

DIVISIONS OF NEPHROLOGY & HYPERTENSION
AND GENERAL INTERNAL MEDICINE



Chronic Kidney Disease (CKD)

Clinical Practice Recommendations
for Primary Care Physicians
and Healthcare Providers



A Collaborative Approach
(Edition 6.0)

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)

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Foreword

KIDNEY disease, some acute but mostly chronic remains the core of this **SIXTH EDITION** of **CHRONIC KIDNEY DISEASE (CKD): CLINICAL PRACTICE RECOMMENDATIONS FOR PRIMARY CARE PHYSICIANS AND HEALTHCARE PROVIDERS — A COLLABORATIVE APPROACH** by Editors Jerry Yee & Gregory D. Krol. This edition represents a significant departure from Editions 1–5. It is now multi-authored, underscoring the complexity of Chronic Kidney Disease, better known in the vernacular as CKD — a disease domain complex that is highly associated with a progressive cardiovascular disease burden. Aside from the multi-authorship of the **SIXTH EDITION**, this work provides exciting illustrations by Dunham Design and immaculate print quality by Dynamic Marketing. As with prior editions, the writing remains consistently concise, precise, and decisive.

INTERESTINGLY, the booklet was originally conceived and written for the Henry Ford Health System. However, like the automotive industry of the City of Detroit, it has significantly transcended its local borders. All told, more than 30,000 copies have been distributed within the United States, Puerto Rico, Mexico, and Canada since its original publication. From the first edition that provided textually based "nuts and bolts" management of CKD through its fifth edition, the booklet has gained in quality and size, while providing up-to-date information. The first edition brought to the fore the importance of the *eGFR* in the screening of this under-recognized entity, CKD. The second and third editions amplified the importance of the cardiovascular complications of CKD. The fourth and fifth editions emphasized evidence-based practice across the continuum of CKD care and provided colorful easy-to-read diagrams. Essentially, it is not a textbook steeped in information that is outdated by the time of printing, but a periodical that reliably informs Primary Care Physicians about CKD essentials. Overall, the content is current and crystallized, ready for translation into clinical practice.

DEDICATED readings of the **HENRY FORD CKD BOOKLET** — as it is known outside of the Henry Ford Health System — are suggested in order to fully comprehend the complexity of CKD. It should be on the "must have" list of Internal Medicine housestaff and Nephrology fellows-in-training as it continues to remain popular among the younger generation of physicians, nurses, and mid-level providers. Its Internet presence accounted for 1,000 downloads in 2010. Translation into other languages is under consideration and there is clamor for mobile device distribution. Most importantly, the booklet has received plaudits from national organizations and societies, and its format and content have been adapted by multiple agencies, including the Michigan Quality Initiative Consortium (MQIC) and the National Kidney Foundations of Michigan and Illinois.

NEW information regarding the *eGFR* is highlighted in the **SIXTH EDITION**. As the underpinning of the stages of CKD, knowledge regarding the functionality of the *eGFR* has matured, with validation across more populations. Standardization of the serum creatinine by isotope dilution mass spectrometry is occurring increasingly across clinical laboratories in the United States. This recalibration lowers the *eGFR* by 6%. Notwithstanding this improvement in *eGFR* reporting, combining this parameter with proteinuria more clearly delineates the risk category of a CKD patient. Principally, proteinuria of $\geq 2+$ on dipstick analysis or within the macro-albuminuric range portends a poorer renal outcome. Lastly, this edition prominently features an international perspective on CKD-Mineral and Bone Disorder.

EXPERT and representation of the respective clinical disease domains of CKD distinguishes and enhances this version. Now, this mini-compendium renders an even broader perspective to CKD with the following contributions:

DIABETIC KIDNEY DISEASE by Susanne Nicholas (UCLA)

HYPERTENSION by Debbie Cohen and Raymond Townsend (Univ. of Penn)

PROTEINURIA by Julie Lin (Brigham and Women's Hospital)

ANEMIA OF CKD by Anatole Besarab (Henry Ford Hospital)

NUTRITION IN CKD by M. Cristina Kilates (Henry Ford Hospital)

CKD-MINERAL AND BONE DISORDER by L. Tammy Ho (Univ. of Chicago)

MEDICATION-RELATED PROBLEMS & SELECTED AGENTS by Carol Moore (Henry Ford Hospital)

KIDNEY REPLACEMENT THERAPY by Jariatul Karim & Lalathaksha Kumbar (Henry Ford Hospital)

WEBSITE MANAGEMENT by Gerard Zasuwa (Henry Ford Hospital)

Each chapter follows the outlines of the previous versions: brief introduction, evidence base, pathophysiology, and guideline- or expert consensus-based diagnosis and therapy. **THE PLAN OF CARE & ACTION PLAN** and the **CHECKLIST** remain outstandingly simple, informative, and efficient formats to present a large body of information into digestible learnings. These two invaluable components of the **SIXTH EDITION** distill numerous guidelines and consensus-based recommendations by level of evidence and grade of quality to improve our practices.

YES! is the feeling that I had upon completing the **SIXTH EDITION**. You, the reader should review it, digest it, practice it, and also, *enjoy* it. I certainly did and still do.

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CHRONIC KIDNEY DISEASE STAGING AND PROGRESSION by Gregory D. Krol

Introduction

Optimal management of patients with chronic kidney disease (CKD) requires appropriate interpretation and use of the markers and stages of CKD, early disease recognition, and collaboration between primary care physicians and nephrologists. Because multiple terms have been applied to chronic kidney disease (CKD), *e.g.*, chronic renal insufficiency, chronic renal disease, and chronic renal failure, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative™ (NKF KDOQI™) has defined the all-encompassing term, CKD. Using *kidney* rather than *renal* improves understanding by patients, families, healthcare workers, and the lay public. This term includes the continuum of kidney dysfunction from mild kidney damage to kidney failure, and it also includes the term, end-stage renal disease (ESRD).

Definition and Interpretation

Management of CKD requires the clear understanding of its definition as proposed by the National Kidney Foundation (NKF). An informed interpretation of the **estimated glomerular filtration rate (*eGFR*) is required**, since the GFR is still considered the best overall index of kidney function in stable, non-hospitalized patients. Kidney damage is defined by any one of the following findings:

- a) pathologic kidney abnormalities
- b) persistent proteinuria
- c) other urine abnormalities, *e.g.*, renal hematuria
- d) imaging abnormalities
- e) $eGFR <60 \text{ mL/min}/1.73 \text{ m}^2$ on two occasions separated by ≥ 90 days and that is not associated with a transient, reversible condition such as volume depletion.

The 5 stages of CKD are based on *eGFR* (*see TABLE*).

CLASSIFICATION OF CHRONIC KIDNEY DISEASE

Stage	Estimated GFR (mL/min/1.73 m ²)	Comment
1	≥ 90	Normal GFR w/ proteinuria
2	60–89	Age-related decline in GFR w/proteinuria
3A 3B*	30–59	Low risk of progression to kidney failure
4	15–29	High risk of progression to kidney failure
5		
5D	<15	Kidney failure
5T		

*Because of greater cardiovascular disease risk and risk of disease progression at lower *eGFRs*, CKD Stage 3 is sub-divided into Stages 3A (45–59 mL/min/1.73 m²) and 3B (30–44 mL/min/1.73 m²). CKD Stage 5 includes patients that may require or are undergoing kidney replacement therapy. Designations 5D and 5T indicate end-stage renal disease patients who undergo chronic dialysis (5D) treatment or have undergone kidney transplantation (5T).

The *eGFR* is primarily determined by serum creatinine (SCr), and the preferred method for estimating GFR is the body surface area-normalized, 4-variable, Modification of Diet in Renal Disease Study (MDRD) Equation based on SCr, age, gender, and ethnicity.

$$\text{eGFR} (\text{mL/min}/1.73 \text{ m}^2) = 186 \times (\text{SCr})^{-1.154} \times (\text{Age})^{-0.203} \\ \times (0.742, \text{ if female}) \\ \times (1.212, \text{ if African American})$$

Replace the constant 186 with 175, if the laboratory uses a standardized SCr (IDMS method). This reduces *eGFR* by 6%.

eGFRs based solely on BUN and creatinine or by 24-h endogenous creatinine clearances, are not required for routine screening of CKD. As with all tests, the *eGFR* has limitations. *eGFR* calculations may be inaccurate in the following circumstances: acute hospitalizations, **acute kidney injury (AKI)/acute renal failure (ARF)**, malnutrition, major limb amputation, cirrhosis, severe obesity, and at the extremes of age. It is not recommended to use *eGFR* in lieu of SCr during AKI/ARF.

Improved *eGFR* equations, CKD-EPI and Cystatin-C equations, remain as research tools, and the 4-parameter MDRD *eGFR* remains the current gold standard. Regardless of the measure, most cases require appropriate appreciation of kidney function and must include an assessment of retrospective and prospective markers of kidney function aside from *eGFR*, including BUN and urinary protein excretion, in order to more completely assess etiology, stability, progression, or improvement in renal function, and to guide therapy.

Normal physiologic age-related changes in kidney function often lower GFRs to ~60–90 mL/min/1.73 m². The age-related decline in GFR is ~1 mL/min/1.73 m²/yr, beginning after 30–40 y.o. In addition and paradoxically, the reduction of muscle mass associated with aging may overestimate the GFR and potentially mislead the healthcare provider.

Notably, the majority of CKD Stage 3 or 4 patients will not develop CKD Stage 5/kidney failure (~1% risk). However, if other evidence of kidney disease is present, *eg*, proteinuria; imaging study revealing small (<9 cm by ultrasonography) or echogenic kidney(s), cysts or stones; resistant hypertension (HTN); or rapid or acute elevations of BUN and SCr, an etiology of CKD must be established and aggressive therapy is warranted. Generally, a kidney-specific imaging study (renal ultrasonogram, CT scan) is not required in the following clinical setting: *eGFR* >60 mL/min/1.73 m² with no proteinuria because the overwhelming majority of such studies are normal.

Epidemiology

Persons with CKD have significantly higher rates of morbidity, mortality, hospitalizations, and healthcare utilization. The prevalence of CKD Stages 2–5 has continued to increase since 1988 as have the prevalences of diabetes and hypertension, which are respectively etiologic in approximately 40% and 25% of CKD cases. The current estimate is that 26 million US persons >20 y.o. have CKD. However, 15.2 % is the more recent CKD prevalence estimate, based on 2003–2006 NHANES data of U.S. adults aged ≥20 y.o., a decrease from the 15.9% cited in the NHANES data collected from 1999–2002. This decrease was reflected in CKD Stage 1 as Stage 3 increased to 6.5% from 2003–2006. The prevalence of CKD Stages 4 and 5 has doubled since 1988–1999, but has remained stable since 2002 at 0.6%.

CKD stage prevalence from NHANES 2003–2006 by the CKD-EPI equation are Stage 1, 4.1%; Stage 2, 3.2%; Stage 3, 6.5%; and Stages 4 and 5 combined, 0.6%. Stratified by age, all CKD stages were more prevalent in persons aged ≥ 60 y.o. (39.4%) than in those aged 40–59 y.o. (12.6%) or 20–39 y.o. (8.5%). By educational level, CKD at any stage was more prevalent among persons with less than a high school education (22.1%) than in persons with at least a high school education (15.7%). CKD prevalence was greater among non-Hispanic blacks (15.6%), non-Hispanic whites (14.5%), and among other ethnicities (13.1%). The prevalences of diabetes and HTN in African Americans with CKD were 60.6% and 96%, respectively, compared to Caucasian prevalences of 45.7% and 90.7%, respectively (United States Renal Data Survey, 2010). Also, CKD prevalence was higher in diabetics than non-diabetics (40.2% v 15.4%), in those with cardiovascular disease (CVD) than in those without it (28.2% v 15.4%), and in those with HTN than in those without it (24.6% v 12.5%).

