

Divisions of Nephrology & Hypertension
and General Internal Medicine

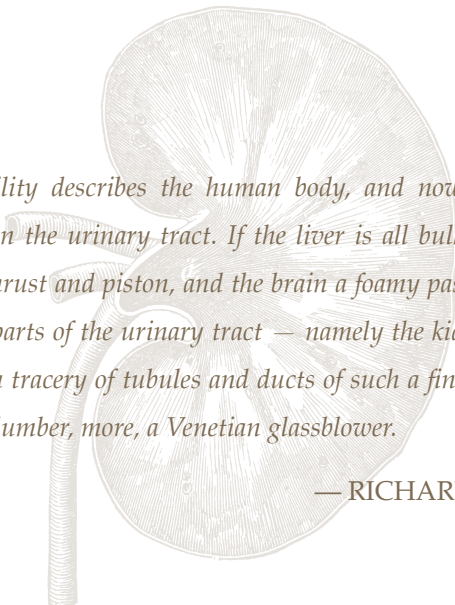


Chronic Kidney Disease

Clinical Practice Recommendations for
Primary Care Physicians & Healthcare Providers



A Collaborative Approach
(Edition 7.0)



Delicate durability describes the human body, and nowhere is this more apparent than in the urinary tract. If the liver is all bulk and thunder, the heart fist and thrust and piston, and the brain a foamy paste of insubstantial electricity, the parts of the urinary tract — namely the kidneys, ureters, and bladder — are a tracery of tubules and ducts of such a fineness as would lay mad a master plumber, more, a Venetian glassblower.

— RICHARD SELZER (1996)

DISCLAIMER. Final treatment recommendations are the responsibility of the prescribing healthcare provider and are in no manner considered the responsibility of Henry Ford Health System, its agents, providers, or the authors.

COPYRIGHT © 2002, 2003, 2004, 2006, 2007, 2011 and 2015. HENRY FORD HEALTH SYSTEM.

All rights reserved. No part of this publication may be reproduced, transmitted, transcribed, stored in a retrieval system, or translated into any language in any form or by any means without written permission of Henry Ford Health System.

Layout and print production of this publication by Dynamic Marketing, LLC.
www.dynamicmarketingllc.com • (248) 585-0426



TABLE OF CONTENTS

DEFINITION AND CLASSIFICATION OF CHRONIC KIDNEY DISEASE	1
NEPHROLOGY CONSULTATION	7
NEPHROLOGY CONSULTATION DIAGRAM	10
PROGRESSION OF CHRONIC KIDNEY DISEASE	11
ACUTE KIDNEY INJURY	13
HYPERTENSION IN CHRONIC KIDNEY DISEASE	16
APPROACH TO HYPERTENSION IN NON-DIABETIC AND DIABETIC CKD DIAGRAM	20
PROTEINURIA IN CHRONIC KIDNEY DISEASE	22
CKD PROTEINURIA EVALUATION DIAGRAM	26
DIABETIC KIDNEY DISEASE	27
ANEMIA OF CHRONIC KIDNEY DISEASE	33
PLAN OF CARE AND ACTION PLAN FOR CKD STAGES 1–4	34
CKD-MINERAL AND BONE DISORDER	41
DYSLIPIDEMIA OF CHRONIC KIDNEY DISEASE	49
NUTRITION IN CHRONIC KIDNEY DISEASE	51
KIDNEY REPLACEMENT THERAPY	54
IMMUNIZATIONS IN CHRONIC KIDNEY DISEASE	57
MEDICATION-RELATED PROBLEMS	60
SELECTED AGENTS	65
CKD WEBSITES OF INTEREST	72
COMMENTS TO AUTHORS	72
WEBSITE MANAGEMENT	72
PURCHASING INFORMATION	72
CHRONIC KIDNEY DISEASE CHECKLIST	73

FOREWORD

CKD Healthcare Providers:

The **Seventh Edition** of *CHRONIC KIDNEY DISEASE (CKD): CLINICAL PRACTICE RECOMMENDATIONS FOR PRIMARY CARE PHYSICIANS AND HEALTHCARE PROVIDERS—A COLLABORATIVE APPROACH* is published for the benefit of the Henry Ford Health System and Henry Ford Medical Group. This version contains the most recent updates in Nephrology care applicable to primary care practitioners.

The Editors, Gregory Krol and Jerry Yee, have once again reached out to experts across the US in their respective nephrological domains in order to compile a concise yet precise CKD booklet that outlines more than just the rudiments of appropriate kidney care. In fact, if one applied all of the knowledge contained herein, there would only be a few nuanced items left for the nephrologist to address, and patients would be confidently treated for the majority of manifestations of CKD.

Several changes between the current and last editions demand attention. First, the general layout has been altered to allow more rapid scanning of contents, and tables and figures have undergone a transformation to a more contemporary “look and feel.” Nearly every chapter is concluded with an attractive Box of bulleted key clinical “pearls.” An Acute Kidney Injury (AKI) chapter by Kathleen Liu has been added, distinct from CKD and summarizes the key clinical diagnostic findings associated with AKI.

Diabetic kidney disease, the preferred term over diabetic nephropathy, has been authored again by Susanne B. Nicholas. The roadmap to altering the natural history of this disorder is clearly delineated and, if successful, will reduce incident end-stage renal disease to as low as 1% in the type 2 diabetic population. The Hypertension in CKD chapter by Raymond Townsend and Debbie Cohen has also been revised to reflect not only JNC 7 but also JNC 8. The diagnosis and treatment of proteinuria, now albuminuria in CKD, is thoughtfully reviewed in its relationship to renal progression by Julie Lin. Anemia of CKD is no longer a “hot topic,” but this subject is concisely and expertly reviewed by Anatole Besarab and Jerry Yee. Nonetheless, patients with anemia should be treated with an “iron forward” strategy.

Controversy remains regarding how to optimally treat the various disease domains of the Chronic Kidney Disease-Mineral and Bone Disorder as discussed by L. Tammy Ho. However, the guidance provided here will more than likely improve bone and mineral outcomes without inducing harm(s) to patients. Controversy also surrounds the treatment of dyslipidemia in CKD. The Kidney International: Improving Global Outcomes advocates a “fire and forget it” strategy, whereas the Kidney Disease Outcomes Quality Initiative Work Group posits a more practical and evidence-based approach, as discussed by Snigdha Reddy.

The Nutrition chapter by Kristen Nonahal remains much the same. However, now a diet of fresh fruits and vegetables is no longer proscribed. In fact, this diet represents an

appealing approach to the management of metabolic acidosis and phosphorus metabolism in some patients, without inducing hyperkalemia. Immunizations are again stressed and timely, particularly since the advent of the new pneumococcal conjugate (PCV13) and the quadrivalent influenza A/B vaccines. Nephrologists pride themselves on being excellent internists, so it is incumbent upon all of us to remember to administer immunizations to CKD patients in a timely fashion.

Kidney Replacement Therapy by Lalathaksha Kumbar and Vivek Soi stresses the importance of choice. That is, choice of modality for end-stage renal disease patients. Peritoneal dialysis (PD) is stressed as the “go to” modality of choice because of the independence and time it grants the patient. When PD is not the choice, appropriate vascular access planning for hemodialysis (HD) must take place. For patients likely unable to thrive with either PD or HD, kidney transplantation is not an option. In this circumstance, clear communication regarding end-of-life care between the physician and patient must occur to avert the futility of inappropriate dialysis, a decision that actually diminishes one’s remaining quality-of-life days.

Commonly prescribed drugs are again summarized in this booklet along with medication-related problems that are associated with specific agents. As before, a comprehensive CKD checklist for the practitioner and a detailed Action Plan round out this Seventh Edition.

In summary, this booklet gracefully fits into the pocket space just vacated by the Sixth Edition and provides quick access to solutions for the complex care of the CKD patient. For the digital-only reader, the Editors will continue to support an online version.

A handwritten signature in black ink, appearing to read "Mark A. Perazella", with a long, sweeping underline that extends to the right.

Mark A. Perazella, MD
Professor of Medicine
Yale University
New Haven

Acknowledgement

The editors greatly appreciate the manuscript expertise of Sarah Whitehouse and the bibliographic assistance of Stephanie Stebens.

DEFINITION AND CLASSIFICATION OF CHRONIC KIDNEY DISEASE

by Gregory Krol, MD

INTRODUCTION

The term chronic kidney disease (CKD), first proposed in 1967, now represents an amalgam of multiple different names for a variety of definitions of kidney disease. Using the word “kidney” versus “renal” is intentional and improves understanding for patients, families, healthcare personnel, and most importantly the public. CKD replaces inexact terms such as chronic renal failure, chronic renal insufficiency, and renal dysfunction. CKD implies an etiology for kidney impairment and the potential for treatment. Thus, establishing a diagnostic cause of CKD is paramount in all cases to optimally manage patients because CKD is becoming more prevalent and expensive and is associated with significant morbidity and mortality.

COSTS, SCREENING AND EPIDEMIOLOGY

In 2011, the total spending for Medicare enrolled patients with end-stage renal disease (ESRD) was \$34.3 billion. ESRD is a Federal administrative term defined by the clinical requirement for renal replacement therapy (RRT) ≥ 90 days by kidney transplantation or any type of dialysis. Medicare HMO costs for ESRD were \$3.62 billion. Hemodialysis costs were \$87,945 per person per year, and corresponding costs for peritoneal dialysis were \$71,630. Obviously, preventing progression to ESRD is important with a cost of several thousand dollars annually.

Today, more than 26 million Americans have CKD at stages 1–5. Despite a national campaign to increase awareness of CKD, many patients are unaware of their illness. Only appropriate screening for CKD can identify these individuals. However, in 2012, the US Preventive Services Task Force advocated against general screening for CKD because screening has not been shown to reduce progression of CKD. The major renal societies rebutted this recommendation because of the tremendous burden of illness and costs of CKD. When identified, the progression of CKD can be attenuated, and cost-savings may be substantial as CKD costs escalate sharply with disease progression toward ESRD.

Screening of high-risk persons for CKD is highly important for hypertensive and/or diabetic individuals because intervention lowers the risk of progression to kidney failure in these groups. In the US for adults ≥ 20 years old, the prevalence of CKD is approximately 27.5% among those with high blood pressure and nearly 34.5% among those with diabetes. Screening individuals with a family history of CKD is also recommended, particularly among certain racial and ethnic minorities. African Americans and Native Americans are 3 to 4 times more likely and Hispanics twice as likely to progress to kidney failure as Caucasians. Cardiovascular disease also associates with CKD, and screening is recommended for all adult patients with coronary artery disease and heart failure. An underappreciated fact is the risk of having a heart attack with CKD is equivalent to that of diabetes. Because only 0.5% of the CKD population are aged 20–39 years, general screening for CKD in this age group is not advised unless additional risks for CKD are present.

Socioeconomically disadvantaged populations, regardless of race and ethnicity, are at higher risk for CKD, and low income/education correlate with CKD as do male sex, older age, and reduced access to healthcare. Other CKD risk groups include the following factors: autoimmunity, urinary tract obstruction, recurrent kidney stones, low birth weight, preeclampsia, insulin resistance, obesity, and acute kidney injury. Isolated or repetitive exposure to hazardous environmental and chemical agents may also cause CKD.

DEFINITION AND INTERPRETATION

No working definition of CKD had been proposed until 2002 when the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) classified the 5 stages of CKD based on the presence of either kidney damage, manifested by albuminuria (>30 mg/g), abnormal kidney biopsy (histology) or imaging studies, or a glomerular filtration rate (GFR) <60 mL/min/1.73 m² (**Table 1**). Chronic hematuria that is proven of renal origin also constitutes CKD, but isolated hematuria is a relatively rare cause of CKD. Isolated electrolyte or acid-base disturbances that are attributable to a renal tubular defect define a small subset of CKD patients. The term “chronic” operationally denotes the presence of the defining abnormality for a minimum of 3 months duration. Consequently, acute kidney injury (AKI) is defined by the presence of any of the aforementioned abnormalities for less than 3 months. Importantly, the greatest risk factor for AKI is CKD.

TABLE 1. CHRONIC KIDNEY DISEASE DEFINITIONS

eGFR persistently <60 mL/min/1.73 m² for 3 months or more

Persistent albuminuria (>30 mg/g creatinine) for 3 months or more

Persistent hematuria (following normal urological evaluation) for 3 months or more

Abnormal renal parenchyma defined by an imaging study or histology

Isolated electrolyte or acid-base disturbances

The NKF-KDOQI established a clinical practice guideline (CPG) based on the severity of estimated GFR (eGFR), using the serum creatinine concentration (SCr, mg/dL) with other variables to calculate an eGFR (**Table 2**). This was done because direct GFR measurements are not readily available clinically, and eGFR calculations generally provide sufficient stratification of the severity of CKD. Stages 1 and 2 CKD, defined respectively as GFRs of ≥90 mL/min/1.73 m² and 60 to 89 mL/min/1.73 m², are generally diagnosed when either coincident albuminuria, hematuria, or an abnormal imaging study is present. Therefore, an elderly individual with an eGFR between 60 and 89 mL/min/1.73 m² with no parenchymal or urine abnormality (*eg*, albuminuria) should not be considered as having the same renal risk for progressive disease as an individual with an equivalent GFR and an abnormal renal imaging or urinalysis. Notably, given the average lifespan of most US adults, the majority will enter CKD stage 2 before experiencing natural death. Stage 3 CKD

is subdivided into stages 3A and 3B, representing GFRs of 45 to 59 mL/min/1.73 m² and 30 to 44 mL/min/1.73 m², respectively. Stages 3B and greater are associated with exponentially increasing cardiovascular risk. Therefore, a GFR of 45 mL/min/1.73 m² represents a diagnostic danger point for CKD patients. Stages 4 and 5 represent advanced CKD, and stage 4 patients with GFR between 15 and 29 mL/min/1.73 m² have a high risk for progression to ESRD. Stage 5 CKD (kidney failure) indicates a GFR less than 15 mL/min/1.73 m², a point at which discussions regarding RRT and end-of-life care should be initiated. A patient undergoing RRT as hemodialysis or peritoneal dialysis is classified as CKD stage 5D, and a patient with a functioning transplanted kidney is classified as CKD stage 5T (**Table 2**).

TABLE 2. CHRONIC KIDNEY DISEASE (CKD) STAGES

NKF CKD Stage (USA)	KDIGO GFR Category (International)	Glomerular Filtration Rate (mL/min/1.73 m ²)	Terms
Stage 1	G1	≥90	Normal or high In the absence of evidence of kidney damage and abnormal urinalysis, neither GFR category G1 nor G2 fulfill the criteria for CKD
Stage 2	G2	60–89	Mildly decreased relative to a young adult level In the absence of kidney damage and abnormal urinalysis, neither GFR category G1 nor G2 fulfill the criteria for CKD
Stage 3A	G3a	45–59	Mildly to moderately decreased
Stage 3B	G3b	30–44	Moderately to severely decreased
Stage 4	G4	15–29	Severely decreased
Stage 5	G5	<15	Kidney failure
Stage 5D	G5	<15	Dialysis
Stage 5T	G5	<15	Kidney transplant

GFR EQUATIONS

The principal clinical purpose of assessing a patient’s kidney function is to facilitate screening, inform treatment decisions, and anticipate complications. However, although the GFR is considered the best overall index of kidney function, it is not the only measure of kidney health that should be ascertained. The precise measurement of GFR is difficult due to daily variation in the SCr. Moreover, direct GFR measurements by inulin, iothexol clearance or

radiolabeled-iothalamate are cumbersome and primarily confined to research protocols. With few exceptions, any GFR ascribed to a patient represents an eGFR.

The eGFR calculations that are endorsed for general clinical use by the National Institutes of Health-funded National Kidney Education Program (NKDEP) are SCr-based and derived from clinical studies of adult patients (18–70 years) with CKD. eGFR equations obviate the requirement for calculation of creatinine clearance by the Cockcroft-Gault equation and 24-h urine collections to determine endogenous creatinine clearance, which is another form of estimating GFR. The 1999 Modification of Diet in Renal Disease Study (MDRD) equations were the first ones used by reference laboratories and embedded into software for clinical application. MDRD Equation 4 was the most frequently utilized and calculated from SCr, age, sex, and race (**Table 3**). The MDRD equations are not valid for patients who have abnormal endogenous creatinine production: vegetarians, individuals who ingest creatine, limb amputees, patients with AKI, morbidly obese persons, and persons with muscle-wasting diseases (eg, HIV/AIDS, cancer, cirrhosis, etc). A reduction in muscle mass and thus creatinine generation may occur with aging, which leads to an overestimation of GFR. A lower SCr (from muscle loss) in such persons will lead to a greater-than-true GFR and creatinine clearance, with potential underdiagnosing of CKD.

The advent of SCr calibration (to an isotope-dilution mass spectrometry standard) across US laboratories has led to a modification of the 4-variable MDRD Equation that decreased the number of CKD stage 3 individuals by 1.6%. Because the MDRD equations were derived solely from persons with CKD, an effort to define a more broadly based GFR equation was established by the CKD Prognosis Consortium. This group analyzed 43 cohorts of CKD and non-CKD participants totaling more than 1 million persons and produced the CKD-EPI Creatinine Equation 2009, which uses the same 4 variables in MDRD Equation 4. CKD-EPI is a set of 8 equations and performs better than the MDRD Equation 4, especially in patients with higher GFRs (young adults). The enhanced performance of CKD-EPI reduces misclassification of CKD, principally persons with an eGFR in the 50 mL/min/1.73 m² range. Also, the CKD-EPI equation more accurately stratified patients for risk of progression to ESRD and mortality. As of January 2013, most large commercial clinical laboratories have published eGFRs using the CKD-EPI equation. Multiple eGFR calculators are available online and as downloadable “apps” (kidney.org >> Professional >> GFR >> GFR calculator).

More recently, eGFR equations using cystatin C (CysC) have emerged. CysC is an 18 kilodalton molecule that like creatinine undergoes glomerular filtration, but unlike SCr, CysC does not undergo proximal tubular secretion (tubular secretion of creatinine represents up to 10-15% of creatinine clearance). Thus, CysC is a superior biomarker of glomerular filtration. Today, CysC is commercially available but not yet standardized like SCr. Alone or in combination with SCr, CysC can be used to determine GFR more accurately. It may also be more useful in clinical circumstances in which the MDRD and CKD-EPI equations are non-validated, such as patients with malnutrition (cirrhosis) or those with HIV/AIDS. Overall, despite ongoing enthusiasm for CysC-based eGFR calculation, particularly when combined with SCr, CysC-based eGFR determinations have not attained sufficient standardization to merit an NKDEP recommendation to supplant the current laboratory practice of estimating GFR by either

TABLE 3. KDIGO ALBUMINURIA CATEGORIES IN CKD

Equation	Calculation	Comment
MDRD equation 4 (1998)	$GFR = 186 \times (Scr)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$	Original equation prior to institution of calibrated SCr
MDRD equation 4 modified (2001)	$GFR = 175 \times (Scr)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$	Use with SCr calibrated to an IDMS reference method
CKD-EPI equation (2009)	<p>Female, SCr ≤ 0.7 $144 \times (Scr/0.7)^{-0.329} \times 0.993^{Age}$ [$\times 1.159$ if African American]</p> <p>Female, SCr > 0.7 $144 \times (Scr/0.7)^{-1.209} \times 0.993^{Age}$ [$\times 1.159$ if African American]</p> <p>Male, SCr ≤ 0.9 $141 \times (Scr/0.9)^{-0.411} \times 0.993^{Age}$ [$\times 1.159$ if African American]</p> <p>Male, SCr > 0.9 $141 \times (Scr/0.9)^{-1.209} \times 0.993^{Age}$ [$\times 1.159$ if African American]</p>	As above Used at Henry Ford Health System

MDRD Equation 4 or the CKD-EPI Equation. In the US, a CysC-based eGFR should generally only be ordered by a nephrologist.

When using eGFR equations, one must appreciate that CKD is defined over a 3-month interval. Therefore, the SCr must be repeated and trended to establish a diagnosis of CKD in an individual who must also be in a steady state of creatinine generation/production. Reviewing historical and obtaining serial SCr levels prevents misdiagnosis of AKI. An isolated SCr above the upper range of normal represents AKI in the absence of a comparative, prior SCr level. However, caution must be applied when trending SCr levels to prognosticate renal outcomes, especially in clinical scenarios where extracellular fluid status, blood pressure, or cardiac output may be rapidly changing, *eg*, diuretic therapy in heart failure, atrial fibrillation, cirrhosis, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) therapy. Trending the SCr to extrapolate renal outcomes requires multiple timepoints and often over 3 or more years.

The importance of albuminuria in CKD is established and the urine albumin-to-creatinine ratio is defined as ≥ 30 mg of albumin excretion per gram of creatinine and is independently associated with all-cause and cardiovascular mortality in CKD (**Table 4**). Heavy albuminuria *per se* in the nephrotic range (albumin excretion >2200 mg per 24 h or >3.5 g total proteinuria per 24 h) is a poor prognosticator even in the face of a high GFR.

To promote the importance of the etiology of CKD and its association with albumin, the Cause-GFR-Albuminuria (CGA) classification has been proposed by the Kidney Disease International Global Outcomes (KDIGO) Work Group (**Table 4**). However, current ICD-9/10 coding guidelines do not specify the use of a CGA format, which explicitly states three of the most important determinants of a kidney disorder. This format is now recommended internationally when documenting and discussing CKD. Table 4 demonstrates how CKD prognosis worsens with either increasing levels of proteinuria or declining GFR.

TABLE 4. PROGNOSIS OF CKD BY GFR AND ALBUMINURIA CATEGORIES: KDIGO 2012

PROGNOSIS OF CKD BY GFR AND ALBUMINURIA CATEGORIES: KDIGO 2012				PERSISTENT ALBUMINURIA CATEGORIES DESCRIPTION AND RANGE		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR CATEGORIES (ml/min/1.73m²) DESCRIPTION AND RANGE	G1	Normal to High	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk.

NEPHROLOGY CONSULTATION

by Gregory Krol, MD and Jerry Yee, MD

INTRODUCTION

In a survey, family medicine physicians (N=89), general internists (N=89), and nephrologists (N=129) evaluated a case of progressive CKD. Family medicine and internal medicine doctors recognized and recommended subspecialist care for progressive CKD less frequently than nephrologists. Their opinions also differed from nephrologists regarding evaluations by consultants and the expectations of nephrologists. The survey recommended the following:

- a) Greater dissemination of existing clinical practice guidelines
- b) Targeted CKD-specific education
- c) Consensus-building and guideline development by family medicine physicians, internists, and nephrologists

Data from dedicated CKD clinics corroborate these findings. Currently, there is a concerted effort from many nephrology societies, as well as the AMA, AHRQ, and ABIM to improve CKD education for primary and specialty care providers.

Timely and appropriate CKD consultation by the nephrologist promotes improved clinical outcomes and reduces the total cost of care for the patient and the public (**p. 10, NEPHROLOGY CONSULTATION DIAGRAM**). It has been estimated that healthcare savings of \$18.5 to \$60.6 billion USD would accrue by reducing the CKD progression rate by 10–30% over the next decade. **The optimal time for consultation is during CKD stages 3B to 4.** Discussions regarding kidney transplantation, modality choice for renal replacement therapy (including kidney transplantation), and end-of-life care should generally be initiated at a GFR of ~15 mL/min/1.73 m². An initial consultation for progressive CKD at stage 5 (estimated glomerular filtration rate [eGFR] <15 mL/min/1.73 m²) is fraught with hazard. Delayed consultation at this stage is associated with an increased cardiovascular morbidity during the transition from stage 4 to 5, delayed vascular access planning for those who will undergo hemodialysis, and delayed peritoneal catheter access planning.

REASONS FOR CONSULTATION

There are multiple reasons for obtaining a nephrology consultation. The most common and significant ones are described below. Normal age-related decline in GFR is 0.8–1 mL/min/1.73 m²/yr after the age of 40 years. Trend analysis of the GFR decline requires historical review and repeated observation. An unexplained, non-reversible, rapid decline in GFR of ≥4 mL/min/1.73 m²/yr is significant and should prompt consultation.

