, based on the stage of disease as defined by the classification system developed by the National Kidney Foundation's Kidney Disease Outcome Quality Initiative.	C	7,8
In general, patients with a GFR below 30 mL per minute per 1.73 m ² should be referred to a nephrologist.	C	7,8
A ratio of greater than 30 mg of albumin to 1 g of creatinine on untimed (spot) urine testing is abnormal and merits further evaluation.	C	7,8

GFR = glomerular filtration rate.

of risk factor reduction (if appropriate) and should be reevaluated periodically.

During the routine health care visit, patients should be asked specifically about clinical and sociodemographic factors that have been implicated as susceptibility or initiation factors for chronic kidney disease. If any of these factors are present, patients should be assessed for albuminuria, and GFR should be estimated. The prevalence of persons at increased risk for chronic kidney disease has not been determined. However, the number of these persons is likely to far exceed the number of patients with the disease. Particular emphasis should be given to patients with diabetes mellitus, hypertension, family history of chronic kidney disease, age older than 60 years, and U.S. racial or ethnic minority status.

Guideline 3 is problematic for family physicians who have the task of identifying patients at risk for kidney disease. In preparing the NKF guideline, the Work Group evaluated evidence for the definition, classification, and prevalence of risk factors (NKF grade R).⁷ However, the issue of universal testing for kidney disease or testing of patients at increased risk for kidney disease has not been studied systematically. In the United States, testing currently is not recommended, except in patients with hypertension, diabetes, or known kidney disease.²⁷

Based on personal opinion and experi-

ence, the Work Group members recommend testing of patients who are at increased risk for kidney disease. In fact, a focus of the public awareness campaign stemming from the NKF guidelines is to encourage patients who think they may be at increased risk to tell their physician, and for the physician to test at-risk patients for albuminuria and GFR. Nonetheless, more research is needed to clearly identify the risks and benefits (both clinical and economic) of testing large segments of the U.S. population.

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