For 2010, the estimated cost of ESRD is \$28 billion, and projected as \$54 billion by 2020. In the last quarter of 2009, the prevalence of ESRD (N=572,569, includes kidney-transplanted patients) was greater than in 2005 (N=485,012). In terms of incidence or newly-initiated ESRD patients, diabetes was etiologic in 37.5%, HTN 24.4%, glomerulonephritis 14.8%, cystic disease 4.7%, and others 18.6%. African American patients are 3.7 times more susceptible for development of ESRD, and Native Americans and Asians are 1.9- and 1.3 times more likely to develop ESRD.

Recognition, Screening and Stratification of CKD

Only 5% and 10% of the general Medicare population undergoes a screening urinalysis or a SCr, respectively. The NKF KEEP (Kidney Early Evaluation Program) screening program is a free community-based survey that identified individuals with CKD over the past 10 years. Since its inception, KEEP has screened >150,000 at-risk individuals with diabetes and/or HTN or those with a first-order relative with “known” kidney disease, diabetes, or HTN. Urine was evaluated for hematuria, pyuria and microalbuminuria. The KEEP population was better educated, had more insurance, and a higher prevalence of HTN, obesity, and diabetes than the NHANES cohort. Specifying CKD as “a low estimated GFR and/or presence of microalbuminuria,” 26% of KEEP/high risk participants had CKD nearly twice that noted in the general population NHANES study. Strikingly, only 2.0% of these high risk patients self-reported a history of kidney disease. These consistent findings over the past decade underscore the lack of recognition and education regarding CKD and the missed opportunities to better manage, prevent, and reduce CKD’s associated premature and increased comorbidities, mortality, and high healthcare costs.

Stratification of CKD into 5 stages focuses the clinician on CKD management aspects. The metabolic abnormalities of CKD evolve in a fairly well established pattern. Anemia of CKD and CKD-Mineral and Bone Disorder (CKD-MBD) often begin during Stage 3. Hypertension is aggravated in CKD Stages 3–5 and acid-base balance, dyslipidemia, and glucose homeostasis become deranged later. During Stages 3–5, reductions in medication dosages may be required because of a lower $eGFR$. The disease domains of HTN, proteinuria, and hyperlipidemia may appear at any stage and therapy must be targeted to specific levels. Lastly, screening for metabolic complications of CKD is typically not recommended in persons with $eGFR >60$ mL/min/1.73 m² and no albuminuria, unless a genetic disorder with a high degree of penetrance is present (autosomal dominant polycystic kidney disease).

The development of CKD multiplies the mortality risk associated with CVD, particularly in CKD Stages 4 and 5. CKD increases CVD morbidity and mortality risks in diabetics by 2- to 4-fold and

in patients with HTN and diabetes by 4- to 8-fold. Further, CKD-attributable CVD risk increases rapidly through CKD Stages 3–5 by several-fold.

At-Risk Groups

CKD carries a 3-fold higher risk of death. Therefore, clinical risk factors for the initiation and/or progression of CKD should be ascertained during routine healthcare encounters and periodically, thereafter. Individuals at increased risk for CKD must be tested for kidney damage and have their *eGFRs* evaluated more frequently. In addition, aggressive risk factor reduction should be carried out in individuals at increased risk for CKD even when CKD is not clinically apparent. A CKD risk factor classification, based on a cardiovascular scheme follows (*see Table, p. 9*).

Hypertension (prevalence 74.5 million) and diabetes (prevalence 23.6 million) are the two most important CKD risk factors. Overall, diabetes is prevalent in 44% of the ESRD population and in HTN 28%. Together, these two disorders constitute 72% of the causes of ESRD. Recently, insulin resistance, obesity, and the metabolic syndrome have been implicated as risk factors.

A family history of kidney disease is a risk factor for CKD. Nearly 24% of ESRD patients have an afflicted first-degree relative, an association that is much stronger in African Americans than whites. Other CKD risk factors include the following: a prior history of AKI/ARF, urinary tract obstruction, stones, reduced kidney mass (solitary kidney), nephrotoxins (analgesics, aminoglycosides, amphotericin, radiocontrast), autoimmunity (SLE), low birth weight, preeclampsia, sociodemographics (older age, male gender, reduced access to healthcare, low income/education level, hazardous chemical or environmental exposures), and certain ethnicities: African American, Native American, Hispanic, and Asian.

Acute Kidney Injury (AKI)/Acute Renal Failure (ARF)

The term ARF is being increasingly supplanted by the term AKI, but precise and consensus-based definitions of AKI have only recently been introduced. AKI is common and occurs at a rate of 522 cases/100,000 pt-yr. Thus far, AKI staging systems that define renal risk, injury, and failure have not consistently predicted renal or morbid outcomes due to select patient-specific demographics, preexisting CKD and comorbidities (*see TABLE, P. 8*). Such systems require further refinement.

AKI often complicates 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. The optimal method of establishing CKD is by examining medical records; renal imaging is the next best method, *eg*, kidney ultrasonography (US) or CT scan. By US, normal, adult kidney sizes are 10–12 cm in the sagittal plane; however, size discrepancies up to 37% may be found.

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 *eGFR* returns to baseline. Rapid recovery of AKI (<7 d) generally requires minimal follow-up, unless there was pre-existing CKD.

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 70% 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 cases of hospital-acquired AKI. Administration of pharmaceuticals such as NSAIDs, antibiotics (aminoglycosides), or iodinated radiocontrast media can induce AKI/ARF. Lastly, volume depleted patients are more susceptible to radiocontrast-induced nephropathy. This disorder accounts for 3–17% cases of hospital-acquired ARF, and this is often preventable (*see MEDICATION-RELATED PROBLEMS IN CKD, p. 51*).

CLASSIFICATION OF ACUTE KIDNEY INJURY / ACUTE RENAL FAILURE

Stage	Serum Creatinine	Urine Output
1 Risk	SCr ↑ of ≥ 0.3 mg/dL SCr ↑ of ≥ 1.5 -2.0-fold	<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

CKD patients undergoing cardiothoracic and/or other emergent surgical procedures that occur with blood loss, sepsis and/or radiocontrast administration have highly increased risk for AKI/ARF. In these circumstances, the GFR cannot be reliably determined since it depends on steady-state creatinine generation and elimination. CKD patients treated with anti-RAS medications commonly develop elevations of BUN and SCr. The potential benefits of chronic anti-RAS treatment likely outweigh a mild stable decline of GFR from ACEI and 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 should generally be continued.*

Progression of Chronic Kidney Disease (CKD)

Fortunately, most patients do not progress from CKD Stage 3 to 5, but ~17% of CKD Stage 4 patients will progress to Stage 5 and ~1% of CKD Stage 3 patients will. However, 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 ESRD. Comprehensive systems targeting early recognition, prevention and management, and treatment by primary care physicians and physician extenders are required at this critical stage in collaboration with nephrologists.

Aside from uncontrolled HTN, one of the strongest prognosticators for declining kidney function is proteinuria. A “spot” urine protein-to-creatinine ratio (UPC) or urine albumin-to-creatinine ratio (UACR) quantifies proteinuria. Generally, UPCs <0.5–1 g protein per g creatinine predict a more favorable prognosis, while UPCs >1 predict more rapid functional decline and more intensive evaluation, *ie*, kidney biopsy.

Modifiable risk factors for CKD progression are HTN, diabetes, morbid obesity, metabolic syndrome, hypercholesterolemia, heavy consumption of non-narcotic analgesic preparations, anemia, and cigarette smoking. Perhaps the best prognosticator for CKD progression is the rate of decline of GFR. Rates of decline >4 mL/min/1.73 m² per year are associated with greater progression risk. In diabetics, annual *eGFR* rates of decline ≥10–12 mL/min/1.73 m² may occur. In heart failure, *eGFR* 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, 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, dysregulated calcium and phosphate metabolism, ECF volume expansion, and the intrinsic chronic inflammatory state of CKD. 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.

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)

COMMENTS

- Determine whether AKI is present in all cases of CKD.
- Evaluate and correct all potentially reversible causes of reduced GFR.
- A partial list of common causes of AKI with acute GFR reductions follows.
 - a) Altered intrarenal hemodynamics: common agents that decrease GFR, eg, NSAIDs (COX-1/-2 inhibitors), ACEIs, and ARBs.
 - b) Drug-induced acute tubulointerstitial nephritis: commonly implicated agents include penicillins, cephalosporins, sulfonamides, rifampin, phenytoin, fluoroquinolones and NSAIDs (non-hemodynamically related ARF).
 - c) ECF volume depletion, especially with NSAID, ACEI, or ARB drug co-administration
 - d) Heart failure
 - e) Hypotension
 - f) Liver disease
 - g) Nephrotoxins: aminoglycosides, pentamidine, foscarnet, amphotericin, *cis*-platinol, and multiple chemotherapeutic agents
 - h) Radiocontrast medium (eg, iodine- or gadolinium-based contrast agent-containing diagnostic procedures)
 - i) Rhabdomyolysis
 - j) Urinary tract outlet obstruction must always be ruled out, particularly in males

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CONSULTATION by Jerry Yee

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 and 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, including AMA, AHRQ, and ABIM to improve CKD education for those who must engage and practice it.

Timely consultation by the nephrologist in CKD promotes improved clinical outcomes and reduces the total cost of care for the patient and the public. It has been estimated that healthcare savings of \$18.5 to \$60.6 billion would accrue by reducing the CKD progression rate by 10–30% over the next decade. **The optimal time for consultation is during CKD Stages 3–4.** As *eGFR* falls below 45 mL/min/1.73 m² (CKD Stage 3B), there is a significant increase in CVD risk. 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 proteinuria. Estimating the GFR is important because this process not only optimizes the time of referral, but also delineates the progression rate of CKD.

Urinary abnormalities, electrolyte imbalances, uncontrolled HTN, or metabolic abnormalities constitute reasons to initiate nephrological consultation. Certain conditions such as malignancy, dementia, multiple comorbidities, or an advanced directive may preclude referral to a nephrologist.

Glomerular Filtration Rate (GFR)

MDRD Study GFR <60 mL/min/1.73 m²
Cockcroft-Gault CrCl <60 mL/min/1.73 m²

Serum Creatinine (SCr)

Males	≥1.5–1.7 mg/dL on two separate occasions, separated by at least 2 wk, unless AKI/ARF is established
Females	≥1.1–1.3 mg/dL on two separate occasions, separated by at least 2 wk, unless AKI/ARF is established

COMMENTS

- Normal age-related decline in GFR is $\sim 1 \text{ mL/min}/1.73 \text{ m}^2/\text{yr}$ after age 30–40 y.o. However, there is significant normal variation. Trend analysis at the individual level is key.
- An unexplained, non-reversible rapid decline in GFR is considered to be $\geq 4 \text{ mL/min}/1.73 \text{ m}^2/\text{yr}$ and should prompt a nephrology consultation.
- GFR is the principal but not the only determinant of SCr levels. Hypercatabolic states or muscle injury may increase the SCr as can increased creatine ingestion (supplement).
- Cimetidine, trimethoprim, corticosteroids, pyrimethamine, phenacetin, salicylates, and vitamin D metabolites can elevate SCr, but do not reduce GFR.
- Cimetidine, trimethoprim, pyrimethamine, probenecid, triamterene, amiloride, and salicylates inhibit tubular creatinine secretion.
- Cephalexin, flucytosine and nitrofurantoin interfere with the creatinine assay and increases the plasma measured level *ex vivo*.
- Tetracycline (anti-anabolic), GI bleeding, and glucocorticoid steroids increase protein catabolism and increase BUN but not SCr levels.