Glomerular Filtration Rate

As GFR falls below 45 mL/min/1.73 m² (CKD stage 3B), there is a significant increase in cardiovascular disease (CVD) risk. GFRs between 45 and 59 mL/min/1.73 m² generally do not presage future kidney failure, in the absence of albuminuria. However, periodic monitoring the GFR of such individuals is recommended. Crossing this eGFR threshold is equivalent to

experiencing a major cardiovascular event. This risk is worsened at any CKD stage by the presence of persistent albuminuria. Thus, the estimation of GFR is important because this process not only optimizes time of referral, but also delineates the progression rate of CKD.

Acute kidney injury (AKI) is a common reason for consultation, and extracellular volume depletion should always be ruled out. Greater than 30% increases of SCr may prompt renal consultation as well. However, these changes should persist for more than 3 months before consultation occurs, as many acute, hemodynamically driven SCr elevations will often dissipate or disappear within this time frame. A search for the cause of AKI, after volume depletion has been corrected or ruled out, includes a kidney ultrasonogram to rule out obstructive uropathy. Lastly, certain conditions such as malignancy, dementia, multiple comorbidities, or an advanced directive may preclude referral to a nephrologist and/or mitigate enthusiasm for the initiation of renal replacement therapy in patients with kidney failure (CKD stage 5).

Estimated Glomerular Filtration Rate (eGFR)

eGFR <45 mL/min/1.73 m², unless albuminuria or AKI is present

Serum Creatinine (SCr)

Males ≥1.5–1.7 mg/dL on two separate occasions, separated by at least 2 weeks, unless albuminuria or AKI is present

≥30% elevation of SCr from baseline that persists for 3 months or more

Females ≥1.1–1.3 mg/dL on two separate occasions, separated by at least 2 weeks, unless albuminuria or AKI is present

≥30% elevation of SCr from baseline that persists for 3 months or more

Administration of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) may produce elevations of SCr. Elevations <30% are anticipated following institution of either agent, and generally do not require evaluation by a nephrologist.

Urine Abnormalities

Renal consultation should be sought when urinary abnormalities persist, especially albuminuria or hematuria. Any isolated urinary abnormality must be confirmed, with the abnormality detected on at least two occasions separated by at least two weeks. Isolated microhematuria without albuminuria is an indication for Urology consultation. The combination of hematuria and albuminuria often indicates glomerular disease, and greater degrees of albuminuria warrant earlier nephrological consultation, particularly since a kidney biopsy may be required to establish a diagnosis. Note that albuminuria increases exponentially, and increases of albuminuria less than approximately 1.7- to 2-fold may not represent true increases in albuminuria and simply reflect variability in albumin excretion.

UA Dipstick ≥1+

UPC ≥0.2 g total protein/g creatinine (normal: ≤0.2)

ACR >300 mg albumin/g creatinine

Imaging Abnormalities

Other problems that nephrologists are consulted for include the evaluation of renal parenchymal abnormalities. The presence of bilateral and small kidneys by any imaging method essentially defines CKD with substantial loss of renal parenchyma. Acquired kidney cysts, which are seen commonly after the 5th decade, are often small and simple. However, increasing size and/or complexity mandates periodic imaging and follow-up, which can be accomplished by either a nephrologist or urologist. The same may be said for patients with symptomatic or asymptomatic kidney stones. The evaluation of renal masses includes imaging studies and careful microscopic examination of the urine. In general, macroscopic structural kidney disease may require urological expertise more than nephrological expertise.

Imaging Studies

X-ray Evidence of vascular or cardiac/valvular calcification and/or bone loss

Electrolyte Abnormalities

Na <132 mEq/L or >147 mEq/L in absence of diuretics
K <3.5 mEq/L w/ ongoing K replacement **or** in absence of diuretics
>5.5 mEq/L w/ ongoing dietary K restriction
HCO₃ <22 mEq/L or >28 mEq/L

Resistant (“Refractory” or “Difficult-to-Treat”) Hypertension

Any BP with: Target organ damage manifested by LVH, stroke, AKI, AMI, or heart failure
SBP/DBP ≥140/≥90 mmHg on 3 medications at maximally tolerated doses, including a diuretic
SBP/DBP ≥140/≥90 mmHg in CKD with albuminuria

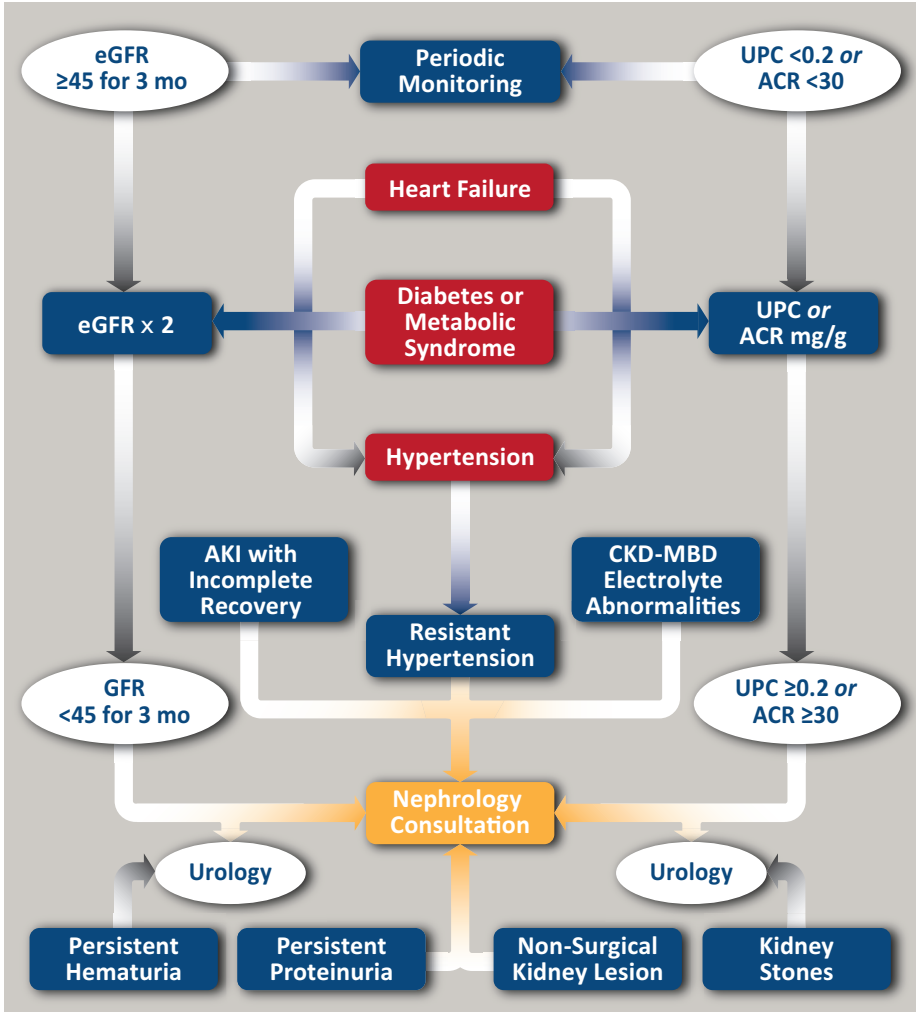
Anemia of CKD

Hemoglobin <12 (female) or <13.5 (male) g/dL, with adequate iron stores: TSAT >20% and ferritin >100 ng/mL (CKD stage 5, ferritin >200 ng/mL)

Chronic Kidney Disease-Mineral and Bone Disorder

Alkaline Phosphatase ≥200 IU/L in absence of liver disease with CKD
Corrected Calcium <8.8 mg/dL or >10.2 mg/dL
HCO₃ <22 mEq/L or >26 mEq/L
Phosphorus (P) >4.6 mg/dL in CKD stages 3–5
Intact PTH (iPTH) >2 × ULN in CKD stages 3–5

NEPHROLOGY CONSULTATION



Considerations for early nephrology consultation. Patients with diabetes, the metabolic syndrome, hypertension, heart failure and combinations of these disorders should undergo evaluations for eGFR and proteinuria. Consultation with a nephrologist is recommended for individuals with persistent hematuria, proteinuria/albuminuria, or eGFR <45 mL/min/1.73m² on occasions separated by at least 3 months, patients with incomplete recovery from acute kidney injury (AKI), or severe electrolyte derangements of Na, K, HCO₃, Ca, Mg, or P. **Abbreviations:** ACR, albumin-to-creatinine ratio (mg/g); AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; CKD-MBD, Chronic Kidney Disease-Mineral and Bone Disorder; UPC, urine protein-to-creatinine ratio (g/g).

PROGRESSION OF CHRONIC KIDNEY DISEASE

by Jerry Yee, MD

INTRODUCTION

Fortunately, most patients do not progress from CKD stage 3 to 5, but approximately 17% of CKD stage 4 and <1% of CKD stage 3 patients progress to CKD stage 5 (kidney failure). The transition to CKD stage 4 is often insidious and under-recognized. Importantly, this transition represents a “clinical event” similar to a stroke or acute myocardial infarction because CKD stage 4 is marked by a major increase in cardiovascular mortality and progression to CKD stage 5. During CKD stage 4, death is a competing risk for progression to end-stage renal disease (ESRD). Comprehensive systems targeting early recognition, prevention and management, and treatment by primary care physicians and advanced practice providers are required at this critical stage in collaboration with nephrologists. This effort includes prevention of repetitive kidney insults attributable to AKI, which could result from repeated bouts of radiocontrast induced nephropathy or repeated therapeutic treatments with a nephrotoxic chemotherapeutic agent(s).

PROTEINURIA

Aside from uncontrolled hypertension (HTN), proteinuria is one of the strongest prognosticators for declining kidney function (**p. 26, PROTEINURIA IN CKD DIAGRAM**). A “spot” urine protein-to-creatinine ratio (UPC) or urine albumin-to-creatinine ratio (ACR) quantifies proteinuria. Generally, UPCs <0.2–1 g protein per g creatinine predict a more favorable prognosis, whereas UPCs >1 predict more rapid functional decline from a glomerular disorder and more intensive evaluation, specifically, kidney biopsy.

RISK FACTORS FOR PROGRESSION

Modifiable risk factors for CKD progression are HTN, diabetes, morbid obesity, metabolic syndrome, hyper-cholesterolemia, heavy consumption of non-narcotic analgesic preparations, anemia, and cigarette smoking (**Table 1**). Perhaps the best prognosticator for CKD progression is the rate of decline of GFR. Rates of GFR decline >4 mL/min/1.73 m² per year are associated with greater progression risk. In diabetics, annual GFR rates of decline ≥10 mL/min/1.73 m² may occur. In heart failure, GFR declines ≥15 mL/min/1.73 m² per year are associated with worse anemia and progression to CKD stage 5. African American ethnicity is a major risk factor for progressive CKD from type 2 diabetic kidney disease (DKD), HTN (nephrosclerosis), and HIV. In general, Native Americans, Hispanics, and Asians have increased risk for type 2 diabetic CKD.

Cigarette smoking aggravates CKD. Risk factors that promote the accelerated atherosclerosis of CKD include elevated angiotensin II levels, proteinuria, secondary hyperparathyroidism, metabolic acidosis, dysregulated calcium and phosphate metabolism, extracellular fluid (ECF) volume expansion, and the intrinsic chronic inflammatory state of CKD. The common endpoint of all these factors is progressive renal fibrosis with a corresponding reduction in function. Strategies that retard the progression of CKD includes optimizing antihypertensive therapy;

stringent glycemic control; cigarette smoking cessation; avoidance of cocaine, NSAIDs, and exposure to nephrotoxic agents; and dietary protein and phosphorus restrictions.

TABLE 1. FACTOR-SPECIFIC INTERVENTIONS TO REDUCE RISK OF CKD PROGRESSION

Classification	Definition	Risk Factor
Category 1	Factor-specific intervention reduces risk	Diabetes, hypertension, obesity, metabolic syndrome, hyperlipidemia
Category 2	Factor-specific intervention likely reduces risk	Smoking, cocaine, nephrotoxic exposure (certain drugs), kidney stones, prostatic hypertrophy (obstruction), radiocontrast media
Category 3	Factor-specific modification may lower risk	High protein intake, obesity, metabolic syndrome, low income and/or educational level, chemical and environmental hazards (lead)
Category 4	Factor-specific modification not possible	Advanced age, male gender, ethnicity (African American, Native American, Hispanic, and Asian), family history of CKD (cystic kidney disease), low birth weight, congenital or acquired solitary kidney, and prior kidney damage (trauma, infection)

ACUTE KIDNEY INJURY

by Kathleen Liu, MD, PhD

INTRODUCTION

The term acute renal failure (ARF) is being increasingly supplanted by the term AKI (acute kidney injury), with rapidly evolving consensus-based definitions of AKI. Currently, serum creatinine- and urine output-based criteria are used to define AKI, which is more precise than prior operational definitions of ARF (**Table 1**). During AKI, the GFR may not be reliably determined since it depends on steady-state creatinine generation and elimination, which may be dramatically altered during AKI.

Several recent studies have suggested that the incidence of AKI is rising in the United States. AKI often complicates chronic kidney disease (CKD), particularly in stages 3–5. Persons with or without preexistent kidney disease may incur permanent decrements in kidney function after single or repeated episodes of AKI/ARF. To establish CKD, the examination of medical records is the optimal method. The next best method to establish CKD is by renal imaging, eg, kidney ultrasonography or computed tomography. By ultrasound, normal, adult kidney sizes are 10–12 cm in the sagittal plane; however, size discrepancies up to 37% between normal kidneys may be found. A lack of cortical thickness (<2 cm) usually indicates CKD.

TABLE 1. CLASSIFICATION OF ACUTE KIDNEY INJURY / ACUTE RENAL FAILURE

Stage	Serum Creatinine	Urine Output
1: Risk	SCr ↑ of ≥ 0.3 mg/dL over 48 h SCr ↑ of ≥ 1.5 - 2.0 -fold over 7 d	<0.5 mL/kg/h for >6 h
2: Injury	SCr ↑ of ≥ 2.0 - 3.0 -fold	<0.5 mL/kg/h for >12 h
3: Failure	SCr ↑ of ≥ 0.3 mg/dL or >3-fold from baseline SCr ≥ 4.0 mg/dL with acute ↑ ≥ 0.5 mg/dL	<0.3 mL/kg/h for 24 h Anuria for 12 h

AKI represents a substantial risk factor for progressive CKD. A single episode of AKI may generate a steeper decline in renal function than normally expected from aging alone. Therefore, patients who develop severe AKI or recover slowly from AKI must be closely monitored, even when the estimated glomerular filtration rate (eGFR) returns to baseline. Although patients who recover to baseline renal function appear to be at increased risk for CKD progression, and the optimal follow-up strategies for these patients have yet to be determined. Patients who do not recover to baseline eGFR or who have underlying CKD likely warrant closer follow-up, with at least annual follow-up for 2–3 years.

RISK FACTORS AND CAUSES OF AKI

AKI is categorized as prerenal, parenchymal, and postrenal etiologies. To eliminate the latter from the differential diagnosis, always rule out urinary outlet obstruction when

establishing an etiology for AKI/ARF, particularly in males with clinically undiagnosed prostatic hyperplasia. AKI continues to occur with increasing frequency and constitutes the majority of Nephrology inpatient consultations. The increased utilization of pharmaceuticals has increased the frequency of immune-mediated (allergic) tubulointerstitial nephritis, particularly from antibiotics.

When challenged by sodium (volume) depletion, CKD patients often develop AKI more rapidly than normal individuals. The consequent prerenal azotemia, from absolute (vomiting, overdiuresis) or relative volume depletion (cirrhosis, nephrosis or heart failure) accounts for nearly 40% of hospital-acquired AKI. Administration of pharmaceuticals such as NSAIDs, antibiotics (aminoglycosides), or iodinated radiocontrast media can induce AKI/ARF. Volume depleted patients are more susceptible to radiocontrast-induced nephropathy (**p. 60, MEDICATION-RELATED PROBLEMS**). CKD patients undergoing cardiothoracic and/or other emergent surgical procedures that occur with blood loss, sepsis and/or radiocontrast administration are at increased risk for AKI/ARF.

CKD patients treated with anti-RAAS medications commonly develop elevations of BUN and SCr. The potential benefits of chronic anti-RAAS treatment likely outweigh a mild stable decline of GFR from angiotensin-converting–enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) use. Generally, increases in SCr of up to 30% and serum K levels of 5.5 mEq/L can be tolerated. However, unless moderate hyperkalemia (K >5.5 mEq/L), oliguria, relative hypotension, or a substantial GFR reduction occurs, these agents generally should be continued due to their overall beneficial effects on retarding the progression of CKD.

AKI represents a risk factor for the development of CKD. In general, the risk increases with decreasing GFR. A CKD stage 4 patient who develops AKI has a much greater risk than an individual at CKD stage 3A. Patients who develop AKI in-hospital that is not easily reversed by volume repletion should be followed up as an outpatient within 3 months of discharge. The development of albuminuria by urinalysis dipstick or another measurement technique during AKI indicates more severe AKI, and these persons should be followed up in the outpatient setting.

KEY SUMMARY POINTS

CKD is the most common risk factor for development of AKI

Determine whether AKI is present in all cases of “presumptive” CKD

Evaluate and correct all potentially reversible causes of reduced GFR

A partial list of common causes of AKI with acute GFR reduction (**see Medication Section**):

- Altered intrarenal hemodynamics: common agents that decrease GFR, *eg*, NSAIDs (COX-1/-2 inhibitors), ACEIs, ARBs, and calcineurin inhibitors
- Drug-induced acute tubulointerstitial nephritis: commonly implicated agents include penicillins, cephalosporins, sulfonamides, rifampin, phenytoin, fluoroquinolones, proton pump inhibitors, and NSAIDs (non-hemodynamically related ARF)
- ECF volume depletion, especially with NSAID, ACEI, or ARB drug co-administration
- Heart failure
- Hypotension
- Advanced liver disease
- Nephrotoxins: aminoglycosides, pentamidine, foscarnet, amphotericin, cis-platinum, and multiple chemotherapeutic agents
- Radiocontrast medium (*eg*, iodine-based contrast agents)
- Phosphate-based bowel preparations
- Rhabdomyolysis
- Urinary tract outlet obstruction must always be ruled out, particularly in males

HYPERTENSION IN CHRONIC KIDNEY DISEASE

by Debbie Cohen, MD and Raymond Townsend, MD

INTRODUCTION

The prevalence of hypertension (HTN) continues to increase. Approximately 74.5 million Americans aged 20 years or older currently have HTN. Aging and obesity are the two most important reasons for this increasing prevalence. HTN frequently accompanies advancing CKD and is often incorrectly assumed as the cause rather than the effect of CKD. Whether CKD causes HTN or vice versa, HTN remains highly associated with cardiovascular outcomes. In one observational study, CKD with HTN had a 22% higher stroke risk compared to HTN without CKD. By contrast, more than a 2-fold increase in stroke risk occurred when the SBP was <120 mmHg. In CKD, heart failure and cardiovascular deaths increased as SBP remained below or approached 120 mmHg (J-curve). DBP should be maintained at ≥ 60 mmHg whenever possible to avoid orthostatic symptoms and end-organ hypoperfusion, particularly in individuals with relatively large pulse pressures, namely ≥ 55 mmHg. However, the recent Systolic Blood Pressure Interventional Trial (SPRINT) revealed cardiovascular benefits of systolic blood pressure reduction to 120 mmHg or less in an older, nondiabetic population with high cardiovascular disease risk. Approximately 30% of the 9300 participants had CKD, and definitive analysis of this group is pending.

AT-RISK GROUPS

African Americans develop hypertensive CKD (nephrosclerosis) much more frequently than Caucasians. Genetic susceptibility to hypertensive nephropathy associated with genetic polymorphisms (eg, APOL1) in African Americans may contribute to this risk. Hypertensive kidney disease in African Americans may not always be attributable to high BP and may reflect an underlying glomerular disorder. Suspect glomerular disease in non-diabetic individuals diagnosed with hypertensive nephropathy if urine protein-to-creatinine ratios (UPCs) are >1 or albumin-to-creatinine ratios (ACRs) are >300 mg/g. African Americans also tend to respond less well than Caucasian patients to monotherapy with beta blockers (BBs), angiotensin-converting-enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). However, ethnicity-related differences in therapeutic response are usually nullified by concomitant diuretic therapy. For example, the response to combined thiazide diuretic-ACEI or ARB therapy is equivalent among the various ethnicities. Therefore, no particular agent should be avoided in patients of African American ethnicity.

Since nondiabetic CKD patients have equivalent or greater risk for the development of cardiovascular disease compared to diabetic patients without CKD, cardiovascular protective measures in addition to antihypertensive therapy must always be considered. Since a given individual's BP response to high sodium intake (salt sensitivity) is not predictable, sodium restriction should generally be enforced in all CKD patients, *ie*, <2000 mg sodium (90 mmol) per day.

BLOOD PRESSURE PROFILE

Hypertension in CKD is considered by default as “resistant HTN,” *ie*, treatment requires three or more antihypertensive agents, one of which is a diuretic, at maximally tolerated doses. The typical BP profile is one with an SBP greatly exceeding DBP, manifested as an elevated pulse pressure (>55 mmHg). A low DBP warrants caution when lowering the BP, particularly in elderly persons who may be prone to cerebral and/or cardiac hypoperfusion when the DBP decreases to <55–60 mmHg. Either the SBP or pulse pressure may be increased in hypervolemic or edematous individuals who must often be treated with diuretics.

PROTEINURIA

Evaluation for and quantitation of albuminuria is recommended for those with a family history of CKD or eGFR is <60 mL/min/1.73 m². Achievement of target BP goals, particularly for the more important SBP, will require two or more antihypertensive medications in most cases, if the initial SBP is ≥20 mmHg above goal (SBP ≥160 mmHg). Therefore, two antihypertensive agents may be initiated at the outset, an anti-renin–angiotensin–aldosterone system (RAAS) drug such as an ACEI or ARB and either a diuretic (eg, thiazide or loop diuretic, the latter predicated by lower GFRs) or calcium channel blocker (CCB). Non-dihydropyridine CCBs (eg, diltiazem, verapamil) are preferred in proteinuric CKD, with appropriate caution during concomitant beta blocker therapy, or with possible contraindication due to bradycardia.

Albuminuria is associated with an accelerated rate of decline of GFR in hypertensive, diabetic, and non-diabetic individuals. Hypertension exacerbates albuminuria and promotes tubulointerstitial inflammation, fibrosis, and tubular atrophy, further elevating BP. Also, albuminuria is an independent risk factor for stroke, left ventricular hypertrophy, and death. In the presence of >1–2 g/d of total proteinuria, the risk for progressive CKD rises after SBP ≥130 mmHg. To retard progression of CKD, nearly all CKD patients will be treated with an ACEI or ARB. Part of their benefit may stem from their antifibrotic effects, an effect shared by mineralocorticoid receptor antagonists (MRAs).

Patients with an SBP of 115–130 mmHg and proteinuria <1 g/d have a relatively lower risk of progression of their CKD. However, an SBP 130 mmHg may be considered optimal for patients with HTN and proteinuria since SBPs ≤120 mmHg have been associated with an enhanced risk of adverse cardiovascular events in proteinuric CKD patients, especially those with stroke or heart failure. Overall, a SBP of 130–140 mmHg in proteinuric CKD patients is recommended, with collaborative renal consultation. As stated previously, pending further results of SPRINT, the question of whether greater blood pressure-lowering will reduce proteinuria cannot be answered at this time.

TREATMENT

The Seventh Report of the Joint National Committee (JNC 7) issued a set of Compelling Indications (**Table 1**) for the treatment of HTN, and these should continue to be followed in CKD. JNC 8 established a higher BP goal and attempted to simplify the treatment of HTN in general and in CKD. Modification of lifestyle and dietary interventions should always be enforced in hypertensive CKD patients since CKD is a salt-sensitive state.

Sodium restriction alone may produce substantial BP reduction and primarily entails reducing the intake of sodium-laden processed foods. However, added sodium represents only about 10% of sodium intake. A 24-h urine sodium collection may reveal excessive sodium intake as the cause of resistant hypertension. If sodium restriction is unenforceable, loop diuretic therapy, at least twice daily, may be required. Other causes of resistant hypertension should be excluded, including NSAID or sympathomimetic ingestion, cocaine, and hyperthyroidism.

Current guidelines from the Kidney Disease: Improving Global Outcomes (KDIGO) and other evidence-based guidelines and recent publications for the management of adult hypertension recommend a goal BP of <140/90 mmHg for diabetic and nondiabetic CKD without proteinuria. The current evidence-base also recommends a goal BP of <140/90 mmHg even in the setting of proteinuria, which differs from the KDIGO-recommended goal BP of <130/80 mmHg in patients with albuminuria. Overall, HTN control in CKD patients is suboptimal with less than one-half of patients achieving target BP levels. In the majority of such cases, the BP regimen can be improved. A suggested regimen for nondiabetic and diabetic CKD patients is outlined (**p. 20, APPROACH TO HYPERTENSION DIAGRAM**). The addition of chlorthalidone to CKD patients with difficult-to-treat HTN may be useful. As with loop diuretic therapy, successful BP-lowering is associated with weight loss and the complication of hypokalemia. Therefore, electrolyte monitoring is essential during dual diuretic therapy.

TABLE 1. JNC 7 COMPELLING INDICATIONS HYPERTENSION TREATMENT

Indication	Treatment
Chronic kidney disease	ACEI, ARB
Diabetes mellitus	ACEI, ARB, BB, CCB
Heart failure	ACEI, ARB, BB, MRA, loop diuretic, thiazide diuretic
High CAD risk	ACEI, thiazide, BB, CCB*
Post-MI	ACEI, BB, MRA
Primary stroke prevention	ARB (losartan)
Secondary stroke prevention	ACEI

Abbreviations: *ACEI*, angiotensin-converting-enzyme inhibitor; *ARB*, angiotensin receptor blocker; *BB*, beta blocker; *CCB*, calcium channel blocker; *MRA*, mineralocorticoid receptor antagonist (epleronone, spironolactone).

MINIMUM THERAPEUTIC TARGETS

BP <140/90 mmHg CKD without proteinuria

BP <130/80 mmHg CKD with proteinuria

FIRST-LINE AGENTS

GFR >20 mL/min/1.73 m² ACEI or ARB

Most CKD patients with HTN require 2 or more antihypertensive medications

SECOND AND THIRD LINE AGENTS

GFR \geq 40	Add thiazide, preferably chlorthalidone, and/or CCB, if anti-RAAS agent is first-line
GFR <40	Add loop agent (<i>eg</i> , bumetanide or furosemide), with twice daily dosing, or torsemide, with once daily dosing, and/or CCB, if anti-RAAS agent started as first-line therapy

FOURTH-LINE AGENTS

HR >80 bpm	β -blocker or α -/ β -blocker
HR \leq 80 bpm	Consider adding MRA (<i>eg</i> , spironolactone or eplerenone), if proteinuria present

SPECIFIC CLINICAL SITUATIONS

Diabetes	ACEI or ARB for type 1 diabetes ARB or ACEI for type 2 diabetes
CAD	β -blocker or α -/ β -blocker (<i>eg</i> , labetalol), CCB
BPH	α 1-blocker (<i>eg</i> , prazosin, terazosin, doxazosin)
Thiazide-resistant HTN	Amiloride or MRA
Primary aldosteronism	MRA

STAGE 2 HYPERTENSION (UNCONTROLLED)

BP	\geq 20/10 mmHg above goal on >2 occasions, separated by \geq 2 d, initiate 2 drugs
----	---

KEY SUMMARY POINTS

Anti-RAAS therapy: SCr increases are common and can often be tolerated

Obtain SCr and serum K levels 7–10 days after initiation of an ACEI or ARB and with changes in anti-RAAS therapy

Increases of SCr 30% above baseline within 3 months of initiating anti-RAAS therapy may be acceptable; greater SCr elevations should be considered as AKI

Avoid dihydropyridine CCB as monotherapy in proteinuric CKD patients

Initial SBP: if \geq 20/10 mmHg above goal initiate a 2-drug regimen, *eg*, ACEI/diuretic, ARB/diuretic, or ACEI/CCB, ARB/CCB in untreated patients

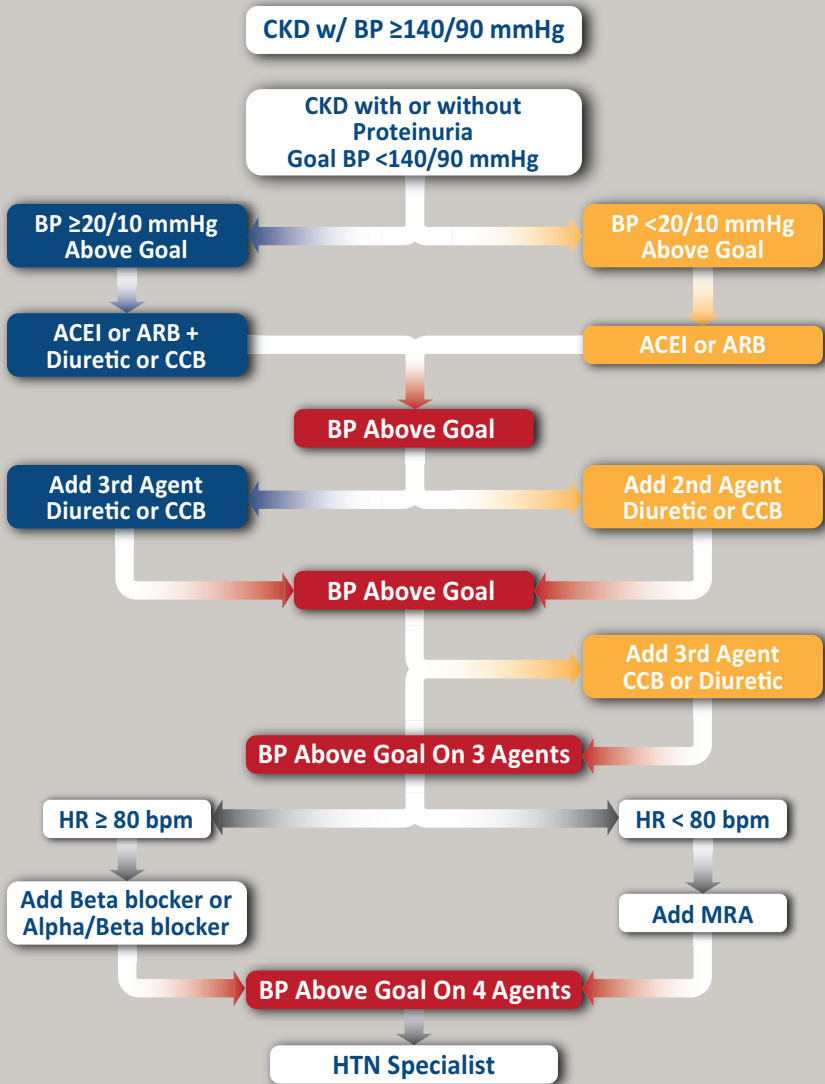
Sodium intake >100 mmol (2300 mg sodium)/24-h and/or ineffective diuretic therapy may be the cause of “resistant” HTN and can be diagnosed by a 24-h urine sodium collection

Sympathomimetic agents (pseudoephedrine, “diet” pills, cocaine) and NSAIDs (COX-1/-2 and selective COX-2 inhibitors) may aggravate HTN

There are differences in BP targets among various guidelines

An approach to hypertension management for nondiabetic and diabetic persons with chronic kidney disease. **Abbreviations:** ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; MRA, mineralocorticoid antagonist.

APPROACH TO HYPERTENSION IN NON-DIABETIC AND DIABETIC CKD



Abbreviations: *ACEI*, angiotensin converting enzyme inhibitor; *ARB*, angiotensin receptor blocker; *CCB*, calcium channel blocker; *MRA*, mineralocorticoid receptor.

At the time of the writing of this booklet, new and important results from the Systolic Blood Pressure Intervention Trial (SPRINT) were published in the New England Journal of Medicine (A Randomized Trial of Intensive versus Standard Blood-Pressure Control by The SPRINT Research Group, November 9, 2015). A brief synopsis of the trial is presented here.

SPRINT evaluated 9631 participants older than age 50 years with a high risk for cardiovascular events in a randomized, controlled, open-label trial. Participants were randomly assigned to either a target systolic blood pressure of <140 mmHg (standard group) or a more intensive target of <120 mmHg (intensive group) at 102 centers. The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes. The study was stopped early (3.3 years) due to a significant reduction in cardiovascular events and all-cause mortality in the intensive group. However, the rates of hypotension, syncope and acute kidney injury were increased in the intensive therapy group. Approximately 30% of the participants in the study had chronic kidney disease (CKD). The analyses of renal end points and progression of CKD are pending. An additional substudy on cognitive dysfunction (SPRINT MIND) is not yet completed.

In light of the SPRINT results, efforts should be made to lower the blood pressure of CKD patients older than 50 years to 120 mmHg. In general, achievement of a blood pressure of 120 mmHg will require 3 antihypertensive medications at maximally tolerated doses. To achieve a systolic blood pressure of 140 mmHg, two antihypertensive medications will be required. Additional lowering of the systolic blood pressure must be done with caution and close monitoring, given the increase in adverse events. Treatment targets should be individualized within the contexts of medication side effects and costs, comorbid conditions, and patient preferences.

—The Editors

PROTEINURIA IN CHRONIC KIDNEY DISEASE

by Julie Lin, MD

INTRODUCTION

The poor prognosis of “lardaceous urine” or urine containing substantial amounts of protein—primarily as albumin—was appreciated in the first half of the 19th century. Increasing albuminuria portends worsening chronic kidney disease (CKD) and cardiovascular disease (CVD) risk, particularly in diabetic, hypertensive, and glomerular kidney disorders. The prevalence of albuminuria is 4–8% worldwide and 10–20% in hypertensive, obese, and/or diabetic populations. Diabetics and persons with estimated glomerular filtration rates (eGFRs) <60 mL/min/1.73 m² should undergo albuminuria testing. Individuals with greater GFRs should only undergo albuminuria evaluation(s), if there is a strong suspicion for CKD (*ie*, strong family history of CKD or other renally associated condition). Proteinuria must be quantified in CKD by the urine protein-to-creatinine ratio (UPC) or a urine albumin-to-creatinine ratio (ACR).

The ACR more reliably classifies individuals with “higher risk” CKD (*ie*, those who might develop progressive disease) after initial stratification into CKD stages 3 and 4 by an eGFR equation. Even small amounts of albuminuria (>10 mg/g) are associated with adverse CV outcomes. Using the combination of eGFR <60 mL/min/1.73 m² and ACR reduces the prevalence of CKD stages 3 and 4 patients by 76%, from 16.3 million to 3.9 million. Note that ACR testing is essentially a nationally standardized laboratory procedure but UPC testing is not. While angiotensin-converting-enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) therapies reduce albuminuria and are associated with reduced risk for developing end-stage renal disease (ESRD), especially in diabetes and hypertension, these agents are increasingly underutilized with increasing CKD stage. Ideally, 70% or more of CKD patients should be treated with these drugs.

TYPES OF PROTEINURIA

Traditionally, normal urinary protein excretion is considered to be <150 mg/d. In normal persons, total urinary proteins are comprised of immunoglobulins, various α - and β -globulins, and Tamm-Horsfall mucoprotein produced by the thick ascending Loop of Henle. Persistently elevated total urinary protein typically signifies one of the following abnormalities:

- a) Glomerular defect(s) in barrier (endothelium, glomerular basement membrane, podocyte/slit diaphragm) function that lead to disproportional increases in albumin excretion.
- b) Impaired proximal tubular reabsorption of proteins, *eg*, tubular injury.
- c) Increased filtration and excretion of low molecular weight protein(s), *ie*, “overflow proteinuria” as may occur with paraproteinemia.

Persistent proteinuria is defined as two or more positive quantitative tests of protein excretion, separated by at least 2 weeks. Common, benign sources of albuminuria/proteinuria include

orthostatic proteinuria, intense activity/exercise, and fever. In nearly all cases, the ACR will be <300 mg/g. Serious causes of albuminuria include glomerular disorders, including DKD, and myeloma. A false-positive urinalysis dipstick result for albuminuria may be seen with a highly alkaline urine, concentrated urine (specific gravity >1.020), gross hematuria, and the presence of mucus, semen, or white cells.

Individuals at increased risk for CKD should undergo testing for albuminuria. The urinalysis dipstick may not register albuminuria when the urine is highly dilute, (*ie*, specific gravity ≤ 1.015). In addition, the dipstick preferentially detects albumin, which is the major urinary protein excreted in proteinuric CKD disorders, *eg*, diabetes, glomerular disorders.

EVALUATION OF ALBUMINURIA

Two or more positive quantitative tests of albuminuria, preferably on first morning urine specimens, should be documented before a diagnosis of persistent proteinuria is established (**p. 26, CKD PROTEINURIA EVALUATION DIAGRAM**).

The urinalysis dipstick favors albumin detection and is relatively insensitive for tubular proteinuria, *eg*, immunoglobulin light chains. Quantitative urinary protein (principally albuminuria) testing by a UPC or ACR is recommended within 3 months of documentation of $\geq 1+$ dipstick albuminuria (corresponds to >300 mg/g or albuminuria classification A3 in the new KDIGO classification) by dipstick analysis. If tubular proteinuria is suspected, specific qualitative and quantitative examinations may be required, *eg*, serum free light chain analysis (Freelite™) and serum and urine immunofixation. For screening purposes, a 24-h urine is unnecessary, but if a serum monoclonal protein is detected, a 24-h urine collection for immunofixation is indicated. Consultation with a clinical laboratory expert is advised to optimize diagnostic yield in such cases.

Early or first morning “spot” UPC ratios are typically expressed in units of mcg/mg, mg/mg, or mg/g and calculated by the ratio of urine concentrations of protein (mg/dL) and creatinine (mg/dL). The ratio corresponds with a daily protein excretion rate in $g/1.73 m^2/d$. A UPC=2 correlates with 2 g of protein per g creatinine for an individual with body surface area of $1.73 m^2$ in a 24-h timed urine collection. A 24-h urine collection for albumin or total protein is rarely required today and is fraught with error(s) by physician and patient alike. However, for patients with glomerular disease, 24-h collections may be necessary when more exact quantitation is required (*ie*, research study). Since the proportion of the protein excretion in glomerular disease increasingly becomes albumin, albumin-specific tests have been devised, *eg*, albumin-specific dipsticks and the ACR, traditionally classified as normal (<30 mg/g), microalbuminuria (30–300 mg/g) and macroalbuminuria (>300 mg/g). Notably, the terms micro- and macroalbuminuria are considered obsolete, and albuminuria is now simply quantitated numerically. Albuminuria should now be described as either normal (<30 mg/g), moderate (30–300 mg/g), or severe (>300 mg/g). Because proteinuria and albuminuria ratios are dependent on urinary creatinine excretion, the prevalence of abnormal UPCs and ACRs increases with age as muscle mass and creatinine generation invariably decrease.

ANTIPROTEINURIC THERAPY

Antiproteinuric therapy is a goal at all stages of CKD. Reducing albuminuria likely reduces interstitial fibrosis and consequently, the progression of CKD. Patients with stable, persistent proteinuria of <1 g/24-h have a relatively small risk of progression to kidney failure compared to individuals with greater proteinuria. However, glomerular proteinuria in the nephrotic range (>2 g/m²/d; 3.5 g/d in adults) has an ominous prognosis and is associated with multiple complications. These include avid sodium retention with hypertension, hypercholesterolemia, hypoalbuminemia, anemia, hypercoagulability, vitamin D deficiency with bone loss, increased infection risk from hypogammaglobulinemia, and an enhanced risk for progression to ESRD. Regardless of the degree of proteinuria, all therapies that reduce proteinuria should be optimized.

ACEIs and ARBs represent first-line antiproteinuric agents and should be utilized whenever possible and at maximally tolerated doses in diabetic and nondiabetic proteinuric CKD. Their benefits extend over the entire spectrum of proteinuric kidney disorders, from minimal amounts of albuminuria to nephrotic range proteinuria. These agents exert differential and beneficial effects on glomerular structural proteins, intraglomerular pressure, local and systemic sympathetic nervous systems, inflammatory pathways, and the systemic blood pressure. Antihypertensive regimens that includes ACEIs or ARBs are more efficacious than regimens that do not include them. Sodium restriction and/or diuretic therapy augment the antiproteinuric therapy of ACEIs and ARBs.

Aldosterone receptor antagonists (ARAs, *eg*, epleronone, spironolactone) and direct renin inhibitors (DRIs) are antiproteinuric. Combinations of ACEIs + ARBs frequently reduce proteinuria by an additional 25–40%. However, dual blockade of the renin-angiotensin-aldosterone system (RAAS) is not recommended as treatment for DKD due to increased complications of hyperkalemia, hypotension, and acute kidney injury (AKI). Three studies of dual blockade of RAAS have demonstrated no benefit in reducing renal (progression of CKD, requirement for dialysis, ESRD) or cardiovascular events (cardiovascular death or first occurrence of a cardiac arrest, heart failure, or nonfatal stroke or myocardial infarction): ALTITUDE (aliskerin + ACEI or ARB), ONTARGET (telmisartan and ramipril), and VA NEPHRON-D (lisinopril + losartan). In conclusion, dual anti-RAAS therapy is not recommended for the treatment of DKD. However, dual therapy that targets proteinuria as a clinical endpoint has not been specifically studied long-term and, if contemplated, should be done in collaboration with a nephrologist.

The non-dihydropyridine calcium channel blockers (NDCCBs), diltiazem and verapamil, also reduce proteinuria and complement ACEI or ARB therapy, whereas dihydropyridine CCBs such as amlodipine and nifedipine demonstrate variable or little effect in further reducing proteinuria. Some data suggest that pentoxifylline and the HMG-Co synthetase inhibitors (“statins”) such as simvastatin and atorvastatin reduce proteinuria. **High sodium intake and suboptimal glycemic control (A1C $>8\%$)** may retard BP-lowering and proteinuria-reducing effects of antihypertensive agents. A sodium intake of ≤ 1500 mg daily is recommended for CKD patients. Whether blood pressure targets should be $<140/90$ mmHg for either subnephrotic or overt proteinuric states remains an area of controversy.

THERAPEUTIC TARGETS FOR PROTEINURIA REDUCTION

UPC	<0.2 (dimensionless ratio; units as mg/dL)
ACR	<30 mg albumin/g creatinine

FIRST-LINE AGENTS FOR PROTEINURIA REDUCTION

Nondiabetic proteinuria	ACEI (ARB, if ACEI-intolerant)
Diabetes, type 1 or 2	ACEI (ARB, if ACEI-intolerant)

SECOND-LINE AGENTS FOR PROTEINURIA REDUCTION

Diabetes, types 1 or 2	(ACEI or ARB) + (NDCCB, diuretic and/or ARA)
------------------------	--

KEY SUMMARY POINTS

Spot UPCs or ACRs are usually sufficient for diagnostic purposes

24-h urine albumin or total protein collections are rarely required for proteinuria evaluations

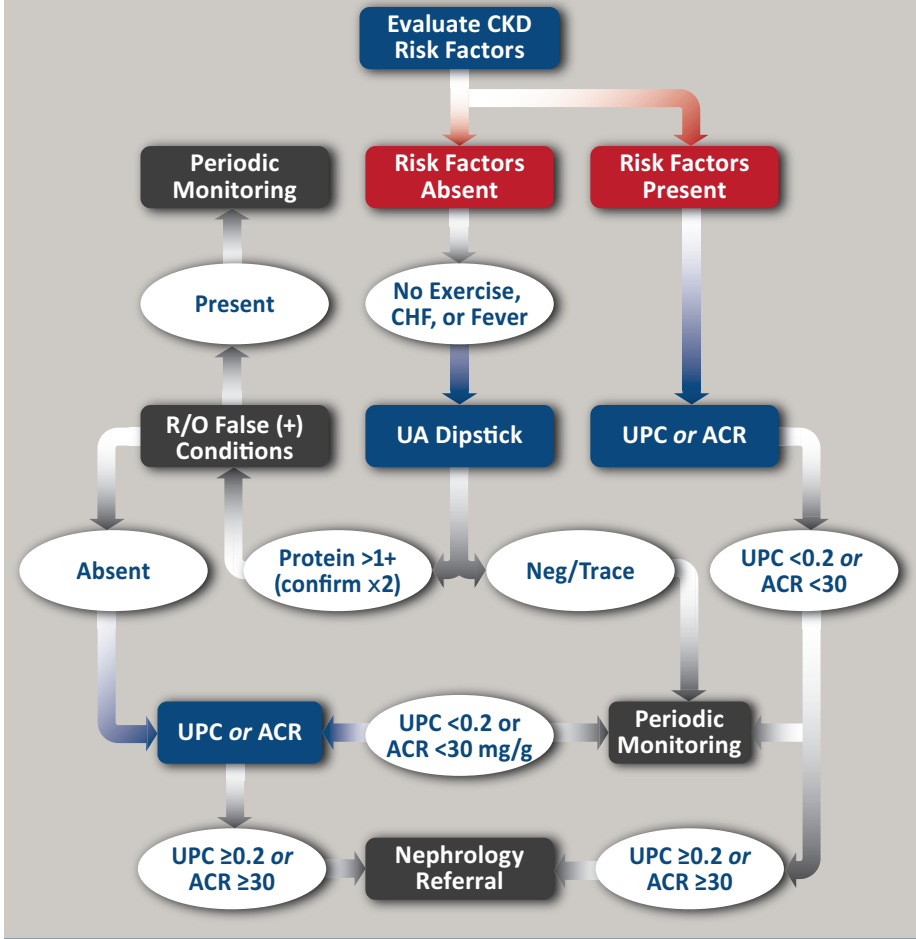
ACR and UPC tests may respectively overestimate albumin and protein excretion in cachectic or elderly patients due to lower creatinine generation rates

ACR and UPC tests may respectively underestimate albumin and protein excretion in muscular patients due to higher creatinine generation rates

Optimal timing of urine protein determination is the first morning void following recumbency and can rule out orthostatic proteinuria

Repeat quantitation of albuminuria or proteinuria by an ACR or a UPC should be conducted 8–12 weeks after a therapeutic intervention that targets albuminuria

CKD PROTEINURIA EVALUATION



CKD risk factors. Clinical: diabetes, hypertension, autoimmune disorders, recurrent urinary tract infections, urolithiasis, urinary tract obstruction, family history of CKD, reduced kidney mass, single kidney, low birth weight, preeclampsia, and exposure to nephrotoxins. **Sociodemographic:** older age, chemical/environmental hazards, low income status, low education level, and certain ethnicities: African American, Native American, Hispanic, and Asian.

Causes of false-positive protein result on UA dipstick: alkaline urine (pH >7), highly concentrated urine, gross hematuria, mucus, semen, leukocytes, radiocontrast, increased creatine supplement ingestion, and contamination by common cleaning solutions that contain chlorhexidine or benzalkonium.

Abbreviations: **UPC**, urine protein-to-creatinine ratio (g/g); **ACR**, albumin-to-creatinine ratio (mg/g).