Electrolyte Abnormalities

Na	<130 mEq/L or >147 mEq/L in absence of diuretics
K	<3.5 mEq/L w/ K replacement or in absence of diuretics >5.5 mEq/L w/ dietary K restriction
HCO ₃	<22 mEq/L or >28 mEq/L

Resistant (“refractory” or “difficult-to-control”) Hypertension

- Any BP With any of the following:
- evidence of target organ damage, *eg*, LVH
 - lack of BP control
 - malignant HTN, *eg*, stroke, AKI/ARF, AMI, heart failure

SBP/DBP	$\geq 140/90$ on 3 medications at full doses, including a diuretic, in non-diabetic patients without CKD
SBP/DBP	$\geq 130/80$ on 3 medications at full doses, including a diuretic, in CKD and/or diabetic patients

Proteinuria

UA Dipstick	$\geq 1+$ (separate occasions, separated by at least 2 wk)
UPC	>0.2 (normal range: <0.2)
UACR	>30 mg albumin/g creatinine (microalbuminuria) >300 mg albumin/g creatinine (macroalbuminuria)

Anemia of CKD

Hb	<12 (female) or <13.5 (male) g/dL, with adequate iron availability by parameters: TSAT >20% and ferritin >100 ng/mL (CKD Stage 5, ferritin >200 ng/mL)
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Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)

Alkaline Phosphatase	≥ 200 IU/L in absence of liver disease with CKD Corrected Calcium <8.8 mg/dL or >10.2 mg/dL
HCO ₃	<22 mEq/L or >28 mEq/L
Phosphorus (P)	>4.6 mg/dL in CKD Stages 3–4
iPTH (intact)	Increasing iPTH levels with time at any CKD stage iPTH elevation above normal range, in combination with hypercalcemia, especially in early CKD stages >150 pg/mL on initial evaluation
Imaging Study	
DEXA	Evidence of vascular or cardiac calcification and/or bone loss

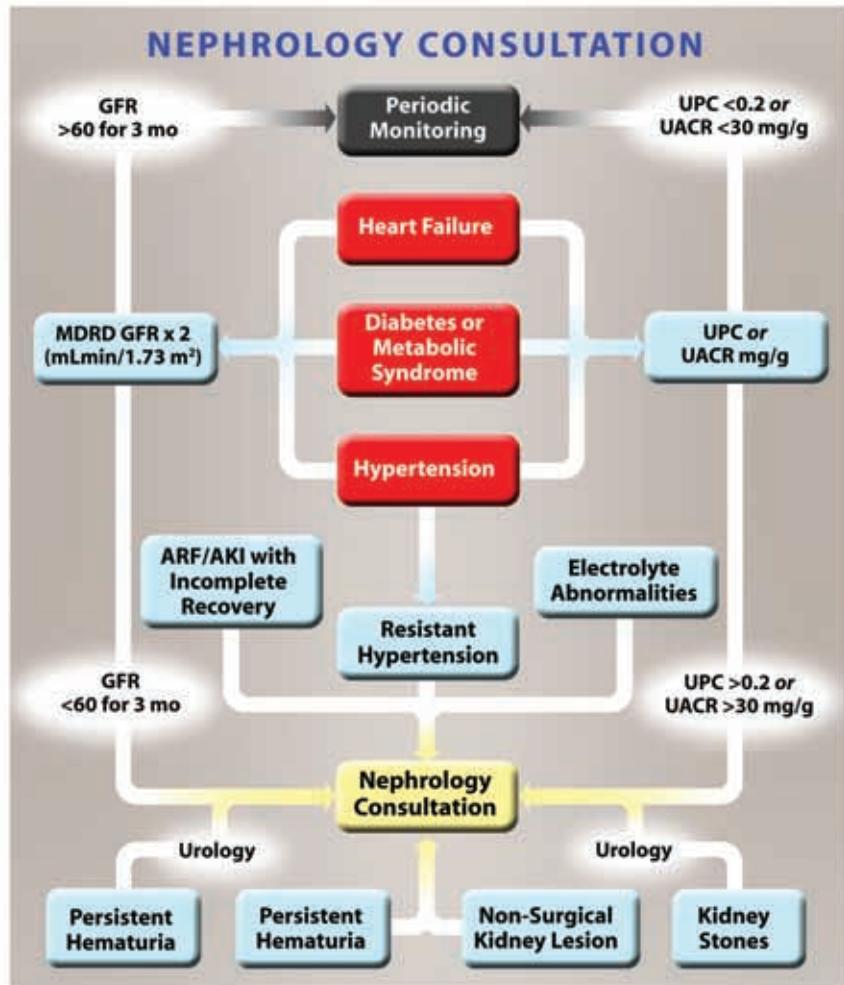
COMMENTS

- *eGFR* declines of >4 mL/min/1.73 m²/yr from any cause should prompt an evaluation for acute kidney injury or rapidly progressive CKD.
- Persistent asymptomatic isolated microscopic hematuria is an indication for nephrology consultation after initial imaging studies and/or urology consultation (urological consultation is recommended in cases of gross hematuria).
- Persistent proteinuria is an indication for consultation by a nephrologist.

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Considerations for early nephrology consultation. Patients with diabetes, the metabolic syndrome, hypertension, heart failure and combinations of these disorders should undergo evaluations for GFR and proteinuria. Consultation with a nephrologist is recommended for individuals with persistent hematuria, proteinuria, micro- or macroalbuminuria, or **GFR <60 mL/min/1.73 m² on two occasions**, separated by at least 3 months, and patients with incomplete recovery from acute renal failure (ARF)/acute kidney injury (AKI) or severe electrolyte derangements of Na, K, HCO₃, Ca, Mg, or P.

Abbreviations: **MDRD**, Modification of Diet in Renal Disease Study; **GFR**, glomerular filtration rate; **UPC**, urine protein-to-creatinine ratio; **UACR**, urine albumin-to-creatinine ratio.

DIABETIC KIDNEY DISEASE by Susanne B. Nicholas

Diabetic kidney disease (DKD) refers to renal disease specific to diabetes that may be biopsy-proven. This term may supplant “diabetic nephropathy” or diabetic CKD and is the terminology used by the National Kidney Foundation.

Introduction

The worldwide prevalence of diabetes mellitus (DM) is expected to be ~366 million by the year 2030, more than 2 times that from the year 2000. In the United States, 23.6 million people have DM and another 57 million have pre-diabetes or impaired glucose tolerance, and, in general, DM is linked primarily to obesity, aging, tobacco use, physical inactivity, and urbanization. DM accounts for >50% of prevalent and ~40% of US incident end-stage renal disease (ESRD) (<http://www.cdc.gov/diabetes/statistics/esrd>), and diabetic ESRD is significantly higher in certain ethnic and racial populations (eg, African American, Mexican American, American Indian, Inuit, Hispanic). However, the majority of people with DM are more than 64 y.o. It is well known that diabetic ESRD is associated with excess morbidity and mortality. In a prospective German study, the 5-yr survival rate was <10% in elderly type 2 diabetics and <40% in the younger type 1 cohort. The elderly, including patients ≥ 75 yr, are less likely to survive long enough to receive a deceased donor kidney transplant compared with non-diabetic patients.

Natural History, Diagnosis, and Screening of DKD

The natural history of DKD has been attenuated by the advent of agents that block the renin–angiotensin–aldosterone system (RAAS). However, if left untreated, there is progression through phases of asymptomatic mesangial extracellular matrix accumulation, microalbuminuria, macroalbuminuria, and finally, overt proteinuric nephropathy. This sequence occurs more frequently in genetically predisposed individuals. During the asymptomatic phase, glomerular hyperfiltration occurs with mesangial scarring. Later, in types 1 or 2 DM, the annual rate of GFR decline accelerates during the proteinuric phases: 1.2–3.6 mL/min/1.73 m²/yr with microalbuminuria and up to 5.4–12 mL/min/1.73 m²/yr in overt nephropathy. Due to the hyperglycemia-induced accumulation of matrix, diabetic kidneys are frequently normally sized when examined by ultrasound (normal: 10–12 cm). Hypertension (HTN) occurs in ~80% of adult diabetics, and a lack of nocturnal BP dipping may precede the microalbuminuric phase, with clear-cut HTN developing during the macro-albuminuric phase. Importantly, HTN may be present in ~70% of patients initiating dialysis for ESRD due to DKD.

Microvascular disease is much more prevalent in type 1 DKD than in type 2 DKD. Specifically, retinopathy marked by the development of new retinal vessels is present in almost all type 1 DKD and ~60% of type 2 DKD. Therefore, the absence of retinopathy or the presence of small kidneys by ultrasound in the latter group should prompt a search for a different etiology of CKD since 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 co-exist with DKD. In some series, diabetic nephropathy may be accompanied by another non-hypertension-related kidney disorder in 5–15% of cases.

In the United States, it is estimated that 50% of diabetic patients will develop DKD. 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. In general, the key markers of CKD are increased urine albumin-to-creatinine ratio (UACR) and increased SCr estimates of GFR (eGFR), <60 mL/min/1.73 m²,

from 2 abnormal readings at least 3 months apart. Microalbuminuria (30–300 mg/24 h; UACR 3–30 mg/g) is the earliest clinical sign of DKD and is typically present in 20–30% of type 1 diabetics ~15 yr after the onset of DM. Progression to macroalbuminuria (>300 mg/24 h; UACR >30 mg/g) is associated with increased progression of CKD and possibly, ESRD. The level of proteinuria >2g/24-h may be identified qualitatively by $\geq 3+$ urine dipstick or followed quantitatively by the urine protein-to-creatinine ratio (UPC; normal <0.2 g/g), or a 24-h urine collection.

The 24-h urine protein is considered the gold standard of urine protein determination as protein excretion may vary with the circadian rhythm, particularly in patients with glomerular disease. Afternoon (after 1600 h) UPC testing may significantly underestimate the morning UPC or 24-h urine protein. Proteinuria >3.5g/24-h is considered nephrotic range proteinuria. A spot morning (0800–1200 hours) UPC has been shown to correlate well with the 24-h urine collection in patients with DKD, and therefore is also a good screening test for DKD and for monitoring patients on a stable treatment regimen. Benign proteinuria that occurs due 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 microalbuminuria, macroalbuminuria, and then to advanced CKD or ESRD are 2.0%, 2.8%, and 2.3%, respectively.

DM and microalbuminuria represent independent risk factors for CVD. In addition, nearly 70–80% of diabetic CKD patients are hypertensive. Thus, routine screening for DKD is recommended for diabetic patients as follows: a) annual testing of urinary albumin excretion by “spot” UACR and *e*GFR in type 1 diabetic patients with ≥ 5 yr duration of DM and b) annual testing of all type 2 diabetic patients from the time of diagnosis. Because several factors may cause transient increases in microalbuminuria, the diagnosis requires at least 2 serial first-morning urine specimens over 2–3 weeks.

Occasionally, proteinuria in DM may herald other possible causes of CKD, particularly glomerular disorders as described above. Suspect other causes when one or more 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 proteinuria or nephrotic syndrome
- d) refractory hypertension
- e) **active** (blood and protein) urinary sediment
- f) manifestations of other systemic disease
- g) presence of >30% reduction in GFR within 2–3 months of the initiation of anti-renin–angiotensin–aldosterone system (RAAS) therapy.

The rate of improvement in renal function following this initial expected physiologic decline in *e*GFR will depend on several patient-related factors, such as disease severity and ethnicity. For example, African Americans typically display earlier and more rapid declines in renal function. The presence of one or more of these clinical scenarios should prompt urgent patient referral to a nephrologist for confirmatory and/or additional diagnoses. **Clinical remission of renal disease has taken place when proteinuria declines to <1 g/24-h, and regression is defined by a decline in proteinuria to <0.3 g/24-h.**

Treatment Considerations

Due to increased CVD risk in diabetic patients, prompt treatment of DKD and other CV risk factors is critical. Therefore, treatment of DKD toward therapeutic targets (*e.g.*, HbA1C, BP, lipids, BMI) involves risk factor reduction to prevent DKD progression and a multimodal approach that addresses lifestyle modification. Such modifications include a DASH (Dietary Approach to Stop Hypertension), restricted dietary sodium intake at <1.5 g/24 h, smoking cessation, restricted dietary intake of saturated fat and cholesterol (<200 mg/24-h), and regular aerobic exercise. Spontaneous remission of microalbuminuria may occur in some patients with types 1 and 2 DM. This may be attributable to improved BP control and/or glycemic control.