DIABETIC KIDNEY DISEASE

by Susanne B. Nicholas, MD

INTRODUCTION

With the anticipated increase in the prevalence of diabetes mellitus (DM), the cost of care for patients with diabetic kidney disease (DKD) is expected to similarly rise. In 2010, an estimated 10.9 million US residents aged ≥ 65 years and 25.6 million adults ≥ 20 years had DM. A total of 215,000 individuals < 20 years had type 1 or type 2 DM and another 1.9 million adults ≥ 20 years had newly diagnosed DM (<http://www/cdc.gov/diabetes/pubs/factsheet11.htm>). These statistics are a sharp increase in the prevalence of DM between 1990 and 2010. These increases were observed not only in all age groups but also in both sexes and all racial/ethnicity groups in the US. The increased prevalence of DM has been linked to obesity, aging, tobacco use, physical inactivity, and urbanization. Worldwide, the epidemic of DM is anticipated to reach ~ 366 million persons by 2030. Currently, DM is defined by hyperglycemia and based primarily on A1C levels $\geq 6.5\%$ (8.6 mmol/L) and an 8-h fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/l). It may also be defined by the 2-h plasma glucose ≥ 200 mg/dL (11.1 mmol/l) during an oral 75-g glucose tolerance test or a random plasma glucose ≥ 200 mg/dL in a patient with classic symptoms of hyperglycemia or a hyperglycemic crisis.

DM is the leading cause of chronic kidney disease (CKD). A term that indicates CKD in the presence of DM regardless of albuminuria or abnormal renal histology, DKD accounted for 44% of all new cases of end-stage renal disease (ESRD) in the US between 1988 and 2008. This percentage is in proportion to the increased prevalence of DM. Currently DKD accounts for $> 50\%$ of prevalent ESRD in the US. Unfortunately, DM is also the leading cause of non-traumatic lower limb amputations, new cases of blindness, heart disease, and stroke. DM is the seventh leading cause of death in US adults. Microvascular complications of the eye, kidney, and nerve are much more prevalent in type 1 compared to type 2 DM. Retinopathy marked by the development of new retinal vessels may be present in nearly all type 1 and $\sim 60\%$ of type 2 DM. Microvascular complications may be prevented with improved glycemic control: for each 1% decline in A1C, the risk of these complications may be reduced by $\sim 40\%$. Further, tight BP control can reduce the risk of heart disease and stroke by 33–50% and microvascular complications by $\sim 33\%$. However, these improvements are not consistent among all racial/ethnic groups as significant disparities exist for the onset and rate of DKD progression. Thus, these high-risk populations may present a challenge and opportunity to better address optimal management strategies of DKD and to improve cost containment.

NATURAL HISTORY AND DIAGNOSIS OF DKD

In the US, an estimated 50% of diabetic patients will develop DKD in the absence of agents that block the RAAS system. Although the natural history of DKD is similar in both types 1 and 2 diabetes, it has been best described in individuals with type 1 diabetes where the onset of disease is marked by hyperfiltration. DKD may progress through a silent phase of accumulation of extracellular matrix in the mesangium, then development of microalbuminuria, macroalbuminuria, and eventually overt proteinuria wherein the major excreted protein is albumin. The terms micro- (30–300 mg/g) and macroalbuminuria (> 300 mg/g) have

been replaced by the single, encompassing term, albuminuria, at a quantitated level that is ≥ 30 mg/g (eg, 150 mg/g or 450 mg/g). In the early phase of structural pathology, three characteristic lesions are observed: diffuse mesangial expansion, diffuse thickening of the glomerular basement membrane (GBM), and hyalinosis of the afferent and efferent arterioles. The characteristic Kimmelstiel-Wilson nodules of mesangial sclerosis are not pathognomonic for DKD and are seen in ~25% of patients with advanced DKD, particularly when DM has been poorly controlled. Recently, a new classification for grading glomerular lesions of DKD was proposed by the Research Committee of the Renal Pathology Society based on results from serial biopsies of patients with type 1 DM: class I or isolated GBM thickening; class II or mild to severe mesangial expansion in $>25\%$ glomeruli without evidence of nodular sclerosis; class III or Kimmelstiel-Wilson nodular sclerosis in >1 glomerulus with nodular increase in mesangial matrix; and class IV or global sclerosis in $>50\%$ glomeruli from classes I and II.

The lesions of type 2 DM are somewhat more heterogeneous and another proposed classification is related to varying amounts of albuminuria: category I represents normal or near normal renal structure (seen in 35% with albuminuria <300 mg/g); category II represents typical diabetic pathology (30% with albuminuria <300 mg/g) as seen in type 1 DKD; and category III represents atypical patterns of renal injury (35% with albuminuria of 30–300 mg/g) with relatively mild glomerular alterations and more severe tubular atrophy, tubular basement membrane thickening and replication, interstitial fibrosis, advanced hyalinosis, and global glomerular sclerosis. Typically, tubular lesions and interstitial fibrosis tend to occur later in the course of either type 1 or type 2 DKD, and the annual rate of decline of glomerular filtration rate (GFR) may accelerate during the proteinuric phases: 1.2–3.6 mL/min/1.73 m²/yr in the presence of albuminuria (30–300 mg/g) and up to 5.4–12 mL/min/1.73 m²/yr in the presence of overt nephropathy (>3000 mg/g). In type 2 DM, there is an incidence of ~3%/yr for the development of nephropathy (overt proteinuria) after 10–20 yr of poorly controlled disease. Compared to type 1 DKD, other nondiabetic renal lesions may be more prevalent in albuminuric type 2 DKD (10–30%), especially glomerulovascular lesions from hypertension. Importantly, the absence of retinopathy or the presence of small kidneys by ultrasound should prompt a search for another etiology of CKD because other primary renal disorders, such as focal and segmental glomerulosclerosis and minimal change disease, among others, may exist in patients with DM. In addition, IgA nephropathy and membranous nephropathy may coexist with DKD, and DKD may be accompanied by another non-hypertension-related kidney disorder in 5–15% of cases.

Occasionally, albuminuria in DM may herald other possible causes of CKD, particularly glomerular disorders as described above. One should suspect other causes when ≥ 1 of the following is present:

- a) absence of diabetic retinopathy or neuropathy.
- b) presence of low or rapidly decreasing GFR.
- c) presence of rapidly increasing albuminuria or nephrotic syndrome.
- d) refractory hypertension.
- e) active (blood and protein) urinary sediment.
- f) manifestations of other systemic disease.
- g) $>30\%$ GFR reduction within 3 months after initiation of anti-RAAS therapy.

DKD SCREENING AND LIMITATIONS OF ALBUMINURIA AS BIOMARKER

DM and albuminuria ≥ 30 mg/g represent independent risk factors for cardiovascular disease (CVD). It is important to be aware of the presence of low-grade albuminuria to assess CVD risk and to follow the progression of CKD. The key markers of CKD are an increased ACR and eGFR < 60 ml/min/1.73 m² from two abnormal readings at least 3 months apart. Albuminuria (30–300 mg/24 h; ACR 3–30 mg/g) is the earliest clinical sign of DKD and typically presents in 20–30% of type 1 DKD, appearing ~15 yr after the onset of DM. Progression to greater degrees of albuminuria (> 30 mg/g) is associated with increased progression of CKD and possibly ESRD. The American Diabetes Association (ADA) recommends routine screening for DKD as follows: a) annual testing of urinary albumin excretion in patients with type 1 DM of ≥ 5 years duration and in all type 2 DM beginning at the time of diagnosis by ACR, and b) eGFR, at least annually in all diabetic adults, regardless of the level of urinary albumin excretion. Because several factors may cause transient increases in albuminuria > 30 mg/g, the diagnosis of albuminuria requires at least two serial first-morning urine specimens over 2–3 weeks.

The extent of overt albuminuria > 2 g/24-h may be identified qualitatively by the presence of a $\geq 3+$ urine dipstick for proteinuria or followed quantitatively by the UPC (normal < 0.2 g total protein/g creatinine), or a 24-h urine collection for total protein or albumin. The 24-h urine collection for total protein is considered the gold standard for urine protein determination as protein excretion varies throughout the day, particularly with glomerular disease. As glomerular disorders worsen, albuminuria increases disproportionately to other non-albumin proteins (tubular, immunoglobulins). A morning specimen is considered optimal for either UPC or ACR evaluations. Proteinuria > 3.5 g/24-h is considered nephrotic range proteinuria. A spot morning (0800–1200 hours) UPC correlates well with 24-h urine protein collections in DKD and represents a good screening test and monitoring tool. Benign albuminuria attributable to fever, intense exercise, postural changes, volume depletion, or acute illnesses should be reevaluated during stable conditions. The typical annual rates of progression of DKD from the diagnosis of DM to albuminuria ≥ 30 mg/g, then > 300 mg/g, and finally to advanced CKD or ESRD are respectively, 2.0%, 2.8%, and 2.3%. These rates may be substantially altered by contemporary treatment protocols, namely reducing the lifetime risk for ESRD to as low as 0.2%.

Despite the foregoing recommendations, it must be emphasized that albuminuria is not considered a surrogate biomarker of either underlying renal structural pathology relative to the natural history of DKD or the benefit of interventions in DKD. Indeed, albuminuria ≤ 300 mg/g may spontaneously remit in up to 40% of type 1 DKD cases. In addition, 30–40% type 1 DKD may not progress to macroalbuminuria even after 5–10 years of follow-up. Serial biopsies in patients with type 1 DKD have revealed progressive accumulation of mesangial matrix despite persistent normoalbuminuria, and others with normal albumin excretion (< 30 mg/g) may have reduced renal function. Results of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) studies have corroborated these observations.

DISPARITIES IN DKD AND GENETIC RISK

Ethnic disparities in DKD in African Americans, Native Americans, Inuit, and Hispanics are considerable. According to the US Renal Data Systems survey of 2011, the incidence of new cases of ESRD in African Americans and Hispanics was, respectively, 3.5 and 1.5 times higher compared to Caucasians. The rates of development of albuminuria have been shown to be higher in Filipinos, African Americans, and Asians compared to white and Hispanic adults. A significant increase also occurs in the rate of progression of DKD to ESRD in African Americans compared to whites. The factors that may contribute to these disparities include socioeconomic, biologic, as well as genetic components. In fact, the genetic susceptibility to DKD is well recognized and familial factors may account for nearly 30% of the variance of urinary albumin excretion rate. A number of genetic studies have been conducted to identify risk variants that might account for some of these disparities. The Family Investigation of Nephropathy in Diabetes (FIND) study group identified gene linkage for DKD on specific chromosomal regions in diabetic families of European Americans and Native Americans and for ACR in diabetic families of African Americans, Mexican Americans, and European Americans. The ultimate goal of these and other genetic analyses is to achieve personalized medicine.

RECENT CLINICAL TRIALS IN DKD

The strongest predictors of progressive DKD are poor glycemic control, hypertension, and glomerular hyperfiltration. Several clinical trials have investigated the role of intensive versus conventional glucose control, dual RAAS blockade, and new agents that target the RAAS to provide guidance for optimal DKD management. Reviews and meta-analyses of randomized trials that compared the surrogate renal endpoints of albuminuria 30–300 mg/g, albuminuria 300–3000 mg/g, and the clinical renal endpoints of doubling of serum creatinine, ESRD and kidney-related death in patients with type 2 DM showed that intensive glucose control reduces the risk of worsening albuminuria at any level. These findings are endorsed by the ADA and the NKF KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and CKD. However, intensive glucose control has been shown to increase the risk of death by up to 22% in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Overall, targeting A1C to ~7% is sufficient to retard kidney disease progression.

Hypertension occurs in 70–80% of adult diabetic patients and a lack of nocturnal BP dipping may precede the onset of albuminuria, with definite hypertension developing as albuminuria worsens. Hypertension may be present in ~80% of patients initiating dialysis due to DKD. The use of the combination angiotensin-converting-enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) has been evaluated and such combinations are not recommended for routine DKD management, despite greater reduction of albuminuria. Combined RAAS blockade has resulted in the development of adverse events including impaired kidney function (acute kidney injury) and hyperkalemia compared to the use of either agent alone. A similar study that investigated the use of the direct renin inhibitor, aliskiren, in combination with an ARB (losartan) found an increased risk of stroke and other adverse events also including hyperkalemia, hypotension, ESRD, or kidney-related death.

MANAGEMENT GUIDELINES

The ADA and the NKF continue to recommend that the mainstay of DKD therapy is the use of anti-RAAS agents, with ACEIs or ARBs, for maximal proteinuria reduction, strict glycemic control, and optimum BP control (see below).

Therapeutic targets

A1C	~7% (estimated average glucose, 154 mg/dl); http://www.diabetes.org/living-with-diabetes/treatment-and-care/blood-glucose-control/a1c/
BP	<140/90 mmHg for CKD without proteinuria
LDL-C	Use 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (ATP 4)
BMI	18.5–24.9 kg/m ²

Lifestyle modification

The increased risk of cardiovascular disease and premature mortality in patients with DM warrant prompt treatment of all cardiovascular risk factors. Therefore, treatment of DKD toward therapeutic targets involves risk factor reduction to prevent DKD progression and a multimodal approach that addresses lifestyle modification. Such modifications include the dietary approach to stop hypertension (DASH diet), restricted dietary sodium intake at <1.5 g/24 h, smoking cessation, restricted dietary intake of saturated fat and total cholesterol (<200 mg/24-h), and regular aerobic exercise.

Glycemic control

An A1C **target** of ~7% prevents or delays the progression of microvascular complications of DM and DKD. However, an A1C target of <7% should be avoided in patients at risk of hypoglycemia and an A1C target should be extended to >7% in those with comorbidities or limited life expectancy and at risk of hypoglycemia. As DKD progresses, the requirements for insulin to maintain glycemic control diminish as renal metabolism and excretion of insulin progressively decrease. Insulin reduction should be considered, and the safety of metformin in CKD stages 4 and 5 should be assessed to prevent lactic acidosis. Metformin is generally well-tolerated at GFRs >45 mL/min/1.73 m². Currently, there is no dependable method to determine the risk of the very rare complication of metformin-induced lactic acidosis.

Blood pressure control

Hyperglycemia enhances sympathetic nervous system output and renal sodium retention, thereby aggravating hypertension. Therefore, a first step in optimizing antihypertensive therapy is maintenance of appropriate levels of glycemia. Hyperglycemia activates the sympathetic nervous system and enhances sodium reabsorption, thereby aggravating hypertension. ACEIs and ARBs represent first-line therapy. When ACEIs, ARBs, or diuretics are used, the SCr and potassium levels should be monitored and the ACR evaluated for response to therapy. In addition, the potential complications of DKD should be managed when eGFR falls to <60 ml/min/1.73 m², especially when uncertainty regarding difficult management issues in more advanced stages of DKD exists. Precautions should be considered, particularly

in the elderly and those with comorbidities, regarding tolerance of specific agents and side effects, such as postural dizziness and postural hypotension.

Albuminuria reduction

A reduction in high biological value protein intake to 0.8–1.0 g/kg body weight/day in the earlier stages of CKD and to 0.8 g/kg body weight/day in the later stages of CKD may reduce urinary albumin excretion. Protein reduction therapy should only be done in conjunction with a certified renal nutritionist. In DM with albuminuria <30 mg per 24-h and BPs >140/90 mmHg, BP should be maintained at <140/90 mmHg. For those with urine albumin excretion >30 mg per 24 hours and BP >140/90 mmHg, maintain BP at <130-140/80-90 mmHg. ACEIs and ARBs should be instituted in those with urine albumin excretion of 30–300 mg or >300 mg per 24 hours. Clinical remission of DKD has occurred with proteinuria declining to <1 g/24-h, and clinical regression has occurred with declines in proteinuria to <0.3 g/24-h. High sodium intake enhances proteinuria, and sodium restriction reduces BP and albuminuria, an effect augmented by successful diuretic therapy.

Cholesterol management

The use of low density lipoprotein cholesterol (LDL-C) lowering medicines, including statins or ezetimibe combination, is recommended to reduce the risk of major atherosclerotic events in patients with DKD. Per KDOQI CPGs, a complete fasting lipid profile at initial evaluation of CKD is recommended, with repeated evaluations to demonstrate adherence to therapy and achievement of lipid targets. This approach differs from the American Heart Association and KDIGO approaches that established statin dose-limited therapies. Recently, the absence of danger signal for malignancy or rhabdomyolysis with simvastatin/ezetimibe was established in the SHARP study, which demonstrated slower progression of CKD with LDL-C lowering.

KEY SUMMARY POINTS

A1C levels of 7% in CKD patients represents adequate control

Treat LDL-C to KDOQI target levels

Statin therapy should be monitored for medication adherence periodically by evaluation of fasting lipid profiles

Elevated triglyceride levels <1000 mg/dL and without pancreatitis require therapeutic lifestyle change

Currently, BP reduction to <140/90 mmHg is considered sufficient if there is no albuminuria

Albuminuria should be lowered as much as possible without using dual anti-RAAS therapy

ANEMIA OF CHRONIC KIDNEY DISEASE

by Anatole Besarab, MD and Jerry Yee, MD

INTRODUCTION

Anemia, defined as a hemoglobin (HGB) of <13 g/dL in adult males and <12 g/dL in postmenopausal females, is common in CKD. Males are 30% more likely to become anemic than females because males have a greater propensity to develop more severe CKD. Older CKD patients and African Americans (4-fold risk increase) are also more likely to develop anemia. The signs and symptoms of anemia of CKD are nonspecific and overlap those of anemia in general. However, fatigue or generalized weakness is nearly a constant finding.

Previously, prospective cohort studies documented a prevalence of anemia of 1% for eGFR 30–60 ml/min/1.73 m², 9% for eGFR <30 ml/min/1.73 m², and 33–67% for eGFR <15 ml/min/1.73 m². In the 1980s, the average HGB for hemodialysis patients was 7–8 g/dL. To maintain this low HGB, multiple units of red blood cell transfusions were required. In advanced CKD, nearly 70% of predialysis patients will have HGB <10 g/dL, half of whom will have an HGB of <9 g/dL. Anemia of CKD has been correlated with reduced quality-of-life (QoL) and diminished exercise tolerance as well as left ventricular hypertrophy, depression, and depressed neurocognitive function. Therefore, the correction of anemia has consumed nephrologists and hematologists since the 1970s, with the presumption that correction of anemia might reduce the progression of CKD and lower death rates, cardiovascular mortality, and incidence of ESRD.

PATHOPHYSIOLOGY

The factors causing anemia of CKD are multifactorial and include blood loss, impaired iron absorption, poor nutrition, and an insufficient bone marrow response to a declining HGB. Blood loss results from increased venipuncture for laboratory testing, occult or overt gastrointestinal bleeding, and impaired platelet function with reduced platelet adhesion and aggregation. Any or all of these factors may coincide and result in anemia. Inflammation intrinsic to the state of advanced CKD may also inhibit compensatory bone marrow responses to anemia via cytokine-mediated suppression of erythropoiesis. In addition, because of the loss of renal parenchyma in progressive CKD, the hormonal level of renally synthesized erythropoietin (90% of erythropoietin is produced by the kidneys) is reduced in relation to the prevailing HGB, thereby slowing the rate of erythropoiesis. However, in two-thirds of patients, the plasma erythropoietin level will be in the normal range, although it should be at a supranormal level. In general, an erythropoietin level is not part of the evaluation of anemia of CKD.

ERYTHROPOIESIS-STIMULATING AGENTS AND CLINICAL TRIALS

The correction of the anemia of CKD through administration of recombinant human erythropoietin (epoetin alfa, EPO) — the first commercially available erythropoiesis-stimulating agent (ESA) — to ESRD patients began in June 1989 and supplanted the use of androgenic steroids as erythropoiesis stimulators. The practice and success of ESA

PLAN OF CARE AND ACTION PLAN FOR CHRONIC KIDNEY DISEASE STAGES 1–4

STAGE & GFR	DESCRIPTION	ACTION
Normal >90 mL/min/1.73 m ²	RISK Factors: age >60 years, obesity, autoimmune disorders, DM, HTN, kidney stones, ADPKD, prior ARF, UTIs, toxic drug exposures, and FH of CKD, especially in African Americans, Native Americans, and Asians	SCREEN for general and specific conditions SCREEN for CKD w/GFR INITIATE CKD risk reduction/intervention strategies
Stage 1 >90 mL/min/1.73 m ²	KIDNEY damage with normal GFR (urinary, imaging or histologic abnormalities). “ CKD ” term is not applied clinically in the absence of albuminuria and/or abnormal imaging and/or abnormal urinalysis	CAUSE: diagnose etiology of CKD IDENTIFY and treat CVD risk factors and comorbid conditions. ALBUMINURIA: identify and quantitate by ACR or UPC ESTIMATE CKD progression rate.
Stage 2 60 – 89 mL/min/1.73 m ²	KIDNEY damage with mild GFR decrease (urinary, imaging or histologic abnormalities) MOST lower GFRs in this range are due to age-related GFR decline “ CKD ” term is not applied clinically in the absence of albuminuria and/or abnormal imaging and/or abnormal urinalysis	CAUSE: diagnose etiology of CKD IDENTIFY and treat CVD risk factors and comorbid conditions ALBUMINURIA: determine presence and quantitate by ACR or UPC ESTIMATE CKD progression rate
Stage 3A 45 – 59 mL/min/1.73 m ² Stage 3B 30 – 44 mL/min/1.73 m ²	MODERATE decline of GFR COMPLICATIONS more frequent at CKD stage 3B as GFR decreases to <45 mL/min/1.73 m ² PROTEINURIA is a serious CV risk factor and has prognostic importance for CKD progression	ESTIMATE CKD progression rate IDENTIFY and treat CVD risk factors and comorbid conditions ALBUMINURIA: determine presence and quantitate by ACR or UPC KIDNEY imaging study, <i>eg</i> , US or CT CONSIDER Nephrology consultation
Stage 4 15 – 29 mL/min/1.73 m ²	SEVERE decline of GFR MAJOR increase in CVD risk, <i>ie</i> , CKD Stage 4 should be considered equivalent to a major CVD clinical event	NEPHROLOGY consultation with transition of CKD care to Nephrology or co-management INITIATE decisions regarding kidney replacement therapy, vascular access, kidney transplantation (GFR ~20), and/or end-of-life discussion DIAGNOSE and treat CVD risk factors and comorbid conditions ALBUMINURIA: determine presence and quantitate by ACR or UPC ADJUST drug-dosing of renally excreted drugs for GFR (may substitute GFR for creatinine clearance)

COMMENTS

- Early recognition, evaluation, and treatment of CKD in a multidisciplinary fashion, decreases morbidity, mortality, and healthcare costs.
- GFRs <45 mL/min/1.73 m² in persons >65 years may not require Nephrology evaluation in all cases, unless there is heavy albuminuria/proteinuria (ACR >300 mg/g or UPC 0.5–1.0 g/g) or a progressive decline in GFR (> 4 mL/min/1.73 m²).
- Always consider reversible etiologies of acute kidney injury (AKI) at any stage of CKD, *eg*, urinary tract outlet obstruction, volume depletion, and adverse drug reactions.
- Avoid or cautiously use nephrotoxic medications and contrast agents as required.
- CKD stage 5 patients require management by a nephrologist.

CLINICAL TESTING	TREATMENT CONSIDERATIONS
<p>BP monitoring: every 12 mo FASTING LIPIDS: every 6–12 mo to validate medication adherence ELECTROLYTES, Glucose, BUN, SCr, GFR: every 12 mo UA for hematuria or proteinuria & microscopic exam</p>	<p>SMOKING cessation WEIGHT reduction, if BMI >30 kg/m² TARGETS: BP: <140/90 mmHg LIPIDS: Use 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (ATP 4) GLUCOSE: Premeal level, 80–130 mg/dL; A1C ~7%</p>
<p>BP monitoring: every 12 mo if normal ELECTROLYTES, Glucose, BUN, SCr, GFR: every 12 mo FASTING LIPIDS: every 6–12 mo to validate medication adherence UA with microscopic evaluation ALBUMINURIA: UPC or ACR every 12 mo, depending on severity</p>	<p>CONSULT Nephrology if GFR declines by ≥4 mL/min/yr ANTIPROTEINURIC therapy with ACEI or ARB TARGETS: BP: <140/90 mmHg LIPIDS: Use ATP 4 guidelines (see above) ALBUMINURIA: UPC <0.2 or ACR <30 mg/g</p>
<p>BP monitoring: every 3–12 mo ELECTROLYTES, Glucose, BUN, SCr, GFR: every 6–12 mo FASTING LIPIDS: every 6–12 mo to validate medication adherence UA with microscopic evaluation ALBUMINURIA: ACR or UPC every 3–12 mo, depending on severity</p>	<p>RULE OUT AKI (eg, obstruction) RENAL DIETITIAN consultation TARGETS: BP: <140/90 mmHg LIPIDS: Use ATP 4 guidelines (see above) HGB: 9–11 g/dL ALBUMINURIA: UPC <0.2 or ACR <30 mg/g</p>
<p>BP monitoring: every 1–3 mo ELECTROLYTES, Glucose, BUN, SCr, GFR: every 3–6 mo CBC, TSAT, ferritin: every 6–12 mo or at each ESA injection CKD-MBD: Ca/P/PTH/Alk Phos/25(OH)D: every 6–12 mo; follow-up levels depend on trend analysis and CKD progression. Evaluate for extraskeletal calcification (aorta, cardiac vessels and valves). ALBUMINURIA: UPC or ACR: every 3–12 mo</p>	<p>RULE OUT AKI (eg, obstruction) NUTRITIONAL assessment at any time during CKD stages 1–5 IMMUNIZE: QIV, PPV 13, PPSV 23, HBV, Tdap and VZ TARGETS: Hb: 9–11 g/dL Iron parameters: TSAT >20%, ferritin >100 ng/mL after oral or IV iron (initiate ESA after achieving iron parameters) Lipids: moderate to high intensity statin therapy Ca & P: normal ranges with P-binders & dietary restriction (no Ca-based P-binders if vascular/valvular calcification) 25(OH)D: ≥30 ng/mL with vitamin D PTH: 130–600 pg/mL, treat with calcitriol or vitamin D analogs if PTH progressively increases NaHCO₃: 22–26 mEq/L and titrate NaHCO₃ therapy ALBUMINURIA: UPC <0.2 or ACR <30 mg/g</p>
<p>BP monitoring: every 1 mo ELECTROLYTES, Glucose, BUN, SCr, GFR: every 1–3 mo CBC, TSAT, ferritin: every 6–12 mo or at each ESA injection CKD-MBD: Ca/P/PTH/Alk Phos/25(OH)D: every 3–6 mo; follow-up levels depend on trend analysis and CKD progression. Evaluate for extraskeletal calcification (aorta, cardiac vessels and valves). ALBUMINURIA: UPC or ACR: every 3–12 mo RENAL REPLACEMENT THERAPY: vascular access surgery evaluation (vascular access site selection, vein mapping, peritoneal catheter insertion)</p>	<p>CKD-specific education: kidney replacement therapy modality NUTRITION: dietary Na and K restriction. Renal dietitian consult IMMUNIZE: QIV, PPV 13, PPSV 23, HBV, Tdap and VZ RENAL-formulated MVI PROTECT non-dominant arm for future vascular access TARGETS: Hb: 9–11 g/dL Iron parameters: TSAT >20%, ferritin >100 ng/mL after oral or IV iron (initiate ESA after achieving iron parameters) Lipids: moderate to high intensity statin therapy Ca & P: normal ranges with P-binders and dietary restriction (no Ca-based P-binders if vascular/valvular calcification) 25(OH)D: ≥30 ng/mL with vitamin D PTH: 130–600 pg/mL, treat with calcitriol or vitamin D analogs, if PTH progressively increases NaHCO₃: 22–26 mEq/L with NaHCO₃ or Na citrate therapy ALBUMINURIA: UPC <0.2 or ACR <30 mg/g HBV Ab titer: ≥10 mIU/mL after 3-dose immunization series</p>

administration to ESRD patients subsequently spread to non-dialysis (ND)-CKD patients who were treated by EPO or darbepoetin alfa, a longer-acting ESA. Subsequently, three multicenter randomized controlled trials that investigated the merits of near-complete correction of the anemia of CKD were conducted. In the final analysis, near-complete anemia correction was ill-advised primarily for two reasons: a) no clinical benefit(s) were seen, and b) danger signals for increased cardiovascular events and death were detected. Notably, the achieved HGBs in these studies were less than the specified target HGBs. Consequently, EPO administration was sharply curtailed following the publication of the trial results of CHOIR, CREATE and TREAT (**Table 1**). After publication of CHOIR and CREATE, the FDA issued this statement in November 2007: “ESAs should be used to maintain a HGB level between 10 g/dL to 12 g/dL. Maintaining higher HGB levels in patients with chronic kidney failure increases the risk for death and for serious cardiovascular reactions such as stroke, heart attack or heart failure.” Consequently, red cell transfusions have increased as ESA usage has measurably declined. In June 2011, the FDA established a target HGB range of 10–12 g/dL, but now the FDA states that ESA dosing should be reduced or stopped at an achieved HGB of 11 g/dL.

TABLE 1. ANEMIA OF CKD TRIALS INVOLVING NON-DIALYSIS CKD PATIENTS TREATED WITH AN ERYTHROPOIESIS-STIMULATING AGENT (ESA)

Name	N (patients)	HGB Target (g/dL)	GFR range (ml/min/1.73 m ²)	Primary endpoint	P value
CHOIR (2006)	603	13.5 vs 11.3	15–50	Death, MI, CHF, CVA	0.03 for composite endpoint favoring lower HGB
CREATE (2006)	1432	13–15 vs 10.5–11.5	15–35	Composite of 8 CV events CKD progression	P=NS for CV events. P=0.03 for ESRD favoring lower HGB
TREAT (2009)	4038	13 vs 9	20–60	Death, CV event, ESRD	P=NS

Abbreviations: *CHOIR*, Correction of Hemoglobin and Outcomes in Renal Insufficiency (*CHOIR*) trial; *CREATE*, Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (*CREATE*) trial; *TREAT*, Trial to Reduce Cardiovascular Events with Aranesp Therapy.

DIAGNOSIS

Operationally, the anemia of CKD specifically denotes anemia as defined above in the absence of iron deficiency and other causes, Iron repletion therapy must be established before dosing with any ESA. The anemia is usually normochromic and normocytic as in the anemia

of chronic disease, and the mean red cell lifespan is shortened. The corrected reticulocyte count is not compensatorily elevated and indicates restricted erythropoiesis. Following the identification of anemia in a CKD patient, the following hematological parameters should be evaluated: CBC with differential and platelet counts and examination of a peripheral blood smear; reticulocyte count; serum folate and vitamin B12 levels; serum iron, total iron binding capacity, and ferritin levels; and thyroid-stimulating hormone. EPO levels, although commercially available, should not be ordered to establish a diagnosis for anemia of CKD. When obtained, the majority of all EPO levels will be low or in the mid-range, indicating an insufficient erythropoietic response, *ie*, EPO levels were still inappropriately low. In cases of anemia that are unresponsive to optimized iron and ESA therapy, an evaluation for hemolytic anemia and direct bone marrow examination may be warranted in collaboration with a hematologist and/or nephrologist.

Iron deficiency must be ruled out in anemia of CKD because ESAs are less effective in the presence of inadequate iron utilization or insufficient storage. Iron absorption may be downregulated at the gut level by the liver-synthesized peptide, hepcidin, which dually regulates intestinal iron uptake and the export of iron from enterocytes or reticuloendothelial cells to transferrin. Transferrin in turn will deliver iron to the developing erythron. Ferritin and TSAT deficiency thresholds are notably different than ferritin and TSAT thresholds in non-CKD patients. Iron deficiency in CKD patients is generally ruled out when the serum ferritin exceeds 100 ng/mL and transferrin saturation (TSAT) is $\geq 20\%$. If either of these criteria is not met, then a trial of iron repletion therapy before ESA administration is warranted. However, a trial of either oral or intravenous iron in the face of iron deficiency in CKD does not guarantee a salutary response, and ESA therapy with EPO or darbepoetin alfa may be required to elevate the HGB.

TREATMENT

Although a minority of individuals whose HGB is maintained at 11–13 g/dL experience an enhanced QoL, the vast majority of CKD patients demonstrate no difference in QoL at HGB 10 versus 13 g/dL. Nonetheless, because the treatment of anemic CKD patients should be individualized, there no longer is a target HGB. However, the majority of ESA-treated patients may be treated to a HGB range of 10–11 g/dL, but even a HGB of 9 g/dL is acceptable in most individuals because there have been no significant differences in clinically measured parameters between 9 and 11 g/dL, *ie*, exercise tolerance, cognitive function, cardiovascular disease measurements, *etc*. The treatment of anemia of CKD may begin after the HGB declines to < 10 g/dL in the absence of a known non-renal cause of anemia such as bleeding. To avoid premature use of ESAs, iron repletion therapy should be carried out if TSAT is $\leq 20\%$ or ferritin is ≤ 100 ng/mL (KDIGO). Iron loading may be accomplished by either oral or intravenous delivery of iron. Oral iron therapy should be given on an empty stomach and absorption may be increased by coadministration of ascorbic acid. When iron repletion achieves a TSAT of $> 20\%$, ESA therapy may be initiated if the HGB remains < 10 g/dL. If the HGB increases to > 10 g/dL, then ESA therapy is unnecessary unless there are supervening circumstances, *eg*, angina threshold of > 10 g/dL. Notably, in the US, the threshold for initiation of ESA therapy by commercial payers

has remained at TSAT >20% and ferritin >100 ng/mL. Therefore, with a HGB declining to <10 g/dL with TSAT and ferritin at these treatment thresholds, ESA therapy may be initiated.

Iron status should be monitored at least every 3 months during ESA therapy as iron will be continually mobilized from the storage sites during successful red cell production and may lead to iron deficiency. More frequent monitoring is dictated by clinical circumstances. Note that additional iron treatment is often futile when TSAT is >30% or ferritin is >500 ng/ml because additional iron therapy will unlikely result in mobilization of iron from storage sites within the reticuloendothelial system to the developing erythron. Escalating ESA therapy when ferritin is >500 ng/ml may be of minimal efficacy, but successful increments of HGB have been achieved by intravenous iron administration at ferritins exceeding 500 ng/ml.

Per the FDA, the only use of ESAs is to avoid blood transfusions in CKD patients. Blood transfusions may sensitize patients to alloantigens and unfavorably influence kidney transplantation therapy in terms of finding a suitable donor or rejecting a transplanted kidney. However, this theoretical circumstance has not been borne out by clinical experience. Symptomatic patients with more profound degrees of anemia should be treated with red cell transfusions because ESA therapy generally requires 2 to 4 weeks to raise the HGB level by 1 g/dL. Generally, weight-based ESA therapy is initiated after iron repletion when the HGB level remains <10 g/dL and continued to maintain a HGB concentration of 9–11 g/dL. EPO is prescribed in biological units but darbepoetin is prescribed in micrograms (conversion factor: 1 mcg darbepoetin equals ~250–350 EPO units). During ESA therapy, HGB monitoring is recommended at least monthly. In practice, a HGB is generally obtained when a patient receives IV iron or ESA therapy with epoetin alfa or darbepoetin alfa and in conjunction with iron parameters. HGB increases of 1 g/dL in a 2-week interval (or 2 g/dL in 1 month) are considered overly rapid and warrant an ESA dose reduction. As the HGB increases and reaches 10 g/dL, the ESA should be titrated downward, in preference to stopping it, to stabilize HGB at a level at ~10 g/dL. The FDA explicitly states that ESA therapy should be stopped if the HGB rises to ≥ 11 g/dL.

If ESA dosing is appropriate at the onset of treatment and there is no increment of HGB after 1 month, the dose of ESA should be escalated monthly in 25% increments, with a ceiling level twice that of the initial weight-based dose. If a suboptimal HGB response is documented at this point (3 months), the patient is considered to have initial ESA hyporesponsiveness. Subsequent ESA hyporesponsiveness is diagnosed after ESA doses that had previously maintained a stable HGB become ineffective. If ESA hyporesponsiveness occurs, a search for the erythropoietic hyporesponse should be initiated including the exclusion of functional (impaired iron availability) or absolute iron deficiency.

INITIAL EVALUATION

Obtain CBC, absolute reticulocyte ct, TSAT, ferritin, vitamin B12, and folate levels. Always rule out other causes of anemia, *eg*, malignancy, and inflammatory conditions. Monitor iron parameters and CBC twice monthly after initiating therapy or until HGB stabilizes within the target range, then monthly. Use the absolute reticulocyte count to assess efficacy.

THERAPEUTIC TARGETS

HGB 9–11 g/dL* (do not exceed HGB 13 g/dL)

TSAT >20% but <50%

Ferritin >500 ng/ml†

CHr >32 pg/cell‡

*Therapeutic phlebotomy should not be undertaken, if the HGB is 13–18 g/dL, in the absence of ESA therapy, unless symptoms are present, *eg*, headache.

†Ferritin >800 ng/mL is **not** a contraindication to the use oral or parenteral iron; interpretation of clinical context and trend analysis of iron utilization is required, particularly with inflammatory states.

‡CHr (mean cellular hemoglobin content of reticulocytes); utility of this parameter has only been validated in hemodialysis-dependent ESRD patients.

MEDICATIONS

Iron

Ferrous sulfate: 130–260 mg elemental iron daily (alternative, ferrous fumarate)

Iron dextran (INFeD®): 500–1000 mg IV infusions of **low** molecular wt iron dextran*

Iron sucrose (Venofer®): 100–200 mg IV infusions in non-dialysis-dependent CKD

Ferumoxytol (Feraheme®): 510 mg IV in non-dialysis-CKD patients (may repeat 3–8 days after initial dose)

*Iron dextran, IV, **high** molecular weight (Dexferrum®), is a distinct and separate product from INFeD® (**see above**) and not recommended by the authors.

Erythropoiesis-stimulating agents (ESAs)

Epoetin alfa (Procrit® or Epogen®): 10–40,000 Units, subcutaneously, every 1–4 weeks; begin therapy at HGB <10 g/dL at starting dose, 100 Units/kg/week

Darbepoetin alfa (Aranesp®): 40–300 mcg, subcutaneously, every 2–4 weeks or monthly; begin therapy at HGB <10 g/dL at starting dose, 0.9 mcg/kg/every 2 weeks (equivalent to package insert dose, 0.45 mcg/kg/week)

NB: ESA therapy requires informed consent at each administration.

KEY SUMMARY POINTS

Diagnosis requires exclusion of iron deficiency (TSAT <20% and ferritin <100 ng/mL) and other correctable, reversible causes of anemia

There is no formal target HGB; treatment should be individualized, and the HGB should be generally maintained at 9–11 g/dL

IV iron therapy is recommended when iron deficiency is present; alternative: oral iron for 1–3 months

The primary goal of erythropoiesis-stimulating agent (ESA) therapy is to prevent blood transfusions

ESA therapy may be initiated if a) HGB <10 g/dL, b) TSAT >20%, and c) ferritin >100 ng/mL (FDA, insurance/commercial payers)

ESA treatment is reduced at HGB 10 g/dL and stopped at HGB 11 g/dL

Treatment of the anemia of CKD requires periodic monitoring at ≤1-month intervals during initiation of iron or ESA therapy and afterward at 1–3 month intervals after HGB stabilization and iron storage repletion (opinion)

CKD-MINERAL AND BONE DISORDER

by Ja Sun Kang, MD and L. Tammy Ho, MD

INTRODUCTION

Renal osteodystrophy (ROD) defines the presence of altered bone structure and composition in chronic kidney disease (CKD) and is but one aspect of CKD-Mineral and Bone Disorder (CKD-MBD), a multi-system disease entity involving abnormalities of mineral metabolism, ROD, and extraskeletal calcification. The understanding of CKD-MBD as a systemic disorder is evolving and emphasizes monitoring and interventions to correct alterations in serum calcium (Ca), serum phosphorus (P), parathyroid hormone (PTH), and vitamin D. No single procedure or test establishes the diagnosis of CKD-MBD. Data indicate that CKD-related bone loss is associated with extraskeletal calcification and may contribute to the excessive cardiac morbidity and mortality of CKD. Calcification occurs most frequently in coronary arteries, large arteries such as the aorta, and cardiac valvular leaflets. Initial evaluation of CKD-MBD includes assessing and establishing baseline levels of Ca, P, PTH, 25(OH)D, alkaline phosphatase, and serum bicarbonate (HCO₃).

BONE DISORDERS

The Turnover/remodeling, Mineralization, and Volume (TMV) classification of ROD relies on bone histology from transiliac biopsy and has four subtypes that may overlap: osteomalacia, adynamic bone disease, osteitis fibrosa, and mixed uremic osteodystrophy (**Table 1**). Historically, the most common lesion was secondary hyperparathyroidism of renal origin (SHPT), which remains the most prevalent lesion in non-dialysis-dependent CKD. However, therapeutic intervention may also increase the risk for adynamic bone disease. Osteoporosis in CKD, as defined by World Health Organization criteria for non-CKD patients, is difficult to diagnose, especially during late CKD. Bone densitometry (DEXA), commonly used in the general population, does not distinguish between cortical (osteoporosis of CKD) versus trabecular bone loss (age-related osteoporosis). DEXA provides no information on bone quality or turnover, which are frequently abnormal in progressive CKD. Nonetheless, bone loss should be monitored periodically. Metabolic acidosis (serum HCO₃ <22 mEq/L) increases net bone resorption (osteoclasts) and reduces calcitriol synthesis and should be corrected.

TABLE 1. RENAL OSTEODYSTROPHY BONE DISORDERS

Lesion	Turnover	Mineralization	Volume
Osteomalacia	↓	Abnormal	↓/Normal
Adynamic bone disease	↓	Normal	↓/Normal
Osteitis fibrosa	↑	Abnormal	Normal/↑
Mixed uremic osteodystrophy	↑	Abnormal	Normal

CA, P, PTH, AND VITAMIN D PHYSIOLOGY

Total serum Ca is 40% ionized (free), 50% albumin-bound, and 10% complexed to P and other organic anions (citrate, oxalate, bicarbonate). Ionized Ca regulates the parathyroid gland (PTG), Ca-sensing receptor (CaR), vitamin D, and PTH (**Table 2**). Low ionized Ca levels reduce CaR stimulation and increase PTH secretion, elevating ionized Ca and renal P excretion and calcitriol synthesis. An average daily dietary P intake is 800–1400 mg, ~80% of which is renally excreted via PTH action. In an individual with normal renal function, low P stimulates calcitriol independently leading to decreased PTH and increased gut absorption of phosphorus. Progressive CKD leads to progressive elevation in P; low P levels in a patient with significant CKD should lead to concerns about additional issues including primary hyperparathyroidism and malnutrition. High P levels raise PTH and are associated with greater cardiovascular disease and all-cause mortality. The traditional thought has been that increased P is one inciting factor in the development of SHPT and CKD-MBD, and goals of therapy have debated the *maintenance* of a normal P range versus reduction to the normal range. Dietary P restriction is beneficial in early CKD, and renal dietary consultation may be sought at any CKD stage. As CKD progresses, dietary therapy alone is unlikely to prevent or correct hyperphosphatemia. Currently, P-binder therapy remains a mainstay of therapy in patients with elevated P levels.

SHPT may develop in late CKD stage 2. PTH levels are elevated in nearly one-third of CKD stage 3 patients and may be increased despite normal Ca and P levels. Vitamin D deficiency,

TABLE 2. CALCIUM, PHOSPHORUS, PARATHYROID HORMONE, AND VITAMIN D ACTIONS

Compound	Source/Distribution	Action
↑ Ionized Ca	Diet, bone resorption	Bone mineralization, CaR activation
↑ CaR stimulation	Kidney, PTG, other	↓ SHPT, ↓ PTG growth
↑ P	Diet, renal P retention, bone resorption	↑ PTH, complexes Ca, ↑ FGF23
↑ PTH	PTG	↑ Ca and ↑ P excretion, ↑ calcitriol synthesis
↑ PTH receptor stimulation	Bone (osteoblast), kidney	See PTH
↑ Vitamin D	Endogenous synthesis; exogenous administration	↓ SHPT, ↑ gut Ca/P absorption, ↑ kidney Ca absorption
↑ VDR stimulation	Bone, kidney, PTG, gut, and other tissues	↓ PTH gene activity

Abbreviations: *CaR*, calcium-sensing receptor; *FGF23*, fibroblast growth factor-23; *P*, serum phosphorus; *PTG*, parathyroid gland; *SHPT*, secondary hyperparathyroidism; *VDR*, vitamin D receptor.

defined by low 25(OH)D levels, is frequent in CKD and may further elevate PTH. In CKD stage 4, hyperphosphatemia from renal P retention occurs. To prevent progressive PTG growth and PTH secretion as CKD worsens, one should screen for and begin treatment of SHPT early. Fibroblast growth factor 23 (FGF23) appears to play a significant role in regulation of bone mineral health in CKD and is associated with increased mortality. Better understanding of this peptide has led to the realization that P homeostasis is more complex than previously appreciated. Osteocyte-derived FGF23 is thus far the most significant of a group of circulating peptides known as phosphatonins. FGF23 binds to receptors on kidney proximal tubular cells and decreases P reabsorption, thereby increasing urinary P excretion. FGF23 binding to its receptor complex is enhanced by Klotho, an osteocyte-derived transmembrane protein. Increases in FGF23 are stimulated by increased dietary intake of phosphorus and elevated phosphorus levels.

Additional actions of FGF23 include direct suppression of PTH and decreased calcitriol synthesis through inhibition of proximal tubular 1α -OHase. FGF23 is significantly elevated in CKD and has a key role in mineral bone homeostasis. In retrospective studies of CKD patients, FGF23 elevation has been linked to mortality and increases in cardiac morbidity. Echocardiographic studies of CKD patients not yet on dialysis have shown that higher c-terminal FGF23 levels correlate independently with new onset of left ventricular hypertrophy (LVH) and reduced ejection fraction. Reports conflict on whether Klotho is expressed in vascular smooth muscle cells and tissue. However, increased levels of FGF23 have been associated with increased vascular calcifications. FGF23 is the subject of much current research aimed at determining its significance as a CKD biomarker, a parameter of successful therapy, or an independent cause of the accelerated vascular calcification in progressive kidney disease. Assays to measure FGF23 are not yet available for wide clinical use.

Metabolic acidosis, defined as a $\text{HCO}_3^- < 22$ mEq/L that is not generated by respiratory alkalosis, is an under-recognized contributor to metabolic bone disease. Acidosis potentiates bone-lytic PTH effects, thereby increasing Ca and P bone resorption. It also increases sympathetic nervous system activity, thereby aggravating hypertension, induces insulin resistance, and promotes muscle-protein catabolism. In addition, metabolic acidosis increases the rate of progression of CKD and induces bone deterioration. Treatment with sodium bicarbonate generally does not produce extracellular fluid volume expansion (eg, edema) or worsen hypertension. If edema or BP elevation occurs, loop diuretic therapy is recommended. Once established, the treatment of metabolic acidosis should always be initiated with sodium bicarbonate (NaHCO_3) or sodium citrate. More recently, a diet of fresh fruits and vegetables effectively treated metabolic acidosis without inducing hyperkalemia.

Vitamin D includes vitamins D2 and D3 and three active D sterols, calcitriol, and two synthetic vitamin D2 compounds (**Table 3**). Renal synthesis of calcitriol is tightly regulated. The circulating calcitriol level does not reflect vitamin D sufficiency, which correlates better with 25(OH)D levels. Vitamin D receptor (VDR) stimulation by active vitamin D sterols suppresses PTH secretion, enhances gut Ca and P absorption, and increases renal Ca reabsorption. As CKD worsens, parathyroid, VDR, and CaR densities are reduced, thereby aggravating SHPT.