The strongest predictors of progressive DKD are the presence of poor glycemic control, hypertension, and glomerular hyperfiltration. **Importantly, as DKD progresses, the requirements for insulin to maintain glycemic control diminish as renal metabolism and excretion of insulin concomitantly and progressively decreases.** A reduction in insulin and/or other antihyperglycemic medications (not metformin) may be required to prevent hypoglycemia. Thus, the three mainstays of optimal DKD treatment are:

- a) strict glycemic control
- b) tight BP control
- c) maximal proteinuria reduction with an ACEI or ARB, singly or in combination.

There are multiple, well-conducted clinical studies which indicate that these strategies retard the progression of DKD. The non-dihydropyridine calcium channel blockers (*e.g.*, diltiazem and verapamil) are anti-proteinuric and may potentiate the anti-proteinuric effects of anti-RAS treatment(s). Even greater inhibition of the RAAS by the addition of a direct renin inhibitor (*e.g.*, aliskiren) or an aldosterone receptor antagonist (*e.g.*, aldosterone or eplerenone) may achieve improved anti-proteinuric effects. New research has uncovered an antioxidant drug, bardoxolone methyl that induces genes that suppress inflammatory mediators as a potential anti-proteinuric agent in the treatment of DKD.

The genetic susceptibility to DKD is well-recognized and familial factors may account for nearly 30% of the variance in urinary albumin excretion rate. As knowledge and understanding of the genetics of DKD improves, it is hoped that in conjunction with the identification of novel urinary biomarkers, greater efficiency and treatment strategies in the management of DKD will become recognized and available.

Therapeutic Targets

HbA1C	<7% (estimated average glucose, 154 mg/dl)
BP	<130/80 mmHg for CKD without proteinuria
LDL-C	<100 mg/dL
BMI	18.5–24.9 kg/m ²

COMMENTS

- To achieve a BP <130/80 mmHg, a beta blocker or a diuretic may be required.
- Consider the following recommendations:
 - a) CKD Stages 1–3, use a thiazide diuretic, loop diuretic (*eg*, 20–40 mg twice daily) or a K-sparing diuretic (*eg*, amiloride, triamterene, spironolactone, eplerenone)
 - b) CKD Stages 4–5, use a loop diuretic (*eg*, furosemide: 40–80 mg twice daily).

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HYPERTENSION IN CKD by Debbie Cohen & Raymond Townsend

Introduction

The prevalence of hypertension (HTN) continues to increase and approximately 74.5 million people in the United States ages 20 y.o. and older have HTN. Aging and obesity are the two most important reasons behind this increasing prevalence. Hypertension frequently accompanies advancing CKD, and it is often improperly assumed as the cause rather than the effect of CKD. In fact, more patients develop HTN from CKD than develop CKD from HTN, *ie*, hypertensive nephrosclerosis. In one observational study, CKD and HTN increased the risk of stroke by 22% compared to equally hypertensive individuals without CKD. By contrast, there was more than a 2-fold increase in stroke risk when the SBP was <120 mmHg. Further, in CKD, heart failure and cardiovascular deaths increased as SBP approached 120 mmHg and below this threshold (*J* curve relationship).

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*, *MYH9*) in African Americans may contribute to this risk. In addition, hypertensive kidney disease in African Americans may not always be attributable to high BP and may reflect an underlying glomerular disorder. Suspect these in non-diabetic individuals diagnosed with hypertensive nephropathy when their UPCs are >1 or UACRs are >300 mg/g. African Americans also tend to respond less well than Caucasian patients to monotherapy with beta blockers (BBs), ACEIs (angiotensin-converting–enzyme inhibitors) and/or ARBs (angiotensin–receptor blockers). However, ethnicity-related differences in therapeutic response are usually nullified by concomitant diuretic therapy. For example, the response to combined thiazide diuretic–ACEI/ARB therapy is equivalent among the various ethnicities. Therefore, no particular agent should be avoided in patients of African American ethnicity.

Since non-diabetic CKD patients have equivalent or greater risk for the development of CVD as 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*, <1500 mg sodium (65 mEq Na) per day.

Blood Pressure Profile

Hypertension in CKD is considered by default as “resistant HTN”, *ie*, treatment requires 3 or more antihypertensive agents at maximally tolerated doses and one of which must be a diuretic. The typical BP profile is a SBP greatly exceeding DBP, manifested as an elevated pulse pressure (>55 mmHg). Either the SBP or pulse pressure may be increased in hypervolemic/edematous individuals who must often be treated with diuretics.

Proteinuria

Evaluation for and quantitation of albuminuria/proteinuria is recommended when there is a family history of CKD or the *eGFR* is <60 mL/min/1.73 m². Achievement of target BP goals, particularly for the more important systolic pressure, will require two or more antihypertensive medications in most cases, if the initial SBP is **≥150 mmHg**, two antihypertensive agents should be initiated, 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 the GFR) or CCB (calcium channel blocker). Lastly, non-dihydropyridine calcium channel blockers (NDHPCCBs: diltiazem,

verapamil) are preferred in proteinuric CKD, with appropriate caution during concomitant beta blocker therapy, or with contraindication due to bradycardia.

Proteinuria accelerates the rate of decline of GFR in hypertensive, diabetic, and non-diabetic individuals. Hypertension exacerbates proteinuria and promotes tubulointerstitial inflammation, fibrosis, and tubular atrophy, further elevating BP. Also, proteinuria, more specifically, albuminuria is an independent risk factor for stroke, LVH, and death. In the presence of >1–2 g/d proteinuria, the risk for progressive CKD rises steeply after SBP \geq 130 mmHg. All of the anti-renin–angiotensin–aldosterone system (anti-RAAS) agents are anti-fibrogenic, including aldosterone receptor antagonists (ARAs).

Patients with a SBP of 115–130 mmHg and proteinuria <1 g/d have a relatively lower risk of progression. However, a SBP of 120–130 mmHg may be considered optimal for patients with HTN and proteinuria since SBPs \leq 120 have been associated with an enhanced risk of adverse cardiovascular events in proteinuric CKD patients, particularly those with stroke or heart failure.

Treatment

The Seventh Report of the Joint National Committee (JNC 7) issued a set of *Compelling Indications* (see TABLE) for the treatment of HTN, which should also be followed in CKD patients. Modification of lifestyle and dietary interventions should always be enforced in hypertensive CKD patients. Sodium restriction can produce substantial BP reductions, and primarily entails reducing the intake of “salty” processed foods. **Currently, there is insufficient evidence to support a SBP goal <130 mmHg in CKD with urine protein-to-creatinine ratio <0.22. In patients with CKD and proteinuria that is >1 g/d, a SBP of 120–130 mmHg is recommended.** 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 blood pressure regimen can be improved.

JNC 7 COMPELLING INDICATIONS HYPERTENSION TREATMENT

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

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; CCB, calcium channel blocker; ARA, aldosterone receptor antagonist (eplerenone, spironolactone).

*Selection of a non-dihydropyridine CCB is preferred in CKD patients with proteinuria.

Therapeutic Targets

BP <130/80 mmHg	CKD without proteinuria
BP 120–129/75–79 mmHg	CKD with proteinuria

First-line Agents

GFR >20 mL/min/1.73 m ²	ACEI or ARB Most CKD patients with HTN require 2 or more antihypertensive medications
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Second and Third Line Agents

GFR ≥40 mL/min/1.73 m ²	Add thiazide and/or CCB, if anti-RAS agent is first-line
GFR <40 mL/min/1.73 m ²	Add loop agent, <i>eg</i> , bumetanide or furosemide (twice-daily dosing) or torsemide (once-daily dosing) and/or CCB, if anti-RAS agent started as first-line therapy

Fourth-line Agents

HR >80 bpm	Beta blocker or alpha/beta blocker
HR ≤80 bpm	Consider adding ARA (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	Beta blocker, CCB, alpha/beta blocker, <i>eg</i> , labetalol
BPH	Alpha-1 blocker, <i>eg</i> , prazosin, terazosin, doxazosin
Thiazide-resistant HTN	Amiloride or ARA
Primary aldosteronism	ARA
Orthostatic hypotension	Target 2-min standing SBP (>120 mmHg)

Stage 2 Hypertension (uncontrolled)

SBP	≥150 mmHg on ≥2 occasions, separated by ≥2 d
DBP	≥90 mmHg on ≥2 occasions, separated by ≥2 d

COMMENTS

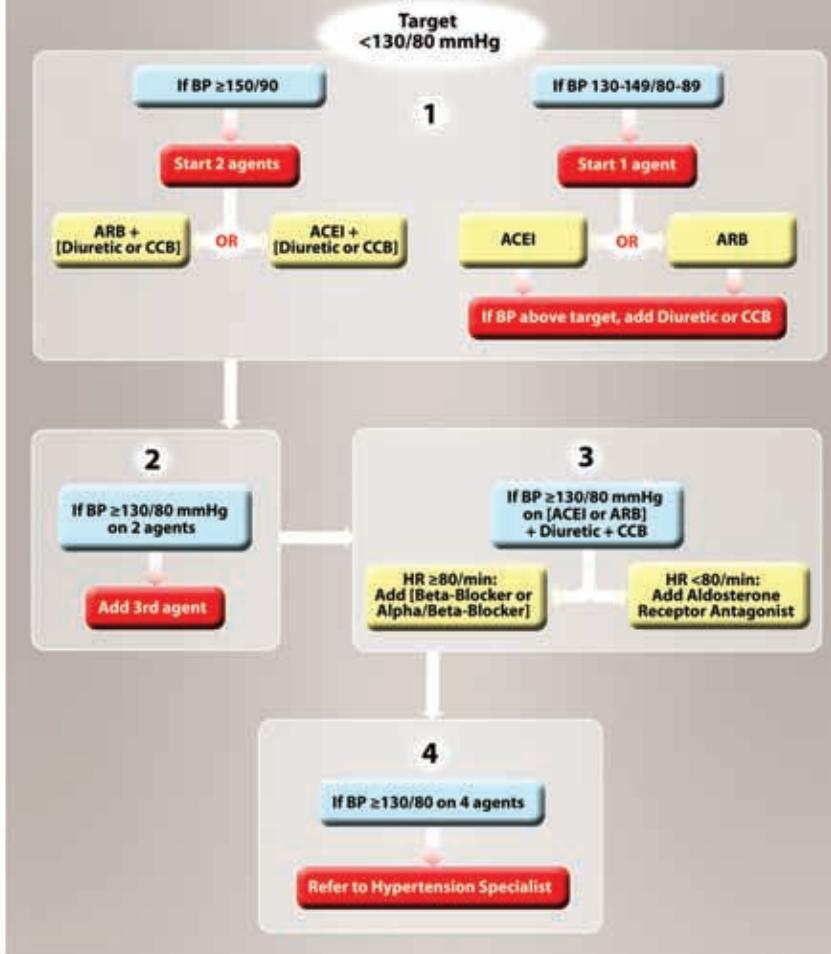
- Anti-RAS therapy: SCr increases are common and can often be tolerated. Obtain SCr and K levels 7–10 days later after initiation of an ACEI or ARB and with changes in anti-RAS therapy.
- Increases of SCr 30% above baseline within 3 months of initiating anti-RAS therapy may be acceptable. Greater elevations should be thoroughly investigated and may require nephrological consultation.
- For baseline SCr ≥2.0 mg/dL, SCr increases ≥1.0 mg/dL may be tolerated.
- Avoid sole use of dihydropyridine CCBs in proteinuric CKD patients.
- Initial SBP: if ≥150 mmHg, begin 2-drug regimens, *eg*, ACEI/thiazide, ARB/thiazide, or ACEI/CCB in patients on no medications.
- Sodium: intake >100 mEq/d and/or ineffective diuretic treatment are common causes of “resistant” HTN. High sodium intake reduces effectiveness of antihypertensive therapies and is determined best by a 24-h urine sodium collection. **AHA sodium limit is 1500 mg/d.**

- Loop diuretics should be generally be used twice daily, in the morning and in the mid- to late-afternoon. Once daily dosing is often ineffective due to compensatory stimulation of the RAAS with sodium retention.
- Thiazide diuretics are generally ineffective, if SCr is >1.7 mg/dL or, if the *eGFR* is <40 mL/min/1.73 m².
 - Metolazone: 5–20 mg/d may be effective at these lower GFR levels due to its greater potency relative to thiazide-type diuretics.
 - Sympathomimetic agents (pseudoephedrine, “diet” pills, cocaine) and NSAIDs (COX-1/-2 and selective COX-2 inhibitors) may aggravate HTN.