TABLE 3. VITAMIN D STEROLS AND ANALOGS

Compound	Chemical Name	Source
Pro-vitamin D2	Ergosterol	Diet
Pro-vitamin D3	7-Dehydrocholesterol	Cholesterol
Vitamin D2 (Calciferol®, Drisdol®)	Ergocalciferol	UV light → ergosterol
Vitamin D3	Cholecalciferol	UV light → 7-dehydrocholesterol
Calcifediol (calcidiol)	25(OH)-cholecalciferol; 25(OH)D3	25-hydroxylation → D3 (liver)
Calcitriol (Rocaltrol®)*	1,25(OH)2-cholecalciferol; 1α-25(OH)2-D3	1α-OHn → 25(OH)D3 (kidney)
Doxercalciferol (Hectorol®)*	1α-(OH)D2	Synthetic D2 prohormone
Paricalcitol (Zemlar®)*	19-nor-1α-25(OH)2-D2	Synthetic D2 analog

*Active vitamin D sterol

MANAGEMENT AND THERAPEUTIC OPTIONS

Nutritional vitamin D, ergocalciferol (plant sources) or cholecalciferol (animal sources), can be used as treatment for hypovitaminosis D at any CKD stage. Currently, no studies clearly support one agent over another, and newer iron-based P-binders have not been greatly studied. A recent Institute of Medicine report noted that 20 ng/mL was a “sufficient” level of vitamin D status for bone health in individuals without illness. However, it is important to consider that the optimal vitamin D level may vary depending on underlying disease status and by race, particularly using currently available assays. Debate continues on the optimal level for vitamin D. Recent discussion has involved the best fraction of 25(OH) D to measure, with some work suggesting that bioavailable vitamin D (or free vitamin D) may more accurately assess deficiency. Lower levels of 25(OH)D, measured by traditional assays, have been reported in African Americans. The contradiction of lower 25(OH)D assays levels in African Americans and inferred better bone health based on higher BMD scores has been a point of focus. This discussion remains theoretical and no changes in prior recommendations or in target levels have been made.

Studies have suggested that 25(OH)D levels >10 ng/mL are optimal for the prevention of rickets and osteomalacia, whereas a level of >30 ng/ml may be necessary to prevent secondary hyperparathyroidism, *ie*, 40–60 ng/ml. Current opinion-based recommendations consider 25(OH)D levels <30 ng/ml to represent vitamin D insufficiency. Use of nutritional supplementation with ergocalciferol may replete 25(OH)D levels but generally will not suppress elevated PTH levels adequately in CKD stages 3–5. Consequently, active vitamin D sterols are often required, *ie*, cholecalciferol or vitamin D analogs. Any active vitamin D

compound can be used concomitantly with vitamin D2 or D3. However, no published studies have analyzed the benefits of concomitant therapy. Careful attention must be paid to serum Ca and P levels during vitamin D intervention(s) since gut Ca and P absorption may lead to Ca and/or P elevations.

Oral vitamin D continues to be recommended in CKD stages 3 and 4 in the setting of documented 25(OH)D deficiency accompanied by PTH values above the normal range. Supplementation without confirmation of vitamin D insufficiency is not recommended. Active vitamin D sterols are recommended when correction of hypocalcemia, vitamin D deficiency, and hyperphosphatemia fail to correct rising elevated PTH levels in CKD stages 3 and 4. Treatment with active vitamin D sterols is indicated when 25(OH)D levels are >30 ng/mL and when corrected calcium is <9.5 mg/dL, P <4.6 mg/dL, and PTH levels are elevated and continue to rise with time. Notably, in CKD stage 4, ergocalciferol therapy may restore 25(OH)D levels to >30 ng/ml but will often fail to suppress an elevated PTH level. Therefore, in CKD stage 4, ergocalciferol to correct low 25(OH)D levels may be combined with an active vitamin D receptor agonist, *ie*, calcitriol or one of its analogues. The optimal PTH levels in CKD are unknown and likely vary with a number of factors, which are not limited to stage of CKD and race. There is growing acceptance that therapy of mineral metabolism should be individualized, *ie*, trend analysis of the above parameters is favored over absolute values. In end-stage renal disease (ESRD) patients, an intact PTH (iPTH) range that is 2–9 × ULN (~130–600 pg/mL) may be acceptable, if there is no trend to increasing or decreasing values. Note that data regarding outcomes to adhering to any PTH range/target are lacking for hard outcome measures such as cardiovascular death. The propensity for cardiac valvular or vascular calcification is greater with Ca-based P-binder therapy, and, consequently, these agents are relatively contraindicated if the serum P exceeds 6.0 mg/dL.

Doxercalciferol, a vitamin D2 prohormone, requires hepatic hydroxylation for activation. Paricalcitol, a calcitriol analog, is active upon administration and does not require *in vivo* activation. Doxercalciferol and paricalcitol exert vitamin D-like actions and are less prone to induce hypercalcemia than calcitriol. Note, there is insufficient evidence to evaluate one agent's benefit over another.

All FDA-approved P-binders are recommended for CKD stage 5. None have ever been approved for earlier stages of CKD, but all of them may be used in earlier stages. Dietary modification under supervision of a renal dietitian should always be carried out either before or during P-binder therapy (**Table 4**). Concern remains regarding the use of Ca-containing binders in this group given the associations between Ca overload and vascular calcification/morbidity in later stages of CKD, especially for CKD stage 5 patients. Ca-based P-binders have been recommended when there is no hypercalcemia and no evidence of coronary, peripheral vascular/cardiac, or valvular calcification. Abdominal plain films and/or echocardiography may be used to evaluate the degree of Ca overload in CKD patients. There is growing opinion that Ca-based binders should be avoided when serum Ca exceeds 9.5 mg/dL and as CKD advances into stage 4 to reduce the risk of cardiovascular calcification. A total daily elemental Ca intake (dietary and supplemental) of 1200 mg is currently recommended in CKD stages 3 and 4. Some advocate a total daily elemental

calcium limit of 1000 mg daily in advanced CKD. Limits on total daily elemental Ca are imposed to prevent excessive Ca loading, adynamic bone disease, and extraskeletal calcification and dystrophic medial arterial calcification that occur earlier in diabetes and CKD. Although bone changes due to aging and menopause need to be considered in treatment of bone health in women with CKD, in this group the effects of Ca supplementation on bone loss and vascular calcifications are not well understood. Current general recommended limits for Ca load for all patients with CKD should be applied. Ca-based P-binders must be used with caution and probably should not exceed 1,000 mg of elemental Ca daily.

Sevelamer hydrochloride, a non-metal anion exchange resin, and lanthanum carbonate are non-Ca-based P-binders. These agents may be used as initial P-binder therapy if arterial/cardiac vascular calcification is present or if the corrected Ca is greater than normal. Sevelamer use is also accompanied by reductions in LDL-C by 30% and increases in HDL-C. **Iron-based P-binders have recently been approved by the FDA and may become viable non-Ca-based alternatives.** Iron-based P-binders do not alter Ca or PTH levels or affect treatment by vitamin D or its analogs. Studies suggest effective P-lowering with these agents, and beneficial iron absorption may occur; however, these drugs are not FDA-approved as hematinic therapy.

TABLE 4. KDIGO TARGETS FOR CKD-MINERAL AND BONE DISORDER*

CKD Stage	Ca (mg/dL)	P (mg/dL)	iPTH (pg/mL)	HCO ₃ (mEq/L)
3	Normal range	Normal range	Normal range	22–26
4	Normal range	Normal Range	Normal range	22–26
5	Lower toward Normal range	Lower toward Normal range	2–9 × ULN	22–26

*KDIGO: Kidney Disease: Improving Global Outcomes, 2009. Trend analysis of each parameter is preferred over treatment(s) directed at absolute parameter levels. Intact PTH (iPTH) levels of 130–600 pg/mL roughly equal 2–9 × ULN. Serum calcium corrected to serum albumin of 4.0 g/dL. Trend analysis of Ca, P, and iPTH is recommended rather than treatment of isolated values.

EVALUATION

Ca, P, iPTH	Every 2 weeks initially in CKD stages 3–4 until normalized, then every 3–12 months depending on stage and trends
HCO ₃	Every 1–4 months, depending on degree of metabolic acidosis
25(OH)D	<30 ng/mL at initial evaluation: begin therapy, then test level every 3 months until ≥30 ng/mL; obtain subsequent levels depending on CKD stage and values

VITAMIN D AND ACTIVE VITAMIN D STEROLS

Vitamin D

- Ergocalciferol (D2) for 25(OH)D <15 ng/mL: 50,000 IU q1 week × 4, then monthly × 8, unless corrected Ca >9.5 g/dL and/or P >4.6 mg/dL
for 25(OH)D 15–30 ng/mL: 50,000 IU monthly × 6, unless **corrected Ca** >9.5 g/dL and/or P >4.6 mg/dL
Vitamin D therapy may require prolonged weekly dosing
Monitor levels every 3 months and continue weekly or monthly dosing accordingly
- Cholecalciferol (D3) for 25(OH)D <30 ng/mL: 1,000–2,000 IU once daily
- Calcifediol [25(OH)D3] for 25(OH)D <30 ng/mL: 10–20 mcg once daily

Active Vitamin D sterols

- Calcitriol Initial dose for CKD stages 3–4: 0.25–0.50 mcg once daily with dosage increase, if required
- Doxercalciferol Initial dose for CKD stages 3–4: 1.0 mcg once daily with dosage increase, if required
- Paricalcitol Initial dose for CKD stages 3–4: 1.0 mcg once daily or 2.0 mcg, 3 times weekly with dosage increase, if required

PHOSPHORUS BINDERS (ALWAYS TAKEN WITH MEALS)

Ca-containing compounds

- Calcium acetate 1.0–1.5 g elemental Ca daily for P >4.6 mg/dL and Ca 8.8–10.2 mg/dL; (PhosLo®) 667 mg of Ca acetate contains 167 mg elemental Ca (25%)
- Calcium carbonate 1.0–1.5 g elemental Ca daily for P >4.6 mg/dL and Ca 8.8–10.2 mg/dL; CaCO₃ dose is 40% elemental Ca
Not FDA-approved at any CKD stage

Non-Ca-containing compounds (Ca-based P-binders are contraindicated if Ca >10.2 mg/dL)

- Sevelamer carbonate (Renvela®) 800–2400 mg 3 times daily for P >4.6 mg/dL and Consider when Ca >9.5 mg/dL and PTH elevated, or if cardiovascular calcification present
- Lanthanum carbonate (Fosrenol®) 500–1000 mg 3 times daily for P >4.6 mg/dL and Consider when Ca >9.5 mg/dL and PTH elevated, or if cardiovascular calcification present
- Sucroferric oxyhydroxide (Velphoro®) 500 mg 3–4 times daily for P >4.6 mg/dL and Ca >10.2 mg/dL (Ca-based P-binder contraindicated)
FDA approved for CKD patients on dialysis
- Ferric citrate (Auryxia™) 420–840 mg 3 times daily or P >4.6 mg/dL and Ca >10.2 mg/dL (Ca-based P-binder contraindicated)
FDA approved for CKD patients on dialysis

METABOLIC ACIDOSIS

NaHCO ₃ tablets	0.5–2.0 mEq/kg daily; target HCO ₃ 22–26 mEq/L
Sodium citrate/citric acid	0.5–2.0 mEq of Na/kg daily; target HCO ₃ 22–26 mEq/L

KEY SUMMARY POINTS

CKD-MBD encompasses bone and mineral disorders as well as vascular calcification

Bone quality cannot be accurately assessed by routine imaging studies such as DEXA

Attempt to normalize Ca and P levels in CKD stages 1–4

Do not use Ca-based P-binder therapy if cardiac or vascular calcification is present

Ca-based P-binder efficacy is decreased during treatment with antacids and/or PPIs

Attempt to correct vitamin D levels to 30 ng/ml or greater with ergocalciferol [D₂], cholecalciferol [D₃], or calcifediol [25(OH)D₃]

Treat secondary HPT of renal origin with cholecalciferol or a vitamin D analog; avoid PTH oversuppression

Treat metabolic acidosis to a target HCO₃ level of 22–26 mEq/L

DYSLIPIDEMIA OF CHRONIC KIDNEY DISEASE

by Snigdha Reddy, MD and Jerry Yee, MD

INTRODUCTION

CKD patients are coronary heart disease-equivalent. Hypercholesterolemia, obesity, and cigarette smoking have been shown to negatively influence CKD outcomes. Moreover, some HMG-CoA synthetase inhibitors (statins) have been associated with slowing the decline of kidney function in CKD and a reduction in proteinuria. Despite these observations, dyslipidemia therapy in CKD has been suboptimal and controversial. Most of the knowledge regarding lipids in CKD is based on studies of hemodialysis patients and has been extrapolated to earlier stages.

LIPID LEVELS

CKD dysregulates normal triglyceride (TG) and cholesterol (C) metabolism. High TG levels, the most common lipid abnormality of CKD, stem from reduced endothelial lipoprotein lipase activity and from lipoprotein abnormalities that reduce receptor binding and lipoprotein uptake with apoC-III-enriched lipids. Other metabolic defects result in increased VLDL remnants (IDL) and ApoB-rich lipids (eg, LDL-C). These defects combine with lowered HDL-C levels (low apoA-1 and -II) to generate a highly atherogenic profile with elevated Lp(a). In ESRD, LDL-C >130 mg/dL is present in 10–45% of non-nephrotic patients, and TG levels are >200 mg/dL in 40–50% of these individuals. Nephrotic range proteinuria stimulates LDL-C synthesis, and high LDL-C may be the dominant abnormality.

LIPID-LOWERING BENEFITS

Clinical practice recommendations for lipid-lowering therapy in CKD are in contrast with the 2014 ACC/AHA guidelines that are not CKD-specific. Based on two large trials (Die Deutsche Diabetes Dialyse Studie [4D] and A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events [AURORA]) in ESRD patients demonstrated no cardiovascular or mortality benefits. However, a large, randomized, controlled trial Study of Heart and Renal Protection (SHARP) of CKD patients treated by *simvastatin/ezetimibe* demonstrated a positive effect of LDL-C–lowering therapy in *non-dialysis-dependent* CKD (mean eGFR, ~27 mL/min/1.73 m²) and ESRD patients. Major atherosclerotic events (combination of non-fatal MI, coronary death, ischemic stroke, or any revascularization event) were reduced by ~17% compared to placebo. There was no effect on reducing the progression of CKD.

LIPID-LOWERING STRATEGIES

Lipid evaluation should be conducted at initial evaluation but treatment decision is not based on the level. Follow-up lipid measurements are recommended to determine adherence to therapy and to determine if a change in treatment is required based on lipid levels. Statin adherence in CKD patients has been reported at <50%. Lipid-lowering therapy in CKD patients with a statin or a statin combined with ezetimibe (eg, *simvastatin/ezetimibe*) is recommended with therapeutic lifestyle changes (TLC). KDIGO recommends treatment with high-intensity statins in CKD patients 18–50 years, with lower risk for adverse side effects, when known

coronary heart disease, diabetes, ischemic stroke, or an estimated 10-year incidence of coronary death or non-fatal MI exceeding 10% (ACC/AHA risk calculator) is present, which is in contrast to the ACC/AHA recommendation of 7.5%. Lower doses of two drugs, simvastatin/ezetimibe, may be considered to decrease the risk of toxicity. Statins are first-line therapy in CKD patients, but there is no preferred agent. There is no evidence that statins or ezetimibe induce a greater incidence of rhabdomyolysis or cancer in CKD patients, compared to the general population. Muscle pain from statin therapy is genetically predisposed and is not an effect of CKD. Trials of different medications in this class of agents may be required until a suitable one is found. Therapy should not be started in statin-naïve ESRD patients; however, cholesterol-lowering agents should be continued in individuals who had already been treated with these drugs before the onset of ESRD. Bile acid sequestrants and niacin may be used, if statins cannot be used or tolerated. TLC is recommended for CKD patients with elevated TGs. Pharmacologic TG therapy is not recommended for TG levels >1000 mg/dL, unless there is a history of pancreatitis. Fibric acid derivatives must be administered cautiously with statins in CKD to avoid hepatic toxicity or myopathy.

EVALUATION

Total cholesterol, LDL-C, HDL-C, and TGs at first evaluation

Follow-up level in 6–12 weeks to determine adherence to treatment or if treatment plan requires alteration

THERAPEUTIC TARGETS

LDL-C

Therapeutic targets are no longer necessary based on the 2013 KDIGO, 2014 ACA/AHA and 2015 ADA guidelines

TREATMENT

Statin or statin/ezetimibe

Moderate-to-high intensity statins for CKD patients with very high risk for atherosclerotic CVD

KEY SUMMARY POINTS

Baseline hepatic transaminase levels may be determined before initiating statin therapy. Repeat levels only if clinically indicated.

Routine monitoring of creatine kinase levels is not recommended

Recommended doses (mg/day) of statins in adults with CKD stages 3A to 5:

- Atorvastatin 20
- Fluvastatin 80
- Pravastatin 40
- Rosuvastatin 10
- Simvastatin 40; simvastatin/ezetimibe 20/10

Ezetimibe (Zetia®): Ezetimibe or colesvelam, cholesterol absorption inhibitors, may be used to reduce statin doses, *ie*, potential benefit from using multiple, low doses of drugs instead of a single high dose in CKD. Ezetimibe requires no dose adjustment at any level of CKD. Colesvelam is contraindicated, if TGs are increased.

Renal dietitian consultation, if fasting TGs \geq 500 mg/dL and/or elevated LDL-C

NUTRITION IN CHRONIC KIDNEY DISEASE

by Kristen Nonahal, RD

INTRODUCTION

Protein-energy wasting (PEW) evolves during the progression of CKD with electrolyte abnormalities, loss of lean body mass, and depressed immunological function. These problems are compounded by anorexia which often accompanies advanced CKD along with poor dietary choice(s), *ie*, lack of high biological value protein (food or combinations of foods that provide all of the essential amino acids). Hypoalbuminemia and related nutritional disorders, including vitamin and mineral deficiencies, are common. Preventing malnutrition through nutritional intervention by a trained renal dietitian is recommended and may avert complications. All patients at CKD stage 4 or 5 should undergo evaluation by a renal dietitian. However, many stages 1–3 CKD patients may benefit from such evaluations as overall dietary intake may be suboptimal. A table of nutritional targets for CKD stages 3–5 patients is provided from which a balanced diet may be derived (**Table 1**).

PROTEIN INTAKE

High biological value protein (foodstuffs that contain all essential amino acids) intake should be maintained while sodium, potassium, and phosphorus intakes are limited. Requirements vary depending on the CKD stage. A protein controlled diet slows the decline in kidney function more than one with a liberal protein intake. Fluid restriction should be instituted only when hyponatremia (Serum Na<130 mEq/L) is present, and the patient is not hypovolemic. The reduction of sodium and phosphate intake is much more important.

POTASSIUM AND PHOSPHORUS INTAKE

Potassium and phosphorus commonly occur together in Western diets. Foods with high potassium levels are provided (**Table 2**). As GFR declines to 15–20 mL/min/1.73 m², potassium retention becomes important and potentially dangerous, especially if there is concomitant NSAID, ACEI, ARB, or MRA intake. Therefore, by CKD stage 4, most patients should undergo some degree of potassium restriction. Sodium chloride (table salt) substitutes must be avoided because these preparations substitute potassium for sodium.

There is no federal requirement for phosphorus content in food to be declared, and sodium phosphate is often used as a food preservative. Consequently, dietary inorganic phosphate intake may be much greater than one appreciates. High phosphate (P) intake leads to hyperphosphatemia as GFR declines and is often treated with P-binder therapy in the absence of a renal dietitian consultation. This approach is suboptimal as the restriction of dietary phosphate intake is often more efficacious than P-binder treatment. No P-binder therapy should be undertaken without the consultation of a certified renal dietitian. A table of high phosphate-containing foods is provided (**Table 3**).

MONITORING THE RENAL DIETARY PRESCRIPTION

A 24-h urine collection for sodium (goal <100 mEq sodium per 24-h), urea nitrogen, and creatinine is highly informative regarding the level of adherence with a renal dietary prescription. A 24-h collection must always be indexed to creatinine. In general, a male should excrete 18–25 mg of creatinine per kg ideal body weight. A female should excrete 15–22 mg per kg ideal body weight. The volume of the collection therefore is less important than the creatinine evaluation. A 24-h urine collection for sodium, potassium, urine urea nitrogen, and creatinine is recommended to obtain information regarding nutritional status, renal function, and suboptimal response to antihypertensive therapy. In the latter case, the measurement of sodium and potassium in the urine as a reflection of dietary intake may demonstrate potential causes of resistant hypertension, *ie*, high sodium intake and/or low potassium intake. To preserve lean body mass a supervised exercise regimen should be considered in conjunction with dietary recommendations. Patients with high BP are advised to follow a Dietary Approaches to Stop Hypertension (DASH) diet, which has proven efficacy; however, modification of the DASH diet may be required in CKD patients due to its high potassium and phosphate content. Patients with proteinuria at any stage of CKD should be referred to a renal dietitian/nutritionist.

TABLE 1. NUTRITIONAL TARGETS FOR CKD STAGES 3–5

CKD Stage	Calories (kcal/kg/d)	Na (mEq/d)	K (mEq/d)	P (mg/d)	Protein (g/kg/d)
3	30–35 [†]	≤65	—	600–1000	0.75
4	30–35 [†]	≤65	40–60	600–1000	0.6–0.8
5	Per dietitian	≤65	40–60	600–1000	0.6–0.8

[†]General recommendation

RENAL-FORMULATED MULTIVITAMINS (MVs)

Nephrocaps [®]	1 capsule once daily
Nephro-Vite [®] Rx 100	1 tablet once daily
Nephron FA [®]	1 tablet twice daily (65 mg iron per tablet)

TABLE 2. HIGH POTASSIUM-CONTAINING FOODS

Avocados	K-salt substitutes, <i>eg</i> , Lite Salt®
Bananas	Mangos, papaya
Blenderized fruits & vegetables	Milk: nonfat, low fat, whole, buttermilk, soy
Bran and bran cereals	Nuts
Broccoli	Nectarines, peaches
Brussels sprouts	Oranges
Cantaloupe, honeydew melon	Spinach
Dried beans, peas, lentils	Tomatoes/tomato products
Dried fruits	Sweet potatoes, white potatoes, yams
Fish: halibut, cod, snapper	Winter squashes: acorn, butternut, hubbard
Greens: collard greens, turnips, beets	Yogurt: plain or fruited

TABLE 3. HIGH PHOSPHORUS-CONTAINING FOODS*

Bran	Nuts, nut butters
Brown rice, wild rice	Organ meats: kidney, liver, pancreas, thymus
Cheese	Pizza
Chocolate, chocolate drinks	Pancakes, waffles, biscuits, especially from mixes
Cola beverages	Processed meats (lunch meats)
Dried beans, peas, lentils	Sardines
Ice cream	Seeds: sunflower or pumpkin
Milk: all types	Whole grain breads
Milk-based puddings or custards	Yogurt

*Food preservatives often contain unknown quantities of hidden phosphate-rich additives that contribute to elevated serum phosphorus levels. Avoid listed ingredients containing the word phosphate or abbreviation “phos” is recommended.

KIDNEY REPLACEMENT THERAPY

by Lalathaksha Kumbar, MD and Vivek Soi, MD

INTRODUCTION

Kidney replacement therapy (KRT) encompasses kidney transplantation, peritoneal dialysis (PD), hemodialysis (HD) and conservative management without dialysis. Anticipation of the need to initiate kidney replacement therapy is a cardinal step in the care of patients with advanced chronic kidney disease. Nearly 41% of CKD stage 5 or end-stage renal disease (ESRD) patients have no pre-ESRD evaluation by a nephrologist and 70% of them initiate KRT with HD catheter instead of the preferred arteriovenous fistula. In these cases, healthcare expenditures during the initial 3 months of ESRD therapy increase by an average of \$30,000 per hospitalized patient.

KIDNEY REPLACEMENT THERAPY

KRT is an expensive government entitlement program: minimal annual patient cost, ~\$36,000 and annual average cost per patient is ~\$70,000. Although CKD stage 5 begins at eGFR <15 mL/min/1.73 m², KRT does not have to begin until a patient develops symptoms of uremia. The American Society of Nephrology in collaboration with the American Board of Internal Medicine through its *Choosing Wisely* campaign recommends the decision to initiate KRT should be part of an individualized, shared decision-making process between patients, their families and their physicians. Among various available KRT modalities, in-center hemodialysis continues to be widely used. Other modalities increasingly being chosen are PD, home HD and nocturnal HD. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) Clinical practice guidelines recommends early referral of patients to nephrologists to offset a trend towards unplanned, in-hospital initiation of KRT usually via catheters which has significant, costly morbidity and mortality. CKD stage 4 patients should receive timely education regarding signs and symptoms of kidney failure, dietary modifications, and modality options (kidney transplant, PD, or HD). Patients should also have early referral to experienced surgeons for vascular access creation for HD or planning for PD catheter placement. Despite increased impetus on early referral, timely nephrology care prior to KRT initiation continues to be a concern.

PERITONEAL DIALYSIS

PD is a viable option for most ESRD patients; however, it was chosen by just 10.9% of ESRD patients who began ESRD care between 2005 and 2007. In 2010, for the second consecutive year, patients initiated on peritoneal dialysis increased and now account for nearly 6.6% of patients with a known modality at the time of initiation. PD is actively promoted by CMS and in many countries, particularly Canada and Mexico. PD is considered the best “first option” for KRT, and many nephrologists in the US agree with this opinion. The trend continues into the first 90 days after KRT, with a nearly 5% gain in patients with peritoneal dialysis as their modality.

The instillation of a hypertonic glucose-containing solution via a trans-abdominal PD catheter provides uremic solute (diffusion) and excess sodium and water removal (convection).

PD catheters should be implanted at least 4 weeks prior to the date of their anticipated use. In patients with unplanned initiation of KRT, growing evidence indicates peritoneal dialysis to be a safe and efficient alternative to tunneled catheter-based hemodialysis. Blood pressure and pulse control are superior with PD compared to conventional HD. PD involves diffusion of uremic solutes and electrolytes from capillaries lining the peritoneal membranes into the externally infused dialysate. The continual nature of PD is suited for heart failure and/or volume-dependent hypertension. PD offers independence by allowing schedule flexibility. PD is advantageous for patients with limited mobility and those who reside in a remote location. It is also a viable alternative to hemodialysis in the setting of end-stage vascular access.

Contraindications to PD catheter insertion include peritonitis, extreme obesity, multiple abdominal surgeries, and recurrent peritonitis. Complications of PD include peritonitis, catheter malfunction, peritoneal fluid leaks, and failure of PD due to membrane loss/fibrosis. Peritonitis can be treated with intraperitoneal or IV antibiotics and may require catheter exchanges. Catheter removal is absolutely indicated when pseudomonas, Methicillin-resistant *Staphylococcus aureus* or fungal peritonitis occurs.

HEMODIALYSIS

About 92% of the incident patients in the United States undergo conventional thrice-weekly hemodialysis in designated in-center dialysis, with typical treatment times of 3–4 h. Some centers offer nocturnal HD where patients sleep during treatment by slow, low-efficiency dialysis. Home HD is conducted in a home environment, 5–6 sessions, weekly for generally 2.5–3 hours. Control of BP and phosphorus are superior with PD, nocturnal PD and home HD compared to conventional thrice-weekly in center HD.

VASCULAR ACCESS FOR HEMODIALYSIS

Optimal HD requires a well-functioning vascular access and this can be provided via autogenous arteriovenous fistulas (AVF), bioprosthetic arteriovenous grafts (AVG), or HD catheters. The AVF is the preferred HD vascular access that most closely satisfies the requirement for adequate blood flow delivery to the dialysis machine. It has the lowest maintenance cost among all vascular access types and is associated with a lower risk of infection and venothromboembolic disease. With this notion, the Center for Medicare and Medicaid Services promoted the “fistula first breakthrough initiative (FFBI)” with an aim to increase the fistula usage for HD. Though fistula creation increased exponentially, 40%–60% of fistula fail to mature leading to continued catheter dependence. Over the last decade, a significant increase in tunnel catheter use for HD coupled with lack of difference in cumulative patency between AVF and AVG have been noted. Long-term systemic effects of AVFs or AVGs especially cardiovascular changes, distal limb ischemia, and possibly pulmonary effects are being recognized. A relook at this strategy led to a significant change from “fistula first” to “catheter last” approach for patients requiring hemodialysis.

An AVF typically is created from a native artery and vein in the distal non-dominant upper extremity. Placement of an AVF should precede the time of anticipated HD by at least 6 months, to ensure sufficient fistula maturation before needle cannulations. When AVF creation is not

feasible, AVG construction should proceed 3–6 weeks before anticipated, although newer graft materials can be used within 2–3 days after placement. The patient should be evaluated by venous mapping, preferably by ultrasound duplex scanning of the non-dominant arm; if unsuitable, the dominant arm may be used for access creation. If both arms are not suitable, then alternatives like peritoneal dialysis may be considered.

The patient and healthcare workers must know the intended surgery site for effective vein preservation during hospitalizations and outpatient care. Protection of superficial hand and forearm veins, particularly of the non-dominant arm, is critical in CKD patients. Dominant laterality is identified by the arm preferentially used by the patient for major daily activities and devoid of risk factors for AVF failure like ipsilateral cardiac devices. The dorsum of the hand should be used for peripheral lines and blood draws. Subclavian vein catheter placements and PICC lines are strongly discouraged and are associated with high central vein stenosis rates; their use may preclude access creation(s). Cardiac AICD and pacemaker placements should be contralateral to the planned vascular access arm, or consideration for epicardial lead pacemaker and subcutaneous AICD should be given. Educational programs reinforcing the above should be provided to patients, their families and other healthcare providers involved in care.

KIDNEY REPLACEMENT THERAPY IN ELDERLY

In the recent years, the elderly have been identified as one of the fastest growing population of patients on dialysis. Between 1996 and 2003, there was a 57% increase in patients over the age of 80 that initiated renal replacement therapy in North America. The number of comorbid conditions can greatly influence a patient's outcomes. Characteristics that were strongly associated with death after the initiation of dialysis include older age, congestive heart failure, malnutrition and non-ambulatory status. One year mortality for octogenarians and nonagenarians after dialysis initiation was 46%, substantially higher than that of age-matched population controls or younger patients initiating therapy. Among nursing home residents with ESRD, the initiation of dialysis is associated with a substantial decline in functional status and low 6-month survival.

Dialysis does prolong survival for elderly patients who have ESRD, but this survival advantage diminishes with high comorbidity scores. Patients who choose conservative pharmacotherapy to minimize symptoms such as fatigue from anemia, pruritus from uncontrolled hyperphosphatemia, and pulmonary congestion can survive a substantial length of time achieving similar numbers of hospital-free days to patients who choose hemodialysis. The choice of vascular access for hemodialysis in the elderly is even less clear. Arteriovenous fistulas are considered optimal dialysis access but outcome in the elderly population is unclear. A recent meta-analysis of available literature revealed an AVF primary failure rate of 37% compared to 27% in non-elderly patients. Uncertainties at various levels for KRT in the elderly population emphasizes the need for an individualized approach with close care collaboration between primary care physicians and nephrologists.

IMMUNIZATIONS IN CHRONIC KIDNEY DISEASE

by Gregory Krol, MD and Jerry Yee, MD

INTRODUCTION

CKD patients are immunocompromised in CKD stage 5 and end-stage renal disease (ESRD); however, immunocompromise has been documented in earlier stages, but the degree is less certain. Nonetheless, CKD patients are immunized less frequently against influenza virus and *S. pneumoniae* than the general population. Influenza and pneumococcal vaccines may be coadministered. CKD patients should receive the following immunizations:

- Quadrivalent, *inactivated* influenza A/B (QIV) or high-dose trivalent (TIV) vaccines.
- Pneumococcal 13-valent conjugate vaccine (PCV13, Prevnar®).
- Pneumococcal polysaccharide 23-valent vaccine (PPSV23, Pneumovax®) 1 year after administration of PCV13.
- Hepatitis B virus (HBV) vaccine (combined hepatitis A/B vaccine [Twinrix®]) may be administered as a 3-dose series: 0, 1, and 6 months (**Table 1**).
- Tetanus diphtheria (Td), Tetanus diphtheria and pertussis (Tdap), and live attenuated zoster vaccine.

HEPATITIS B VIRUS

HBV vaccination is advised in patients with progressive CKD, and immunization in CKD stage 4, pre-ESRD, is recommended because “late” stage 5 vaccination produces lower rates of seroconversion. In CKD stage 5, antigen presenting cell and CD4 cell defects occur. Consequently HBV-antibody responses to HBV are less intense and less durable. Immunocompetence, measured by achievement of an antibody titer >10 mIU/mL, occurs in just 50–70% of ESRD patients. HBV vaccines are contraindicated in persons with yeast allergy.

Hepatitis C virus (HCV)-positive patients can be safely immunized against HBV. Booster vaccinations with tetanus toxoid, diphtheria, and acellular pertussis vaccines (Tdap) may be administered alone or in combination with any of the vaccines listed below.

TABLE 1. HEPATITIS B VACCINES: DOSES AND SCHEDULES

Group	Recombivax HB®			Engerix B®		
	Dose (mcg)	Vol (mL)	Schedule (months)	Dose (mcg)	Vol (mL)	Schedule (months)
>20 y.o. Stages 1–4	10	1.0	3 doses: 0, 1, and 6	20	1.0	4 doses: 0, 1, 2 & 6
>20 y.o. Stage 5	40	1.0†	3 doses: 0, 1, and 6	40	2 × 1.0 at 1 site	4 doses: 0, 1, 2 & 6

All vaccination doses are administered by intramuscular route

†Special formulation (Recombivax HB Dialysis Formulation®)

The HBV antibody titer should be evaluated 2 months after the final dose. If the titer is <10 mIU/mL, repeat entire dosing series and determine antibody response after 1–4 months. CKD/ESRD patients at risk for hepatitis A (eg, chronic liver disease, HCV, HIV, multiple sexual partners, homosexual males, and IV drug users) should be vaccinated with hepatitis A vaccines (Havrix® and Zaqta®) if seronegative.

INFLUENZA VIRUS

United States Renal Data System data revealed that Medicare patients with CKD were 5.4 times more likely to receive an influenza vaccine versus employer group health plan patients with CKD (43% v 8%). The Agency for Healthcare Research and Quality advocates that CKD patients be vaccinated yearly to decrease morbidity and mortality related to influenza. QIV immunization is now comprised of two “A” [one is H1N1] and two “B” virus strains and may be coadministered with pneumococcal vaccines, Prevnar 13® and Pneumovax®23. Alternatively, high-dose TIV may be substituted for QIV in patients ≥65 years old.

VARICELLA-ZOSTER

Varicella zoster (VZ) reactivation may be precipitated by the immunosuppression that follows organ transplantation or in advanced CKD. VZ immunizations are available as two, live, *attenuated* virus vaccines (Varivax®, Zostavax®). These may be administered in CKD patients. Varivax is a pediatric, adolescent, and adult immunization for prevention of primary varicella infection (chickenpox). Zostavax is administered to adult patients for prevention of herpes zoster. Patients undergoing consideration as organ transplant recipients should optimally receive VZ immunizations pretransplantation but not after.

VACCINES

FDA-approved vaccines that are *commonly* administered to CKD patients are briefly described below.

Quadrivalent or high-dose trivalent inactivated influenza vaccines

QIV Single, annual dose IM, upper arm

High-dose TIV Single, annual dose IM, upper arm for patients ≥65 years old

Intranasal live, *attenuated* influenza virus vaccine (FluMist®) is not FDA-approved for CKD patients.

S. pneumoniae vaccines

Prevnar 13® Single, 0.5-mL IM (deltoid) injection of PCV13 for prevention of pneumonia and invasive disease and 1 year prior to initial Pneumovax administration, if possible.

Refer to the package insert regarding the timing of the Prevnar and Pneumovax vaccinations based on the patient’s naïve or previous *S. pneumoniae* immunization status.

Pneumovax®23 Single, 0.5-mL (25 mcg) IM (deltoid) injection of PPSV23 for prevention of invasive disease.
Alternative subcutaneous injection is permitted.

Revaccinate after 5 years with a single booster dose of Pneumovax®23 after the first administered dose in persons 65 years or older who were less than 65 years at time of first vaccination.

Varicella vaccines

Varivax® Single, 0.5-mL SQ injection at 0 and 3 months for children (1–12 years) and at 0 and 1 month for adolescents and adults.

Zostavax® Single, 0.65-mL SQ injection for adults older than 50 years for prevention of shingles.

Tetanus, diphtheria (Td) & Tetanus, diphtheria and pertussis (Tdap) vaccines

Td Dose 1 of initial series: 0.5-mL IM injection, upper arm.
Doses 2 and 3: 4–8 weeks between doses 1 and 2 and 6–12 months between doses 2 and 3.
Booster doses: 0.5-mL IM injection every 10 years after initial series.

Tdap One dose is recommended for adults ≥19 years of age. Substitute a one-time dose of Tdap for Td booster; then administer Td booster every 10 years.

MEDICATION-RELATED PROBLEMS

by Gregory Krol, MD and Jerry Yee, MD

INTRODUCTION

Potentially adverse complications of drugs or medication-related problems that commonly occur in CKD are enumerated. Such adverse effects may occur in the context of acute kidney injury (AKI) or CKD. Caution is warranted when using any of the listed agents in CKD. Alternative therapies should be explored in each clinical circumstance and the risk-to-benefit ratio of any agent must be determined by the prescribing individual. The clinician is advised to determine all medications that require dose adjustments based upon GFR in steady-state conditions. Pharmacy consultation is advised to optimize drug dosing particularly in cases of acute kidney injury.

ACUTE KIDNEY INJURY / ACUTE RENAL FAILURE

Azotemia: exenatide (Byetta®) has been associated with AKI.

Crystalline tubular damage: Acyclovir (Zovirax®), indinavir (Crixivan®), sulfadiazine, triamterene, triamterene/HCTZ combinations (Dyazide®, Maxzide®), topiramate (Topamax®), and orlistat (Xenical®).

Decreased creatinine secretion: Trimethoprim (Proloprim®, Bactrim®, Septra®, Sulfatrim®, Polyprim®), probenecid (Benemid), spironolactone (Aldactone®), amiloride (Midamor®), triamterene (Dyrenium®), pyrimethamine (Daraprim®), salicylates, and cimetidine (Tagamet®).

- GFR is not reduced, although eGFR will be lowered; BUN does not change.

Decreased GFR: ACEIs and ARBs reduce efferent arteriolar resistance.

- ARBs produce less SCr elevations than ACEIs.

Intratubular Calcium Phosphate precipitation: Oral sodium phosphate solutions (OSPs) may induce AKI in CKD patients via intratubular calcium-phosphate precipitation with nephrocalcinosis and are contraindicated in CKD patients. OSPs include Visicol® and Osmo-Prep®.

Intrarenal vasoconstriction with decreased GFR: NSAIDs, COX-1/-2, selective COX-2 inhibitors, and calcineurin inhibitors (CNIs, eg, cyclosporine, tacrolimus) may reduce GFR, promote sodium retention (edema), and aggravate hyperkalemia. Long-term use of CNIs can result in nephrotoxicity in 25–60% of patients and is often associated with elevated blood concentrations underscoring the importance of monitoring CNI blood levels.

Tubulointerstitial nephritis (interstitial nephritis):

- This disorder may represent 9–17% of cases of in-hospital ARF and is often the etiology of ARF of unknown origin. The most common sign of acute tubulointerstitial nephritis is hematuria, although classically, leukocyte casts are associated with this disorder. Microscopic evaluation of the urine should be used to confirm this often “missed” disorder.
- Allergic antibiotic-associated interstitial nephritis is common.

- Lithium (Eskalith®, Lithobid®) is associated with tubulointerstitial nephritis and in some cases, nephrotic syndrome.
- Idiosyncratic reactions to NSAIDs may induce immune-mediated acute or chronic interstitial nephritis.
- Idiosyncratic reactions to NSAIDs may induce interstitial nephritis, typically in association with minimal change disease and heavy proteinuria (see above).
- Acute interstitial nephritis that has not improved within 2–4 weeks, following withdrawal of the offending agent, may be empirically treated with a 30-day course of glucocorticoid steroids.

Contrast-induced nephropathy (CIN): Prophylactic volume expansion with sodium chloride- or sodium bicarbonate-based solutions reduces the incidence of AKI in non-edematous, stable CKD patients.

Stage 3–5 patients (GFR <60 mL/min/1.73 m²), with or without diabetes.

- **Saline:** Isotonic (normal) saline or isotonic sodium bicarbonate prophylaxis is recommended for non-diabetic and diabetic CKD patients. Hospitalized, non-edematous, hemodynamically stable CKD patients should receive an infusion of isotonic sodium bicarbonate or 0.9% saline at 1 mL/kg bodyweight for up to 12 hours before, during and 12 hours after contrast administration.
- **Drugs:** Stop diuretics (if feasible), NSAIDs, and metformin before contrast delivery.
- **Radiopaque medium:** Isosmolal radiocontrast (iodixanol, Visipaque®, 290 mOsm/kg) has reduced the risk of ARF in higher risk patients, *ie*, diabetes.
- **Diabetes:** Glycemic control should be achieved prior to acute contrast delivery, *eg*, serum glucose <150 mg/dL.
- **N-acetylcysteine (NAC):** This agent has not been definitively proven to reduce the risk of developing radiocontrast-induced nephropathy. If used, administer 1200 mg po q-12 h for 4 doses: 1200 mg 13 h pre-contrast administration, 1200 mg 1 h pre-contrast and 1200 mg twice daily following contrast administration.
- **Dialysis:** Dialysis/hemofiltration is not recommended as prophylaxis.
- **ACEI or ARB therapy:** Withdrawal pre-contrast administration may be beneficial.
- **Metformin:** stop drug for 48 h following procedure. Recheck SCr and restart drug after SCr returns to baseline. If repeat SCr is above baseline, then continue to hold metformin and recheck SCr in several days to determine an improving or declining trend in kidney function.

Gadolinium (Gd): Gd-based contrast agent (GABCA) procedures, *eg*, MRI/MRA, are rarely associated with AKI. However, Gd-chelates used for MRI contrast enhancement, are associated with a fibrotic skin disorder, nephrogenic systemic fibrosis (NSF) that may also involve visceral organs. The risk of developing NSF is estimated to be 1–4% in advanced CKD. Therefore, alternatives to Gd-based imaging studies should be aggressively sought in CKD stages 4 and 5 and ESRD individuals.

Three GBCA, gadopentetate dimeglumine (Magnevist™), gadodiamide (Omniscan®), and gadoversetamide (Optimark®), are contraindicated for patients with AKI or severe CKD because NSF risk is deemed higher in these individuals. Four GBCAs that are approved for MRIs

carry new labeling explicitly warning of the risk of NSF associated with GBCA: gadofosveset trisodium (Ablavar[®], Vasovist[®]); gadoxetate disodium (Eovist[®]); gadobenate dimeglumine (Multihance[®]); and gadoteridol (Prohance[®]). Clinicians are advised to screen for AKI or severe CKD before administering the agent and to monitor kidney function post-receipt of Gd. Serial hemodialyses for prompt removal of Gd and risk reduction for NSF, on 2–3 consecutive days and within several hours of the receipt of Gd, should be entertained in CKD stages 4 and 5 and in ESRD patients.

NB: Gadodiamide and gadoversetamide may cause spurious hypocalcemia by interfering with laboratory total serum calcium assays. Avoid this problem by avoiding Ca measurements for several hours post-GBCA administration.

HYPERKALEMIA

Decreased cellular K uptake: α/β blockers, *eg*, labetalol (Trandate[®], Normodyne[®]) and non-selective β -adrenergic blocking agents, *eg*, propranolol (Inderal[®], Inderal[®] LA).

Decreased renal K secretion:

- Anti-RAAS therapy with ACEIs and ARBs: ARBs produce less severe K elevations and reduce GFR less than ACEIs.
- Decreased distal nephron K secretion: Amiloride (Midamor[®]), pentamidine (Pentam-300[®], Pentacarinat[®]), triamterene (Dyrenium[®]) and triamterene/HCTZ combinations (Dyazide[®], Maxzide[®]), trimethoprim (Proloprim[®]) and trimethoprim/sulfamethoxazole combinations (Bactrim[®], Septra[®], Sulfatrim[®], Polyprim[®]).
- Interference with prostaglandin metabolism: NSAIDs, COX-1/-2 and selective COX-2 inhibitors decrease renal K secretion by interfering with prostaglandin metabolism, which produces intrarenal vasoconstriction.
- Aldosterone receptor antagonist: Spironolactone (Aldactone[®]) and epleronone (Inspra[®]).

High K-containing foods: Patients should be counseled on the avoidance of high-K containing foods (see **NUTRITION IN CKD**).

COMMENTS

Renal dietary consultation is recommended for persistent hyperkalemia (K >5.5 mEq/L) and/or when polystyrene sulfonate (Kayexelate[®]) is considered for treatment of hyperkalemia. The routine use of polystyrene sulfonate is not recommended.

Rule out pseudohyperkalemia from elevated platelet counts, *eg*, >750,000 plt/mm³, severe leukocytosis, *eg*, >50,000 WBC/mm³, or most commonly, prolonged tourniquet time, before treating hyperkalemia.

- Consult Nephrology prior to initiating hyperkalemia therapy with polystyrene sulfonate (this compound may cause bowel perforation/necrosis).
- Mild hyperkalemia (K, 5.0–5.5 mEq/L) usually requires no treatment, other than dietary potassium restriction.

DIABETIC KIDNEY DISEASE

Hypoglycemia: CKD decreases renal elimination of the active moiety or metabolite(s) of certain agents, thereby increasing the risk for hypoglycemia. The following agents may require dose reductions.

- Insulin is eliminated/metabolized by the kidney often requiring a dose reduction of insulin of 25–50%.
- Meglitinides: Nateglinide (Starlix®) requires no dose adjustment in CKD but repaglinide (Prandin®) does require dose adjustment in CKD.
- Sulfonylureas: Glipizide (Glucotrol®), glyburide (Diabeta®, Micronase®). Glipizide is preferred in CKD as it lacks active metabolites (glyburide has active renally eliminated metabolites).
- Other: Sulfonamide antibiotics, quinine, disopyramide, and gabapentin (Neurontin®).

Fluid retention/heart failure exacerbation: Thiazolidinediones, *eg*, pioglitazone (Actos®), rosiglitazone (Avandia®) should be used cautiously in CKD.

Other: DPP-IV inhibitors, *eg*, sitagliptin (Januvia®) and saxagliptin (Onglyza®) have a low-risk for hypoglycemia. Sitagliptin requires dose-adjustment in CKD. Metformin is generally contraindicated in moderate to severe CKD (**see below**).

COMMENTS

- α -glucosidase inhibitors: Acarbose (Precose®) and miglitol (Glyset®) do not cause hypoglycemia unless combined with other agents that may induce hypoglycemia such as sulfonylureas or insulins, but are not recommended for eGFR <25 mL/min/1.73 m².
- GLP-1 receptor agonists: Exenatide (Byetta®) is contraindicated for eGFR <30 mL/min/1.73 m²; liraglutide (Victoza®) may be preferred as it requires no dose adjustment in CKD.

METABOLIC ACIDOSIS

Bicarbonate loss in urine:

- Carbonic anhydrase inhibitors, *eg*, glaucoma therapy drugs: dorzolamide (Trusopt®), dorzolamide/timolol (Cosopt®), and brinzolamide (Azopt®).
- Acetazolamide (Diamox®) and methazolamide (Neptazane®) dosages should be reduced in CKD and are ineffective at GFR <10 mL/min/1.73 m².

Lactic acidosis: Metformin hydrochloride (Glucophage XR®, Fortamet®, Riomet®), and metformin-containing drug combinations: glyburide/metformin (Glucoavance®), glipizide/metformin (Metaglip®), rosiglitazone/metformin (Avandamet®), saxagliptin/metformin (Kombiglyze XR®).

- Metformin is contraindicated, if GFR <50 mL/min/1.73 m², *ie*, SCr >1.5 mg/dL in males or 1.4 mg/dL in females in CKD or AKI.
- Stop metformin before iodinated radiocontrast administration, then hold for 48 h post-procedure. Reevaluate SCr and restart drug if SCr returns to baseline.