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APPROACH TO HYPERTENSION TREATMENT IN CKD



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

PROTEINURIA IN CHRONIC KIDNEY DISEASE by Julie Lin

Introduction

The poor prognosis of “lardaceous urine” or that which contained protein was appreciated in the first half of the 19th century. Elevated albuminuria/proteinuria portends worsening CKD and CVD risk, particularly in diabetic, hypertensive and patients with glomerular disorders. The prevalence of proteinuria is 4–8% worldwide and 10–20% in hypertensive, obese, and/or diabetic populations. Diabetics and persons with $eGFRs <60 \text{ mL/min}/1.73 \text{ m}^2$ should undergo proteinuria testing. Individuals with higher $eGFRs$ should only undergo proteinuria 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 patients by UPC (urine protein-to-creatinine) ratio or UACR (urine albumin-to-creatinine ratio; also termed ACR).

Using UACR more reliably classifies individuals with “higher risk” CKD (*ie*, those who might develop progressive disease) who have been stratified into CKD Stages 3 and 4 by the MDRD 4-variable $eGFR$ equation. Using the combination of $eGFR <60 \text{ mL/min}/1.73 \text{ m}^2$ and proteinuria by UACR reduces the prevalence of CKD Stages 3 and 4 patients by 76%, from 16.3 million to 3.9 million. Note that UPC testing is not nationally standardized due to variation in laboratory methodology; however, UACR testing is standardized. The presence of even small amounts of albuminuria ($>10 \text{ mg/g}$) is associated with adverse cardiovascular outcomes. While ACEI (angiotensin-converting enzyme inhibitor) and/or ARB (angiotensin-receptor blocker) therapies reduce albuminuria and are associated with reduced risk for developing ESRD (especially in diabetes and hypertension), they are underutilized. Ideally, 70% or more of patients should be treated with these drugs.

Types of Proteinuria

Traditionally, normal urinary protein excretion is considered to be $<150 \text{ mg/24-h}$; total urinary proteins measured are comprised of immunoglobulins, assorted globulins, and Tamm-Horsfall mucoprotein. Persistently elevated total urinary protein signifies:

- a) defect(s) in the glomerular basement membrane
- b) impaired tubular protein reabsorption, *eg*, tubulointerstitial nephritis
- c) increased filtration of low molecular weight protein(s),
ie, “overflow proteinuria” as may occur with light chains.

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. Serious causes of proteinuria include glomerular disorders and myeloma. “False positive” albuminuria results by urine dipstick include highly alkaline urine, concentrated urine, gross hematuria and the presence of mucus, semen or white cells.

Individuals at increased risk for CKD should undergo testing for proteinuria. The urinalysis dipstick may not register proteinuria 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 Proteinuria

Early or first morning “spot” UPC ratio (urine protein and urine creatinine expressed as mg/dL) correlates with the daily protein excretion rate (g/24-h). A UPC = 2 correlates with 2 g of proteinuria per 24-h and approximates the 24-h urine total protein collection, a collection fraught with error(s). Since the majority of protein excretion in glomerular disease is albumin, albumin-specific tests have been devised, eg, albumin-specific dipsticks and the UACR, traditionally classified as normal (<30 mg/g), microalbuminuria (30–300 mg/g) and macroalbuminuria (>300 mg/g). Notably, a new classification system that eschews the terms micro- and macroalbuminuria may be established in the near future.

Quantitative urinary protein (principally albuminuria) testing by UPC or UACR is recommended within 3 months of documentation of $\geq 1+$ proteinuria by dipstick analysis. Two or more positive quantitative tests, preferably on first morning urine specimens, should be documented before diagnosing persistent proteinuria (**see CKD PROTEINURIA EVALUATION, P. 27**).

The urine dipstick favors albumin detection and is relatively insensitive for tubular proteinuria, eg, immunoglobulin light chains. If tubular proteinuria is suspected, specific qualitative and quantitative examinations may be required, eg, serum free light chain analysis (FreeliteTM) 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.

Anti-Proteinuric Therapy

Anti-proteinuric therapy reduces tubulointerstitial fibrosis and thus, progression of CKD. Patients with stable, persistent proteinuria of <1 g/24-h have a very small risk of progression to kidney failure compared to individuals with greater proteinuria. However, glomerular proteinuria in the nephrotic range (>2 g/m²/d; 3.0–3.5 g/24-h in adults) has an ominous prognosis and is associated with edema, hypercholesterolemia, hypoalbuminemia, anemia, lipiduria, vitamin D deficiency, and greater risk for progression to ESRD. Irrespective of the degree of proteinuria, all therapies that reduce proteinuria should be optimized for BP control of <130/80 mmHg as tolerated. Anti-renin-angiotensin–aldosterone (RAAS) agents, ACEIs and ARBs, represent first-line anti-proteinuric drugs and should be utilized whenever possible. These agents are indicated in the treatment of diabetic and non-diabetic proteinuric CKD.

Antihypertensive regimens that include anti-RAAS therapy are more efficacious than regimens that do not include ACEIs or ARBs, and their benefit is maximized in CKD patients that manifest either >0.5 g/d of proteinuria, UPCs >0.22, or microalbuminuria by UACR. The anti-RAAS therapies exert differential, beneficial effects on glomerular structural proteins, intraglomerular pressures, local and systemic sympathetic nervous systems, inflammatory pathways, and the systemic blood pressure. Notably, no specific agent reduces tubular proteinuria.

Recently, aldosterone receptor antagonists (ARAs) and direct renin inhibitors (DRIs) have demonstrated anti-proteinuric properties. Non-dihydropyridine CCB (calcium channel blockers), diltiazem and verapamil, also reduce proteinuria and complement the anti-RAAS agents. Combinations of such agents (ACEI + ARB) frequently reduce proteinuria by an additional 25–40%. However, dual-agent anti-RAAS therapies involving ACEIs or ARBs (VA NEPHRON-D) with other antiproteinuric agents, eg, (**ACEI or ARB**) + **ARA** or (**ACEI or ARB**) + **DRI** (ALTITUDE) should be initiated and monitored by a nephrologist. The goal of attaining target BP supersedes additional use of antiproteinuric agents. Recent data suggest that pentoxifylline and HMG-Co synthetase inhibitors, simvastatin and atorvastatin, may reduce proteinuria.

Finally, *high sodium intake* and *poor glycemic control* may retard BP-lowering and proteinuria-reducing effects of antihypertensive agents. Sodium intake of ≤ 1500 mg daily is recommended for patients with CKD.

Therapeutic Targets for Proteinuria Reduction

UPC	<0.2 (dimensionless ratio; units as mg/dL)
UPC	<200 mg/g (protein as mg/dL; creatinine as g/dL)
UACR	<30 mg/g

First-line Agents for Proteinuria Reduction

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

Second-line Agents for Proteinuria Reduction

Diabetes, types 1 or 2	(ACEI or ARB) + CCB
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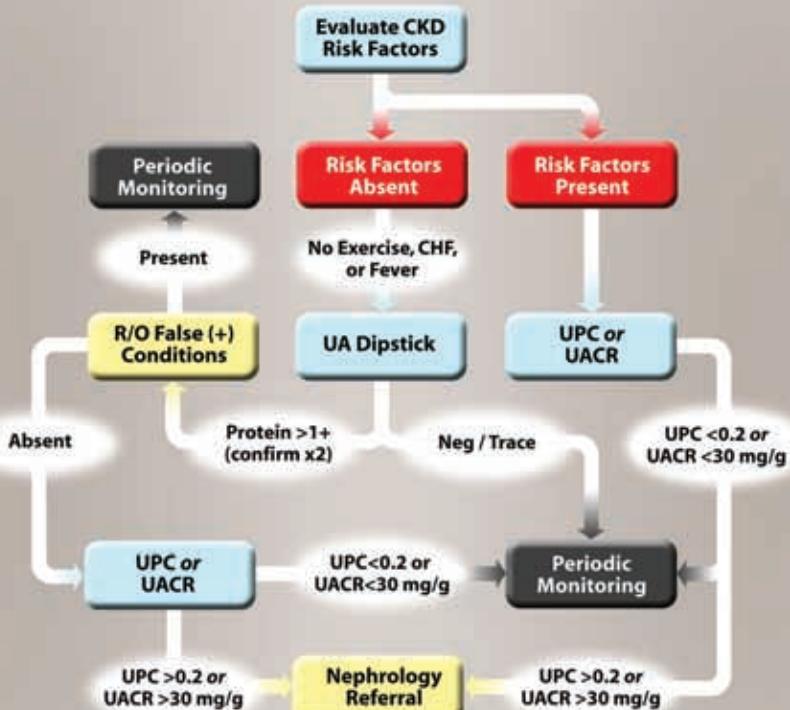
COMMENTS

- Repeat quantitation of proteinuria by a UACR or a UPC at 8–12 wk intervals after therapeutic interventions that aim to reduce proteinuria to minimize UACR or UPC.
- 24-h urine protein collections are rarely required for proteinuria evaluations as spot UPCs are usually sufficient.
- False-positive UA dipstick protein reactions may result from alkaline urine ($pH > 7$), gross hematuria, mucus, semen, leukocytes, radiocontrast, exogenous creatine supplementation, and contamination by certain cleansing solutions, *eg*, chlorhexidine or benzalkonium.
- Optimal timing of urine protein determination is the first morning void following recumbency, which should help rule out orthostatic proteinuria.
- UPC and UACR tests may underestimate protein excretion in muscular patients, but may overestimate excretion in cachectic patients.

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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 ($\text{pH} > 7$), 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; **UACR**, urine albumin-to-creatinine ratio.

ANEMIA OF CHRONIC KIDNEY DISEASE by Anatole Besarab

Introduction

Anemia of CKD is defined as a Hb (hemoglobin) <12 g/dL (female) or <13.5 g/dL (male), with adequate iron availability by parameters: TSAT (transferrin saturation) >20% and ferritin >100 ng/mL. In CKD Stage 5, the ferritin target is >200 ng/mL.

Anemia of CKD usually begins during CKD Stage 3, *i.e.*, GFRs <60 mL/min/1.73 m². Anemia occurs in 42%, 54% and 76% of CKD Stage 3, 4 and 5 patients, respectively, and is more severe in diabetics. Anemia multiplies the mortality risks of diabetes, heart failure, and CKD. Treatment of anemia of CKD is associated with improved vitality and socialization, but has not been shown to decrease LVH or cardiovascular or all-cause mortality. Iron deficiency should be corrected before administration of any ESA (erythropoiesis stimulating agent).

The **KDOQI™ CLINICAL PRACTICE GUIDELINE AND CLINICAL PRACTICE RECOMMENDATIONS FOR ANEMIA IN CHRONIC KIDNEY DISEASE: 2007 UPDATE OF HEMOGLOBIN TARGET** states a Clinical Practice Recommendation for a Hb target of **11.0 to 12.0 g/dL** and a top-level Hb of 13.0 g/dL in CKD.

To obtain reimbursement for ESA therapy, the Hb must be <10 g/dL on the date that an ESA is first prescribed, and reimbursement is dependent upon payors' coverage policies. Lastly, an attestation of medical necessity for ESA treatment may be required for reimbursement by third party payors.