Mitochondrial damage: Nucleoside analogs, *eg*, zalcitabine (ddC, Hivid®), didanosine (ddl, Videx®), stavudine (d4T, Zerit®), lamivudine (3TC, Epivir®), abacavir (Ziagen®), and tenofovir (TDF, Viread®), alone or in combination with other anti-HIV drugs.

NEUROTOXICITY

Extrapyramidal side effects: Metoclopramide (Reglan®) should be reduced by 25–50% in CKD stages 3–5 and only used short-term.

Mental status changes/Neurotoxicity/Seizures:

- Acyclovir (Zovirax®) and valacyclovir (Valtrex®) should undergo total daily dose reductions of 50–75% in CKD stages 3–5.
- Cefipime (Maxipime®): Reduce total daily dose by >50% in CKD stages 4–5.
- Meperidine hydrochloride (Demerol®) metabolite, nor-meperidine, accumulates and can induce seizures; contraindicated in advanced CKD.

Neuropathy:

- Colchicine (Colcris®): Relatively contraindicated in CKD and may induce myopathy and/or neuropathy. Use no more than 0.6 mg daily in CKD stages 4 and 5. Limit duration of use to 6 consecutive months.
- Nitrofurantoin (Macrochantin®): Absolute contraindication in CKD stages 4 and 5 due to risk of irreversible peripheral neuropathy.

HEPATOTOXICITY

Hypersensitivity(DRESS* syndrome): This syndrome usually develops 2–4 weeks after initiation of treatment with allopurinol when standard dosages (20–400 mg/day) are administered to patients with CKD. Allopurinol (Zyloprim®) should generally not be administered at total daily doses exceeding 200 mg in CKD stages 3–5.

*Drug Rash with Eosinophilia and Systemic Symptoms

SELECTED AGENTS

by Gregory Krol, MD and Jerry Yee, MD

INTRODUCTION

A list of agents commonly used in CKD care follows, grouped by drug class.

ALKALI (BASE) THERAPY

Sodium bicarbonate

Indication: Alkali replacement therapy in CKD to prevent protein wasting, decrease bone demineralization and increase vitamin D synthesis

Tablet: 325 mg (3.87 mEq HCO₃) and 650 mg (179 mg Na; 7.74 mEq HCO₃)

Initiate therapy if HCO₃ <22 mEq/L on two occasions, separated by ≥2 weeks

CKD: 23–46 mEq/d in 2–3 divided doses to provide 0.5–2.0 mEq HCO₃/kg/d to attain target serum HCO₃ 22–26 mEq/L

Do not co-administer with Ca-based P-binders or iron salts

Consult Nephrology if HCO₃ <22 mEq/L or NaHCO₃ therapy >46 mEq/d

Baking Soda

Indication: Alkali replacement therapy in CKD to prevent protein wasting, decrease bone demineralization and increase vitamin D synthesis

1 tsp: 500 mg Na, ~23 mEq HCO₃ (~3, 650-mg NaHCO₃ tablets)

Initiate therapy if HCO₃ <22 mEq/L on two occasions, separated by ≥2 weeks

CKD: 2–3 divided doses totaling 0.5–2.0 mEq HCO₃/kg/d to attain target HCO₃ of 22–26 mEq/L

Do not co-administer with Ca-based P-binders or iron salts

Consult Nephrology if HCO₃ <22 mEq/L or NaHCO₃ therapy >46 mEq/d

ERYTHROPOIESIS-STIMULATING AGENTS (ESAs)

Most experts recommend maintaining HGB at 9-11 g/dL during ESA therapy. Iron stores should be replenished prior to initiation of therapy with an ESA. Consult a nephrologist for assistance in ESA dosing. The conversion rate of epoetin alfa to darbepoetin is ~225–260 units of epoetin alfa to 1 mcg darbepoetin alfa.

Darbepoetin alfa (Aranesp®)

Indication: Anemia of CKD; begin therapy at HGB <10 g/dL, if TSAT >20% and ferritin >100 ng/mL

Single-dose vial: 25, 40, 60, 100, 150, 200, 300, and 500 mcg

CKD: 40–100 mcg subcutaneously every 1–4 weeks (0.45 mcg/kg/weekly)

Therapy is initiated weekly and may be extended to longer intervals when HGB is stabilized

Consult nephrologist for assistance in appropriate dosing

PACKAGE INSERT: http://pi.amgen.com/united_states/aranesp/ckd/aranesp_pi_hcp_english.pdf

Epoetin alfa (recombinant human erythropoietin; Epogen®)

Indication: Anemia of CKD; begin therapy at HGB <10 g/dL

Single-dose vial: 2000, 3000, 4000, 10,000, and 40,000 units

Multi-dose vial: 20,000 units (20,000 units per 1 or 2 mL)

CKD: 10,000–40,000 units subcutaneously every 1–4 weeks (50–100 units/kg/weekly).

Consult nephrologist for assistance in appropriate dosing

PACKAGE INSERT: http://pi.amgen.com/united_states/epogen/epogen_pi_hcp_english.pdf

IRON THERAPY (ON EMPTY STOMACH)

Iron therapy may be initiated at any level of hemoglobin. The degree and mode of replenishment depend on the degree of deficiency and tolerability of the patient to oral iron or IV iron therapies. Iron should be administered to replenish and maintain iron stores to the following levels.

TSAT >20% and ferritin >100 ng/mL in CKD stages 3–5. Consult a nephrologist for assistance in appropriate dosing of parenteral iron and ESAs, which should not be initiated until the HGB is <10 g/dL

Oral formulations

These agents should only be taken on an empty stomach. Take oral iron 2 hours before or 4 hours after antacids and at least 1 hour after thyroid hormone. When effective at replenishing and maintaining iron stores, oral iron formulations are preferred in non-dialysis CKD patients. However, oral iron agents are tolerated poorly by many patients and also, the dose required to replenish iron stores is often greater than can be delivered in a timely fashion, thus necessitating parenteral iron. ESRD patients on chronic hemodialysis (HD) receive IV iron at HD and should not receive concomitant oral iron products. Any iron preparation, oral or IV, may be concurrently administered with an ESA.

Ferrous sulfate

Indication: Iron replacement and repletion therapy in CKD

Oral and liquid preparations with 100–325 mg ferrous sulfate (20% elemental iron)

CKD: typical dose is 1–2, 325 mg ferrous sulfate tablets, 3 times daily

Ferrous fumarate

Indication: Iron replacement and repletion therapy in CKD

Oral and liquid preparations with 90–324 mg ferrous fumarate (33% iron)

CKD: typical dose is 1–2, 325 mg ferrous fumarate tablets, 3 times daily

Intravenous formulations

Iron dextran, low molecular weight (INFeD®)

Indication: Iron replacement and iron repletion therapy in CKD

Single-dose vial: 50 mg iron per 1 mL in 2- or 10-mL vials

CKD: 500–1000 mg iron as 2 separate doses of 250–500 mg IV, as required to replenish/maintain iron stores

- Standard dilution: 500–1000 mg iron in 250–1000 mL of normal saline.
- Only FDA-approved as a 100 mg IV dose, following a 25 mg IV test dose.
- Anaphylactoid reaction rate is ~0.7%.

PACKAGE INSERT: http://pi.watson.com/prescribing_info.asp?type=pi&product_group=1251

Ferric gluconate (Ferrlecit®)

Indication: Iron replacement and iron repletion therapy in CKD

Single-dose ampule: 62.5 mg iron per 5 mL (12.5 mg/mL)

CKD: 500–1000 mg iron as 125-mg dose infusions, as required to replenish/maintain iron stores

- Undiluted, slow IV push: 125 mg iron over 10 minutes.
- Standard dilution for infusion is 125 mg iron in 100 mL normal saline.
- Delivery rate not to exceed 250 mg iron over 60 minutes.
- Product is FDA-approved in ESRD as a 125-mg dose IV.

PACKAGE INSERT: <http://products.sanofi-aventis.us/ferrlecit/ferrlecit.html>

Iron sucrose (Venofer®)

Indication: Iron replacement and iron repletion therapy in CKD

Single-dose vial: 100 mg iron per 5 mL (20 mg/mL)

CKD: 500–1000 mg iron as 100–300-mg infusions, as required to replete/maintain iron stores

- Undiluted slow IV push: 100–200 mg over 2–5 minutes.
- Standard dilution for infusion is 100 mg iron in 100 mL normal saline.
- Delivery rate: <150 mg iron over 60 minutes, *ie*, 300 mg over 120 minutes.
- Product is FDA-approved for CKD stages 3–5, including ESRD.

PACKAGE INSERT: venofer.com/VenoferHCP/images/IN2340%20Rev%2010_05.pdf

Ferumoxylol (Feraheme®)

Indication: Iron replacement and iron repletion therapy in CKD

Single-dose vial: 510 mg iron per 17 mL (30 mg/mL)

CKD: 510 mg iron IV with a second 510 mg dose IV 3-8 days later, as required to replete/maintain iron stores

- No test dose is required.
- Undiluted slow iv push: 510 mg in >17 seconds.
- Delivery rate not to exceed 30 mg per second.
- Product is FDA-approved for CKD stages 3–5, including ESRD.
- Ferumoxylol may affect the diagnostic ability of MRI for up to 3 months. Gd-based studies should be conducted prior to ferumoxylol administration.

PACKAGE INSERT: <http://www.feraheme.com/documents/Feraheme%20PI.pdf>

PHOSPHORUS BINDERS (ALWAYS TAKEN WITH MEALS)

Calcium acetate (PhosLo®)

Indication: P-binder therapy in CKD

GelCap or tablet: 667 mg (25% elemental Ca/169 mg elemental Ca)

CKD: 1–3 capsules taken with meals up to 3 times daily

Consult Nephrology if daily elemental Ca dosage exceeds 1000 mg (≥6 capsules daily)

- FDA-approved for CKD stages 1-5 and ESRD..

Calcium carbonate (Tums® and others)

Indication: P-binder therapy in CKD

Multiple preparations: 400–1250 mg (40% is elemental Ca) per unit dose

CKD: 500 mg elemental Ca taken with meals up to 3 times daily

Sevelamer carbonate (Renvela®)

Indication: P-binder therapy in CKD

Renvela® Tablet: 800 mg tablet or Renvela® Powder: 0.8 g or 2.4 g packets

CKD: 800–2400 mg taken with meals up to 3 times daily

Consult Nephrology if daily sevelamer hydrochloride dose is >4800 mg

PACKAGE INSERT: renvela.com/docs/renvela_PI.pdf (FDA-approved for CKD stage 5)

Lanthanum carbonate (Fosrenol®)

Indication: P-binder therapy in CKD

Tablet: 500, 750, and 1000 mg tablets

CKD: 500–1000 mg taken with meals up to 3 times daily

Consult Nephrology if daily lanthanum carbonate dose is >3750 mg

PACKAGE INSERT: http://pi.shirecontent.com/PI/PDFs/Fosrenol_USA_ENG.pdf

- FDA-approved for CKD stage 5.

Sucroferric oxyhydroxide (Velphoro®)

Indication: P-binder therapy in CKD

Tablet: 500 mg tablet (500 mg elemental iron, equivalent to 2,500 mg sucroferric oxyhydroxide)

CKD: 500 mg taken with meals up to 3 times daily

PACKAGE INSERT: <http://www.velphoro.us/>

<http://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=237da26c-f38c-4faa-93ad-735e71c9d0c1&type=pdf&name=237da26c-f38c-4faa-93ad-735e71c9d0c1>

- FDA-approved for CKD patients on dialysis.

Ferric citrate (Auryxia®)

Indication: P-binder therapy in CKD

Tablet: 1000 mg tablet (210 mg elemental iron, equivalent to 1 g ferric citrate)

CKD: 2000–4000 mg taken with meals up to 3 times daily

PACKAGE INSERT: http://keryx.com/wp-content/uploads/Auryxia_PI_Keryx_112014.pdf

- FDA-approved for CKD patients on dialysis.

VITAMIN D

Rationale for vitamin D treatment in CKD is to replenish vitamin D stores, not to suppress PTH.

Ergocalciferol (D₂; Calciferol®, Drisdol®)

Indication: Nutritional vitamin D deficiency, *eg*, 25(OH)D level <30 ng/mL

Softgel: 1.25 mg (50,000 IU)

CKD: 50,000 IU once weekly × 4 then once monthly × 8, if 25(OH)D <15 ng/mL, unless corrected Ca is >9.5 g/dL and/or P >4.6 mg/dL, and 50,000 IU once monthly × 6 if 25(OH)D is 15–30 ng/mL unless corrected Ca is >9.5 g/dL and/or P >4.6 mg/dL

- Note, longer durations of weekly vitamin D therapy may be required.
- Monitor levels every 3 months, then continue once weekly or monthly dosing as determined by clinical circumstances and vitamin D levels.

Cholecalciferol (D3)

Indication: Nutritional vitamin D deficiency, *eg*, 25(OH)D level <30 ng/mL

Tablet: 1000 IU, 1750 IU, 2000 IU or Softgel: 1000 IU, 2000 IU, and 5000 IU

Renally formulated vitamin preparation (Vital-D-Rx™) contains 1750 IU cholecalciferol

CKD: 1750–5000 IU once daily.

ACTIVE VITAMIN D STEROLS

Active vitamin D sterols should only be initiated when 25(OH)D level >30 ng/mL. Consult nephrologist if PTH remains elevated after 3 months of therapy. In CKD, vitamin D has rarely caused hypercalcemia at recommended doses. ESRD patients generally receive active vitamin D sterols.

Calcitriol [1 α ,25(OH)2D3; Rocaltrol®]

Indication: Prevention and treatment of SHPT in CKD stages 3–5

Capsule: 0.25 and 0.5 mcg

Intravenous Solution: 1 mcg/mL or 2 mcg/mL vial

CKD Stage 3: iPTH >70 pg/mL: 0.25-0.5 mcg once daily with monitoring of corrected Ca and P every 2 weeks initially

CKD Stage 4: iPTH >110 pg/mL: 0.25–0.50 mcg once daily with monitoring of serum corrected Ca and P every 2 weeks initially

CKD Stage 5/ESRD: If iPTH >150 pg/mL: Initiate 0.5 mcg per HD (titrated to goal PTH, maximal dose, 2 mcg/HD) with monitoring of serum corrected Ca and P every 2 weeks initially

PACKAGE INSERT: rocheusa.com/products/rocaltrol/pi.pdf

Doxercalciferol [1 α (OH)D2; Hectorol®]

Indication: Prevention and treatment of SHPT in CKD stages 3–5

Capsule: 0.5, 1.0, and 2.5 mcg capsule

Intravenous Solution: 2 mcg/mL vial

Maximum daily dose in CKD Stage 3 or 4: 3.5 mg

CKD Stage 3: iPTH >130 pg/mL: 1.0 mcg once daily with increases of 0.5 mcg and monitoring of serum corrected Ca and P every 2 weeks initially

CKD Stage 4: iPTH >130 pg/mL: 1.0 mcg once daily with increases of 0.5 mcg and monitoring of serum corrected Ca and P every 2 weeks initially

CKD Stage 5/ESRD: iPTH >150 pg/mL: Initiate 1–2 mcg per HD (titrated to goal PTH, maximum dose, 8 mcg per HD treatment with monitoring of serum corrected Ca and P every 2 weeks initially

PACKAGE INSERT: hectorol.com/~media/Files/HectorolUS/Hectorol%20Capsule%20PI%20Text_2006-01.pdf

Paricalcitol [19-nor-1 α -(OH)2D2; Zemplar®]

Indication: Prevention and treatment of SHPT in CKD stages 3–5

Capsule: 1.0, 2.0, and 4.0 mcg capsule

Intravenous Solution: 2 mcg/mL and 5 mcg/mL vial

CKD Stages 3–4: iPTH <130-600 pg/mL: 1.0 mcg once daily or 2.0 mcg 3 times weekly, with dose increases of 1.0 mcg daily and monitoring of serum Corr Ca and P every 2 weeks. iPTH >500 pg/mL: 2.0 mcg once daily or 4.0 mcg 3 times weekly, with dose increases of 1.0 mcg daily and monitoring of serum corrected Ca and P every 2 weeks

CKD Stage 5/ESRD: If iPTH >130 pg/mL: Initiate 1–2 mcg per HD (titrated to goal iPTH, maximum dose 15 mcg per HD treatment) with monitoring of serum corrected Ca and P every 2 weeks initially

PACKAGE INSERT: rxabbott.com/pdf/Zemplarcappi.pdf

CALCIMIMETICS

Cinacalcet (Sensipar®)

Indication: Treatment of SHPT in ESRD

Tablet: 30, 60, and 90 mg tablet

Maximum daily dose: 180 mg

CKD Stage 5/ESRD: Initiate 30 mg once daily (titrated every 2–4 weeks to goal PTH) with monitoring of serum corrected Ca and P every 2 weeks

- Initiate cautiously in patients with Ca <8.4 mg/dL.
- Monitor frequently for hypocalcemia during therapy.
- **Intact PTH levels should only be obtained at least 8 hours after dose is taken.**

PACKAGE INSERT: pi.amgen.com/united_states/sensipar/sensipar_pi_hcp_english.pdf

RENAL-FORMULATED MULTIVITAMINS

Non-iron containing formulations

ESRD patients should be prescribed non-iron containing formulations as they receive IV iron at HD. ESRD patients should take their vitamin in the evening

Renal Softgels, NephPlex® Rx, Nephrocaps® Nephro-Vite Rx®: 1 tablet once daily

Indication: Vitamin supplementation in CKD stages 3–5

Tablet/Softgel: B vitamins, vitamin C 40–60 mg and folic acid 1 mg

Renal Vital-Rx™ for CKD: 1 tablet once daily

Indication: Vitamin supplementation in CKD stages 3–5, with vitamin D

Tablet: 1750 IU cholecalciferol (D3), B vitamins, and folic acid 1 mg

Iron-containing formulations

Nephron FA® for CKD: 1 tablet twice daily

Indication: Vitamin supplementation in CKD stages 3–5, with iron deficiency

Tablet: B vitamins, vitamin C 40 mg, folic acid 1 mg, sodium docusate 75 mg, and ferrous fumarate 200 mg (66 mcg elemental iron)

Niferex® for CKD: 1 capsule once daily

Indication: Vitamin supplementation in CKD stages 3–5, with iron deficiency

Tablet: Vitamin B12 25 mcg, folic acid 1 mg, and iron polysaccharide complex (150 mg elemental iron)

KEY SUMMARY POINTS

Do not take Ca-based P-binders with iron salts or NaHCO₃

Dietary and prescribed elemental Ca should not exceed 1000–1200 mg daily

Ca-based binders should not be initiated in those with a Ca >10.2 mg/dl or where there is evidence of vascular calcification

Consult Nephrology if prescribed elemental Ca >1200 mg, corrected Ca >10.2 mg/dL or P >4.6 mg/dL

CKD WEBSITES OF INTEREST

American Society of Nephrology:

<http://asn-online.org>

Greenfield Health Systems:

<http://GHSrenal.com>

Immunizations:

http://www.acponline.org/clinical_information/resources/adult_immunization/

Kidney Disease: Improving Global Outcomes (KDIGO™):

<http://kdigo.org>

National Kidney Disease Education Program:

<http://nkdep.nih.gov>

National Kidney Foundation:

<http://www.kidney.org>

National Kidney Foundation of Michigan:

<http://www.nkfm.org>

COMMENTS TO AUTHORS

Please direct comments regarding this publication to the Editors by email:

Jerry Yee: **JYee1@Hfhs.Org** and Gregory Krol: **GKrol1@Hfhs.Org**

WEBSITE MANAGEMENT

The reference list and updated editions of CHRONIC KIDNEY DISEASE (CKD): CLINICAL PRACTICE RECOMMENDATIONS FOR PRIMARY CARE PHYSICIANS AND HEALTHCARE PROVIDERS — A COLLABORATIVE APPROACH (EDITION 7.0) can be obtained from Greenfield Health Systems website in Adobe portable document format (pdf), with online references.

GHSRENAL.COM/CKD/HFHS_CKD_GUIDELINES_V7.0.PDF

Webmaster: Gerard Zasuwa at **Gzasuwa1@Hfhs.Org**

PURCHASING INFORMATION

Jerry Yee, MD

Henry Ford Hospital, Division of Nephrology and Hypertension

2799 West Grand Blvd., CFP-514, Detroit, MI 48202-2689

JYee1@Hfhs.Org

CHRONIC KIDNEY DISEASE CHECKLIST

CKD IDENTIFICATION

- MDRD GFR <60
- UPC ≥0.2
- ACR ≥30 mg/g
- Hematuria
- Kidney stones
- Structural defect
- Small kidney sizes

CVD RISK REDUCTION

- Aspirin
- Beta blocker
- Smoking cessation
- Weight reduction
- Statin
- ACEI or ARB

IMMUNIZATIONS

- HBV (and anti-HBV titer)
- PPV13
- PPSV23
- Tdap, booster
- Zoster vaccine (live)

HYPERTENSION

- BP <140/90 mmHg
- Diuretic
- ACEI or ARB
- JNC 7 Indication(s)
- UNa <100 mEq/24-h
- UPC <0.2

ANEMIA OF CKD

- HGB <12 g/dL (female)
<13 g/dL (male)
- R/O blood loss and other causes of anemia
- TSAT <20%
- Ferritin <100 ng/mL
- Vit B12 & Folate
- Iron therapy: po / iv
- Inflammation
- ESA treatment

RISK ASSESSMENT

- Hypertension
- Diabetes
- Metabolic syndrome
- Morbid obesity
- Elevated LDL-C
- Heart failure
- Family history of CKD
- Racial/ethnic groups
- Autoimmunity
- Environmental toxin
- Nephrotoxic drug
- Cigarette smoking
- Preeclampsia
- Recurrent UTIs
- Prior Hx of AKI/ARF
- Multiple kidney stones

PROTEINURIA

- ACEI or ARB
- DRI or MRA
- BP optimized
- NDHPCCB
- Aldosterone or epleronone
- Pentoxifylline

CKD-MBD

- Ca & P in normal range (at any iPTH level)
- iPTH 130–600 pg/mL
- Trend Alk Phosphatase
- Extraskelatal calcification
- 25(OH)D >30 ng/mL
- Vitamin D2 or D3
- Active vitamin D
- P-binder Rx

METABOLIC ACIDOSIS

- HCO₃ 22–26 mEq/L
- NaHCO₃ Rx
- Protein restriction

RULE OUT AKI

- R/O obstruction
- R/O hypovolemia
- Heart failure
- Hypotension
- Pseudo-AKI, e.g., cimetidine, trimethoprim
- Nephrotoxic drug
- NSAID, COX-1/2
- Rhabdomyolysis
- Radiocontrast agent
- Phosphate cathartic

DYSLIPIDEMIA

- Statin therapy per CV risks and ACC/AHA calculator

RENAL NUTRITION

- Protein restriction
- Na & K restriction
- P restriction
- Renal MVI
- Caloric restriction
- Renal dietitian evaluation

DIABETES

- BP <140/90 mmHg
- ACEI or ARB
- A1C ~7%
- ACR <30 mg/g
- Glipizide preferred
- Statin therapy

LATE-STAGE CKD

- Patient education
- Modality choice
- Medication reconciliation
- Adjust drug dose(s)
- Protect access arm
- Access evaluation
- Transplant referral
- Advanced directives
- End-of-life discussion

Abbreviations: *ALK Phos*, alkaline phosphatase; *MRA*, aldosterone receptor antagonist; *DRI*, direct renin inhibitor; *EAG*, estimated average glucose; *ESA*, erythropoiesis-stimulating agent; *ACR*, albumin-to-creatinine ratio; *UPC*, urine protein-to-creatinine ratio; *TSAT*, transferrin saturation; *NDHPCCB*, non-dihydropyridine calcium channel blocker; *QIV*, quadrivalent inactivated influenza vaccine.

NEPHROLOGY CONSULTATION MAY BE CONSIDERED AT ANY STAGE OF CKD



DIVISIONS OF NEPHROLOGY & HYPERTENSION
AND GENERAL INTERNAL MEDICINE