Pathophysiology

The primary reason for anemia in CKD is an absolute or relative deficiency of renal erythropoietin (EPO) synthesis. Individual sensitivity and responsiveness to an ESA is highly variable and dosing requirements are heterogeneous. Occult causes of blood loss and iron deficiency must be ruled out in all patients as a cause of hyporesponsiveness to ESA treatment. Less commonly, vitamin deficiencies, *e.g.*, B₁₂ and folate, and inflammatory causes of ESA resistance should be ruled out secondarily. Inflammation upregulates hepcidin, a liver-synthesized protein that reduces gut iron absorption and impedes iron release from the reticuloendothelial system to the developing erythron. Finally, effective iron delivery is required for optimal ESA-stimulated production of fully hemoglobinized red blood cells.

Iron Deficiency

Iron deficiency is common in CKD. CKD patients should be iron replete before initiating ESAs. To correct iron deficiency, oral iron should always be tried initially, and multiple iron salt preparations are available. However, to achieve iron repletion, parenteral iron may be required in non-dialysis CKD patients. Multiple studies attest to the safety of several parenteral iron preparations, including iron sucrose [FDA-approved], ferumoxytol [FDA-approved], and *low molecular weight* iron dextran [used "off label"].

Safety

During anemia treatment, Hb elevations of 1–2 g/dL per month are generally well tolerated. More rapid increments are not advised. Recent clinical trials describe an increased risk of blood clots, strokes, and heart attacks in CKD and dialysis patients, in association with treatment to Hb levels of ~13 g/dL, particularly at high doses of ESA. FDA and ESA manufacturers have agreed to revised product labelings that include a “black box warning” with an FDA-approved target Hb of 10–12 g/dL (*see below*). However, the heterogeneity of responses to ESA/iron-based anemia therapy among patients and even over time in the same patient makes the targeting of an exact Hb difficult. Lastly, ESA dosing has been extended to once monthly intervals in several clinical trials.

Therapeutic Targets

Hb 10–12 g/dL[†] (**do not exceed Hb 13 g/dL**)

TSAT >20% but <50%

Ferritin >100 ng/mL[‡]

CHR >32 pg/cell*

[†]Therapeutic phlebotomy should not be undertaken, if the Hb 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 inflammation.

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

Evaluation

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

Treatment

Iron

Ferrous sulfate: 200 mg elemental iron/24-h (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[®]): 500–1000 mg *iv* in non-dialysis-dependent CKD

*Iron dextran, *iv*, *high* molecular weight (Dexferrum[®]), is a distinct and separate product from INFeD[®] (*see above*).

Erythropoiesis-Stimulating Agents (ESAs)

Epoetin alfa (Procrit[®] or EpoGen[®]): 10–40,000 Units, subcutaneously, q1–4 wk; begin therapy at Hb <10 g/dL at starting dose, 100 Units/kg/wk.

Darbepoetin alfa (Aranesp[®]): 40–300 mcg, subcutaneously, q2–4 wk *or* q1 mo; begin therapy at Hb <10 g/dL at starting dose, 0.9 mcg/kg/q2 wk (equivalent to package insert dose, 0.45 mcg/kg/wk)

NB: ESA therapy entails informed consent at each administration. In hemodialysis patients, administration of vitamin D may reduce ESA utilization.

COMMENTS

- Ascorbic acid (vitamin C) should be co-administered with iron in achlorhydric patients (250 mg per iron tablet), during H₂ antagonist or PPI therapy, or after gastric ulcer surgery (eg, Billroth II surgery).
- Ca-based P-binders bind iron salts.
- Consult a nephrologist before initiating ESA treatment, if oral iron therapy does not achieve Hb ≥10 g/dL or if parenteral iron is considered.
- Dose conversion ratio of epoetin alfa to darbepoetin alfa is ~225–260 to 1.
- EPO levels should *not* be measured as part of a routine anemia evaluation.
- ESAs are contraindicated during acute blood loss.
- Iron salts should only be ingested on an empty stomach.
- Iron salts bind fluoroquinolones, tetracyclines, Ca-based P-binders, and levothyroxine. Administer thyroid hormones separately from iron.
- Parenteral iron is contraindicated during active infection.

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CKD-MINERAL AND BONE DISORDER by L. Tammy Ho

Introduction

Renal osteodystrophy (ROD) defines the presence of altered bone structure and composition in 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 Ca (serum calcium), P (serum phosphorus), PTH (parathyroid hormone), 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 CVD morbidity and mortality of CKD. Calcification occurs most frequently in coronary arteries, aorta, and cardiac valvular leaflets. Initial evaluation of CKD-MBD includes assessing and establishing baseline Ca, P, PTH, vitamin D [$25(\text{OH})\text{D}$], alkaline phosphatase, and serum HCO_3 levels.

Bone Disorders

The TMV (turnover/remodeling, mineralization, and volume) classification of ROD relies on bone histology from transiliac biopsy and has 4 subtypes that may overlap: osteomalacia, adynamic bone disease, osteitis fibrosa, and mixed uremic osteodystrophy (*see TABLE*). Historically, the most common lesion was secondary hyperparathyroidism (SHPT), and this is still the most prevalent lesion in non-dialysis-dependent CKD. However, therapeutic interventions have increased the prevalence of adynamic bone disease. Osteoporosis in CKD, as defined by WHO criteria for non-CKD patients, is difficult to diagnose, especially in late CKD stages. Bone densitometry, commonly used in the general population, provides no information on bone quality or turnover, and these are frequently abnormal in progressive CKD. Nonetheless, bone loss should be monitored periodically. Lastly, metabolic acidosis ($\text{HCO}_3 < 22 \text{ mEq/L}$) increases net bone resorption (osteoclasts) and reduces calcitriol synthesis and should be corrected.

RENAL OSTEODYSTROPHY BONE DISORDERS

Lesion	Turnover	Mineralization	Volume
Osteomalacia	↓	Abnormal	↓ / Normal
ABD	↓	Normal	↓ / Normal
Osteitis fibrosa	↑	Abnormal	Normal / ↑
MUO	↑	Abnormal	Normal

Abbreviations: ABD, adynamic bone disease; MUO, mixed uremic osteodystrophy.

Ca, P, Parathyroid Hormone (PTH), and Vitamin D Physiology

Total serum calcium is 40% ionized (free), 50% albumin-bound and 10% complexed to P and organic anions. Ionized Ca regulates the parathyroid gland (PTG) Ca-sensing receptor (CaR), vitamin D, and PTH. 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 P. Progressive CKD leads to progressive elevation in P; low P levels in a patient with significant CKD should lead to consideration of other additional underlying issues such as malnutrition. High P levels raise PTH and are associated with greater CVD 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, diet alone is likely to be an ineffective intervention to prevent or correct hyperphosphatemia. Currently, P binders remain a mainstay of therapy in patients with elevated 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 [as 25(OH)D] deficiency 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, screen for and begin treatment of SHPT early. Please note the developing story of Fibroblast Growth Factor 23 (FGF23). Bone-derived FGF23 is one of an undefined number of circulating peptides known as phosphatonins. FGF23 acts on kidney proximal tubular cells and decreases P reabsorption, thereby increasing urinary P excretion. FGF-23 apparently directly suppresses PTH and decreases calcitriol synthesis by inhibiting proximal tubular 1 α -OHase inhibition. FGF-23 is significantly elevated in CKD and is the subject of much current research aimed at determining its significance as a CKD biomarker or parameter of successful therapy, with other phosphatonins.

Metabolic acidosis defined as a serum HCO₃ <22 mEq/L that is not generated by respiratory alkalosis is under-recognized. Acidosis potentiates bone-lytic PTH effects, thereby increasing Ca and P bone resorption. It also increases SNS activity, aggravating hypertension, induces insulin resistance, and promotes muscle-protein catabolism. Treatment with sodium bicarbonate generally does not produce ECF volume expansion (*e.g.*, edema) or worsen HTN. 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 (NaHCO₃) or another alkali.

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	↑ ionized Ca, ↑ 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; **PTG**, parathyroid gland; **SHPT**, secondary hyperparathyroidism; **P**, serum phosphorus; **VDR**, vitamin D receptor.

Vitamin D includes vitamins D2 and D3 and three active D sterols, calcitriol, and two synthetic vitamin D2 compounds. Renal synthesis of calcitriol is tightly regulated. Its 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, aggravating SHPT (*see TABLE*).

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
Calcidiol	25(OH)-cholecalciferol; 25(OH)D3	25-OH'n → D3 (liver)
Calcitriol (Rocaltrol®)*	1,25(OH) ₂ -cholecalciferol; 1α-25(OH) ₂ D3	1α-OH'n → 25(OH)D3 (kidney)
Doxercalciferol (Hectorol®)*	1α-(OH)D2	Synthetic D2 prohormone
Paricalcitol (Zemplar®)*	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, 25(OH)D levels <30 ng/mL represent vitamin D insufficiency. However, these agents may not sufficiently suppress PTH elevations in CKD Stages 3–5, despite replenishing vitamin D stores. Consequently, active vitamin D sterols may be required to suppress PTH to target levels. Any of these compounds can be used concomitantly with vitamin D2 or D3.

Oral vitamin D is recommended in CKD Stages 3 and 4, and active vitamin D sterols are recommended to prevent and treat early SHPT and CKD-MBD. Treatment (with active vitamin D sterols) is indicated when 25(OH)D levels are >30 ng/mL; *Corrected calcium (Corr Ca)* is <9.5 mg/dL; P <4.6 mg/dL; and PTH levels are elevated and continue to rise with time. The optimal PTH levels in CKD are unknown and likely vary with a number of factors, not limited to stage of CKD and race. An iPTH range that is 2–9 × ULN (~130–600 pg/mL) may be acceptable, with the growing acceptance that therapy of mineral metabolism should be individualized, *i.e.*, trend analysis of the above parameters is favored over absolute values.

$$\text{Corr Ca (mg/dL)} = \text{Total serum Ca} - [0.8 \times (4 - \text{Albumin})]$$

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.

Ca-based P-binders are recommended in CKD Stages 3 and 4 for P >4.6 mg/dL when the corrected Ca is <10.2 mg/dL and there is no evidence of coronary, peripheral vascular/cardiac valvular calcification. During Ca-based P-binder therapy, the total daily elemental Ca intake (dietary + prescribed) should not exceed 2000 mg daily. This limit is imposed to prevent excessive Ca loading and extraskeletal calcification and dystrophic medial arterial calcification that occur earlier

in diabetes and CKD. 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 >10.2 mg/dL. These drugs do not alter Ca or PTH levels and do not affect treatment by vitamin D or its analogs. Sevelamer typically reduces LDL-C by 30% and raises HDL-C. Lastly, the Ca \times P product as a therapeutic parameter is no longer used.

KDIGO™ TARGETS FOR CKD-MINERAL AND BONE DISORDER*

CKD Stage	Ca [†] (mg/dL)	P (mg/dL)	iPTH (pg/mL)	HCO ₃ (mEq/L)
3	NL range	NL range	2–9 \times ULN	22–26
4	NL range	NL Range	2–9 \times ULN	22–26
5	Lower toward NL range	Lower toward NL range	2–9 \times ULN	22–26

*KDIGO: Kidney Disease: Improving Global Outcomes, 2006. Trend analysis of each parameter is preferred over treatment(s) directed at absolute parameter levels. PTH levels of 130–600 pg/mL roughly equal 2–9 \times ULN. [†]Serum calcium corrected to serum albumin of 4.0 g/dL. Trend analysis of Ca, P, and intact PTH is recommended rather than treatment of isolated values.

Evaluation

Ca, P, iPTH	Every 2 wk initially in CKD Stages 3–4 until normalized, then every 3–12 mo depending on stage and trends
Serum HCO ₃	Every 1–4 mo, depending on degree of metabolic acidosis
25(OH)D	<30 ng/mL at initial evaluation; begin therapy, then repeat level every 3 mo until \geq 30 ng/mL; subsequent levels are evaluated depending on CKD stage and levels.

Vitamin D and Active Vitamin D Sterols

Vitamin D

Ergocalciferol (D2) 25(OH)D <15 ng/mL: 50,000 IU q1 wk \times 4, then every 1 mo \times 8, unless corrected Ca >9.5 g/dL and/or P >4.6 mg/dL (new)
 25(OH)D 15–30 ng/mL: 50,000 IU q1 mo \times 6, unless *Corr Ca* >9.5 g/dL and/or P >4.6 mg/dL
 Please note, often longer durations of weekly therapy may be required.
 Monitor levels every 3 mo and continue weekly or monthly dosing, accordingly.

Cholecalciferol (D3) 25(OH)D <30 ng/mL: 1,750 IU once daily (new)

Active Vitamin D Sterols

Calcitriol Initial dose for CKD Stages 3–4: 0.25–0.50 mcg once daily

Doxercalciferol Initial dose for CKD Stages 3–4: 1.0 mcg once daily (*see COMMENTS*)

Paricalcitol Initial dose for CKD Stages 3–4: 1.0 mcg once daily or 2.0 mcg, 3 times weekly (*see COMMENTS*)

COMMENTS

- **Active vitamin D sterols:** therapeutic choices at CKD Stages 3–5 include calcitriol, doxercalciferol or paricalcitol. Treatment plan includes periodic monitoring of Ca, P, albumin and PTH (*see ACTION PLAN*) and rarely induces Ca or P elevations that warrant their discontinuation.
- **Active vitamin D sterols:** may co-administer with ergocalciferol, if SHPT is present because ergocalciferol rarely suppresses PTH to target levels.
- **Active vitamin D sterols:** initiate during CKD Stages 3–4, if Ca <9.5 mg/dL, P <4.6 mg/dL, and PTH greater than target range.
- **Ergocalciferol:** consider in CKD Stages 3 and 4, if corrected Ca <9.5 mg/dL, P <4.6 mg/dL, PTH elevated, and 25(OH)D <30 ng/mL.
- Refer to the **MEDICATION RELATED PROBLEMS IN CKD** section for FDA-regulated labeling of the recommended doses of these agents in CKD. The lack of evidence supporting a definitive goal PTH and a clearcut therapeutic regimen makes this area controversial. Consequently, drug manufacturer labeling may differ from recommendations from consensus organizations such as KDIGO™ and from the practices of “experts” in the field. Recommended guidelines should not substitute for clinical judgment. Due to the absence of definitive evidence, any treatment plan should include periodic monitoring of Ca, P, albumin, and PTH (*see ACTION PLAN*), with therapy based on trend analysis. Only rarely should a single abnormal value of Ca or P warrant discontinuation of active vitamin D sterols.

Phosphorus Binders (always taken with meals)

Calcium acetate (PhosLo®)	1.0–1.5 g elemental Ca daily for P >4.6 mg/dL and Ca 8.8–10.2 mg/dL; 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; CaCO ₃ dose is 40% elemental Ca Not FDA-approved at any CKD stage
Sevelamer HCl (Renagel®)	800–2400 mg 3 times daily for P >4.6 mg/dL and Ca >10.2 mg/dL (Ca-based P-binder contraindicated) FDA-approved for CKD Stage 5
Sevelamer Carbonate (Renvela®)	800–2400 mg 3 times daily for P >4.6 mg/dL and Ca >10.2 mg/dL (Ca-based P-binder contraindicated) FDA-approved for CKD Stage 5
Lanthanum Carbonate (Fosrenol®)	500–1000 mg 3 times daily for P >4.6 mg/dL and Ca >10.2 mg/dL (Ca-based P-binder contraindicated) FDA-approved for ESRD

Metabolic Acidosis

NaHCO ₃	0.5–2.0 mEq/kg daily; target HCO ₃ 22–26 mEq/L
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PLAN OF CARE AND ACTION PLAN FOR CHRONIC KIDNEY DISEASE STAGES 1–4

Stage & GFR	Description	Action
Normal >90 mL/min/1.73 m²	RISK factors: age >60 years, obesity, autoimmune disorders, DM, HTN, kidney stones, ADPKD, prior AKI/ARF, UTIs, toxic drug exposures, and FH of CKD	SCREEN for general and specific conditions SCREEN for CKD w/ eGFR INITIATE CKD risk reduction / intervention strategies
1 >90 mL/min/1.73 m²	KIDNEY damage with normal GFR (urinary, imaging or histologic abnormalities)	ESTABLISH etiology of CKD DIAGNOSE and treat CVD risk factors and comorbid conditions
2 60 – 89 mL/min/1.73 m²	KIDNEY damage with mild GFR decrease (urinary, imaging or histologic abnormalities) MOST lower GFRs in this range are due to age-related GFR decline and do not require evaluation, if no proteinuria is present	ESTIMATE CKD progression rate DIAGNOSE and treat CVD risk factors and comorbid conditions
3A 45 – 59 mL/min/1.73 m²	MODERATE decline of GFR COMPLICATIONS more frequent at CKD Stage 3B as GFR ↓ to <45 mL/min/1.73 m ² . PROTEINURIA is a serious CV risk factor and has prognostic importance for progression of CKD	ESTIMATE CKD progression rate DIAGNOSE and treat CVD risk factors and comorbid conditions KIDNEY imaging study, eg, US or CT CONSIDER Nephrology CONSULTATION
3B 30 – 44 mL/min/1.73 m²		
4 15 – 29 mL/min/1.73 m²	SEVERE decline of GFR MAJOR increase in CVD risk, ie, CKD Stage 4 should be considered equivalent to a major CVD clinical event	NEPHROLOGY consultation with transition of management and care INITIATE decisions regarding kidney replacement therapy, vascular access, and kidney transplant DIAGNOSE and treat CVD risk factors and comorbid conditions ADJUST drug dosing for CKD stage

COMMENTS

- Early recognition, evaluation, and treatment of CKD in a multidisciplinary fashion, decreases morbidity, mortality, and healthcare costs.
- eGFRs <45 mL/min/1.73 m² in older persons (age > 65 yo) may not require Nephrology evaluation in all cases, unless there is heavy proteinuria (UACR >0.5 or UPC 0.5–1.0) or a progressive decline in eGFR (> 4 mL/min/1.73 m²).

Clinical Testing	Treatment Considerations
BP monitoring: every 12 mo FASTING lipid profile: every 12 mo LYTES, Glucose, BUN, SCr: eGFR every 12 mo UA for hematuria or proteinuria & microscopic exam	SMOKING cessation WEIGHT reduction DAILY aspirin: 81 mg once daily TARGETS BP: <130/80 mmHg LIPIDS: LDL-C <70–100 and TG <150 mg/dL GLUCOSE: FBS <130 mg/dL, HbA1C <7%
BP monitoring: every 12 mo LYTES, Glucose, BUN, SCr, eGFR: every 12 mo LIPID profile: every 12 mo UA with microscopic evaluation UPC if non-diabetic: every 12 mo UACR if diabetic: every 12 mo	CONSULT Nephrology if eGFR declines by ≥ 4 mL/min/yr TARGETS BP: <130/80 mmHg LIPIDS: LDL-C <70–100, TG <150 mg/dL; non-HDL-C <130 mg/dL PROTEINURIA: UPC <0.2; UACR <30 mg/g; anti-proteinuric therapy with ACEI and/or ARB
BP monitoring: every 3–12 mo LYTES, Glucose, BUN, SCr, eGFR: every 6–12 mo CBC , reticulocyte ct, TSAT, ferritin if Hb 10–12 g/dL: every 12 mo CONSIDER Ca / P / PTH / 25(OH)D evaluations UACR or UPC: every 3–12 mo	Avoid nephrotoxins; rule out AKI/ARF, eg, obstruction TARGETS BP: <130/80 mmHg LDL-C: <70–100, TG <150, and non-HDL-C <130 mg/dL Hb: 10–12 g/dL, TSAT >20%, and ferritin >100 ng/mL UACR: <30 mg/g or UPC <0.2 with anti-RAS drug
BP monitoring: every 3–12 mo LYTES, Glucose, BUN, SCr, eGFR: every 3–12 mo CBC: Hb <10 g/dL every 1–3 mo until Hb 10–12 g/dL; then every 3–6 mo TSAT and ferritin if Hb <13 g/dL (males) or 12 g/dL (females) and after therapy BASELINE Ca / P / PTH / Alk Phos / 25(OH)D Ca / P / PTH / Alk Phos , depending on baseline and CKD progression 25(OH)D , depending on baseline and response to treatment EVALUATE for extraskeletal calcification UPC or UACR: every 6–12 mo	Avoid nephrotoxins; rule out ARF (eg, obstruction) NUTRITIONAL assessment at any time during CKD Stages 3–5 TARGETS Hb: 10–12 g/dL, TSAT >20%, ferritin >100 ng/mL with oral and/or iv iron and/or erythropoiesis stimulating agent Ca & P: to normal range with P-binders (no Ca-based P-binders if vascular / valvular calcification) 25(OH)D: ≥ 30 ng/mL with vitamin D2 / D3 iPTH: 130–600 pg/ml with calcitriol or vitamin D analogs if iPTH progressively increases NaHCO3: 22–26 mEq/L and titrate NaHCO3 therapy UPC: <0.2 or UACR <30 mg/g with anti-RAS drug
BP monitoring: every 3–6 mo LYTES, Glucose, BUN, SCr, eGFR every 3–12 mo CBC, TSAT, ferritin: every 3–6 mo BASELINE Ca / P / PTH / Alk Phos / 25(OH)D ; then repeat levels every 6–12 mo EVALUATE for extraskeletal calcification UPC or UACR: every 3–12 mo	CKD-specific education: kidney replacement therapy modality IMMUNIZATIONS: TIV, PPV-23, and HBV (consider Tdap, VZ) REINFORCE dietary prescription RENAL-formulated MVI PROTECT dominant (handwriting) arm VASCULAR access surgery evaluation TARGETS Hb: 10–12 g/dL, TSAT >20%, ferritin >100 ng/mL with oral and/or iv iron and/or ESA (darbepoetin or epoetin) Ca & P: to normal range with P-binders (no Ca-based P-binders if vascular / valvular calcification) 25(OH)D: ≥ 30 ng/mL with vitamin D2 / D3 iPTH: to 130–600 pg/mL with calcitriol or vitamin D analogs, if iPTH progressively increases NaHCO3: 22–26 mEq/L with NaHCO3 therapy UPC: <0.2 or UACR <30 mg/g with anti-RAS therapy (consider stopping anti-RAS therapy if GFR <20) HBV Ab titer: ≥ 10 mIU/mL

- Always consider reversible etiologies of acute kidney injury (AKI)/acute renal failure (ARF) at any stage of CKD, eg, urinary tract outlet obstruction, volume depletion, and adverse drug reactions.
- CKD Stage 5 patients require management by a nephrologist

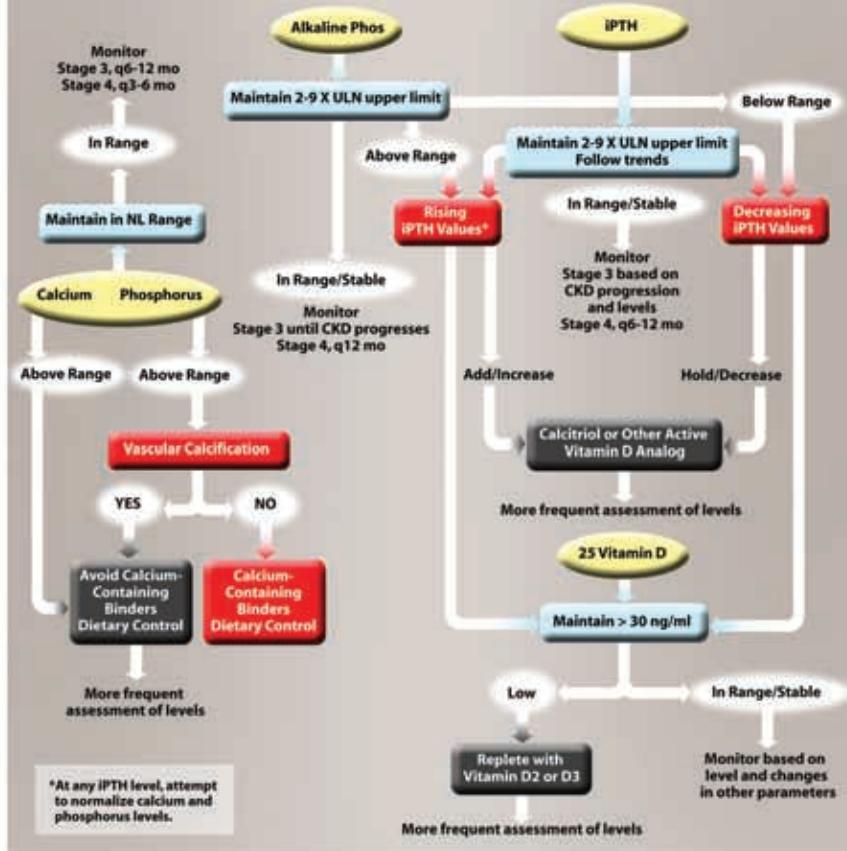
COMMENTS

- Baking soda is essentially NaHCO₃. It can be used to treat metabolic acidosis when NaHCO₃ is unavailable. 1 tsp of baking soda is equivalent to ~23 mEq Na and HCO₃.
- Calcium carbonate is poorly solubilized in high gastric pH (H₂ antagonists, PPIs, achlorhydria), reducing its efficacy.
- Aluminum-containing antacids are contraindicated in CKD because diminished renal excretion may cause adynamic bone disease, anemia and dementia.
- Acetate (calcium acetate) and carbonate (calcium carbonate) anions are metabolized to bicarbonate.
- Suboptimal drug combinations:
 - a) two Ca-based P-binders
 - b) Ca-based P-binder with NaHCO₃
 - c) sevelamer with Ca-based P-binder
 - d) lanthanum carbonate with Ca-based P-binder

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MANAGEMENT OF MINERAL-BONE DISEASE IN CKD



CKD-MBD treatment algorithm. Variables of interest are depicted as yellow ovals and parameter goals as blue rectangles. Appropriate management first requires establishment of baseline parameters followed by their trend analyses and periodic monitoring of the inter-relationships among these variables.

DYSLIPIDEMIA OF CHRONIC KIDNEY DISEASE by Jerry Yee

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 recently 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. 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 (triglyceride) levels stem from reduced endothelial lipoprotein lipase activity and 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 (*e.g.*, LDL-C). These defects combine with lowered HDL-C levels (low apoA-I and -II) to generate a highly atherogenic profile, with elevated Lp(a). In ESRD, LDL-C >130 mg/dL are present in 10–45% of non-nephrotic patients and TG levels are >200 mg/dL in 40–50% of these individuals. Importantly, **non-HDL-C [Total-C – HDL-C]**, which reflects serum TGs, correlates best with overall CVD risk in CKD and does not require assessment in the fasted state. Nephrotic range proteinuria stimulates LDL-C synthesis, and high LDL-C may be the dominant abnormality.

Lipid-Lowering Benefits

CKD clinical practice recommendations for lipid-lowering therapy in CKD are less evidence-based than NCEP ATP III guidelines due to a lack of large randomized, controlled trials. Two large trials (4D and AURORA) in ESRD patients demonstrated no cardiovascular or mortality benefits. A recent large, randomized controlled trial (SHARP) of CKD patients treated by *simvastatin/ezetimibe* demonstrated a positive effect of LDL-C-lowering therapy in *non-dialysis-dependent CKD* (*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-lowering therapy in CKD is recommended, if TGs >200 mg/dL and/or LDL-C >100 mg/dL after 3 months of therapeutic lifestyle changes (TLC). Lipid evaluation should be conducted at initial evaluation, 2–3 months after treatment changes, and at least, annually afterward. Treatment goals are equivalent to ATP III criteria for CHD and/or diabetes. LDL-C should be lowered to <100 mg/dL, with an optional, more aggressive goal of <70 mg/dL. Statins are first-line therapy in CKD patients with elevated LDL-C, but there is no preferred agent. Ezetimibe may be added to statin therapy. Bile acid sequestrants and niacin may be used, if statins cannot be used. Lastly, the target for combined dyslipidemia in CKD (TGs >200 mg/dL; non-HDL-C ≥130 mg/dL) is a non-HDL-C <130 mg/dL (*see CKD DYSLIPIDEMIA TREATMENT*).

Gemfibrozil is considered the fibric acid derivative (fibrates) of choice for CKD patients with elevated TGs. Fibrates must be administered cautiously with statins in CKD to avoid hepatic toxicity or myopathy. However, there is no evidence that statins induce a greater incidence of rhabdomyolysis in CKD patients, compared to the general population. Muscle pain from statin therapy is genetically predisposed and is not an effect of CKD.

Therapeutic Targets

TG	<150 mg/dL
LDL-C	<70–100 mg/dL (diabetes: optional goal is <70 mg/dL)
Non-HDL-C	≤130 mg/dL (= Total-C – HDL-C)

Evaluation

TG, LDL-C	Every 2–3 mo until treatment goal achieved, then every 6–12 mo
Non-HDL-C	Every 2–3 mo until treatment goal achieved, then every 6–12 mo

Treatment

“Statin”	Dose that reduces LDL-C to ≤70–100 mg/dL
Gemfibrozil	Limit to 300 mg twice daily for GFR <50 mL/min/1.73 m ²

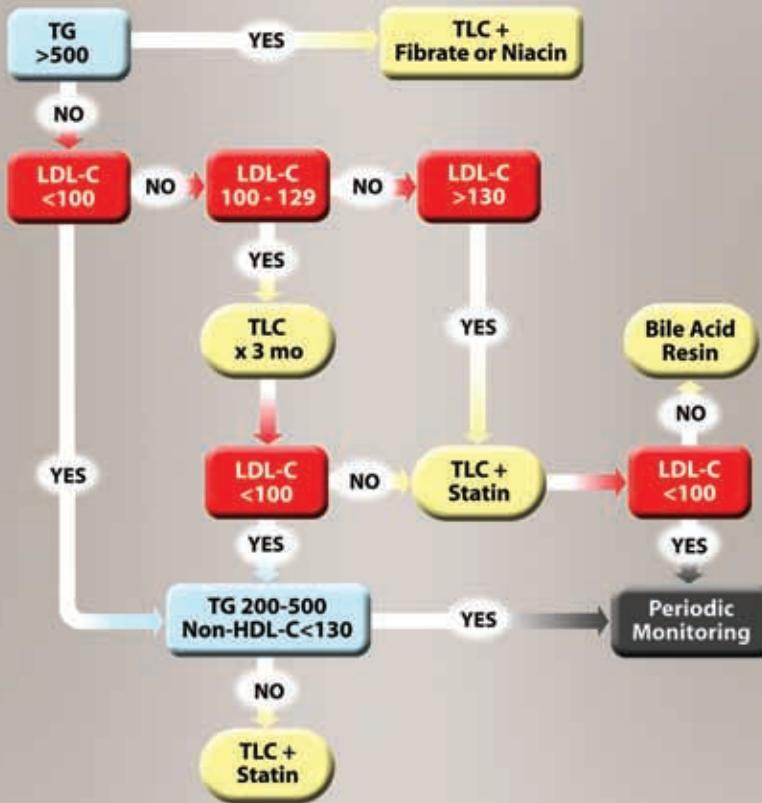
COMMENTS

- Baseline hepatic transaminase levels should be determined before initiating statin therapy, after 2–3 months of treatment and periodically afterward.
- Bile acid sequestrants are contraindicated, if TGs are >400mg/dl.
- CKD dose adjustments: atorvastatin and pravastatin do not require dose adjustments. It is unknown, if dose adjustments are required for simvastatin and fluvastatin. Lovastatin: a 50% dose reduction recommended, if GFR <60 mL/min/1.73 m².
- Ezetimibe (Zetia®): a cholesterol absorption inhibitor may be substituted, if statin therapy is not tolerated. Ezetimibe requires no dose adjustment at any level of CKD.
- Ezetimibe or coleselvam 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. Coleselvam is contraindicated, if TGs are increased.
- Non-HDL-C may be evaluated in the non-fasting state.
- Renal dietitian consultation, if fasting TGs ≥500 mg/dL and/or elevated LDL-C.
- Triglycerides: if TGs ≥200 mg/dL, non-HDL-C is the therapeutic target.

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CKD DYSLIPIDEMIA TREATMENT



Treatment of dyslipidemia in CKD. CKD patients are categorized in the highest NCEP cardiovascular disease risk group. LDL-cholesterol (LDL-C) reduction to <70-100 mg/dL is the primary treatment target. Secondary targets are triglyceride (TG) reduction to <150 mg/dL and non-HDL-cholesterol (non-HDL-C) reduction to <130 mg/dL. Therapeutic lifestyle changes (TLC) should be reinforced throughout the duration of treatment.

Abbreviations: NCEP, National Cholesterol Education Program; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglycerides.

Comments. HMG-CoA synthetase inhibitors (statins) are first-line agents for LDL-C elevations and should be maximized before adding a second therapeutic class of LDL-C lowering drugs. Bile acid sequestrants are contraindicated if TG >400 mg/dL.

NUTRITION IN CHRONIC KIDNEY DISEASE by M. Cristina Kilates

Introduction

Malnutrition evolves during the progression of CKD with electrolyte abnormalities, muscle mass reduction, and depressed immunological function. These problems are compounded by anorexia that often accompanies advanced CKD and poor food choice(s), *ie*, lack of high biological value protein. Hypoalbuminemia and related nutritional disorders, including vitamin and mineral deficiencies are common. Preventing malnutrition through periodic visits to a trained renal nutritionist for nutrition surveillance is recommended and may avert complications.

Protein Intake

High biological value protein intake should be maintained, while sodium, potassium, and phosphorus intake are restricted. Protein targets vary depending on CKD Stage (*see NUTRITIONAL TARGETS FOR CKD*). A controlled protein diet slows the decline of kidney function more than one with more liberal protein intake. Fluid restriction should only be instituted, if hyponatremia is present. The reduction of sodium and phosphate intake is much more important than restricting fluid intake, unless there is hyponatremia ($S_{Na} < 130 \text{ mEq/L}$).

Monitoring

A 24-h urine collection for sodium (goal $<100 \text{ mEq Na per 24-h}$), urea nitrogen and creatinine is highly informative regarding the level of compliance with a dietary prescription. 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 DASH (Dietary Approaches to Stop Hypertension) diet, which has proven efficacy. Modification of a DASH diet will be required in CKD patients because of its high potassium and phosphate contents. Lastly, patients with proteinuria at any stage of CKD should be referred to a Renal Dietitian/Nutritionist.

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)

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

HIGH POTASSIUM-CONTAINING FOODS

Avocado	K-salt substitutes, eg, Lite Salt*
Baked beans	Fresh peaches
Bananas	Mangoes
Blenderized fruits and vegetables	Milk
Brans	Nuts
Broccoli	Oranges, nectarines
Brussels sprouts	Papaya, pomegranate
Cantaloupe	Spinach
Chocolate	Tomatoes
Dried beans, legumes, peas	Sweet potatoes, white potatoes, yams
Dried fruits	Winter squashes (acorn, butternut, hubbard)

HIGH PHOSPHORUS-CONTAINING FOODS*

Baked beans	Nuts, nut butters
Bran	Organ meats
Brown rice, wild rice	Pizza
Cheese	Pancakes, waffles, biscuits
Chocolate and chocolate drinks	Processed meats: hot dogs, sausage, turkey
Cola	Sardines
Ice cream	Seeds
Milk, milk mixes	Whole grain breads
Milk-based coffees and puddings	Yogurt

*Food preservatives often contain “unlabeled” and unknown quantities of phosphate-rich preservatives and may contribute to hyperphosphatemia.

COMMENTS

- Caution is advised during administration of combination drugs with K-sparing diuretics: amiloride, triamterene, ACEIs, ARBs, and ARAs.
- Renal nutritionist consultation is recommended at any stage or CKD.
- Renal-formulated MVIs may be combined with iron salts.

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IMMUNIZATIONS IN CHRONIC KIDNEY DISEASE by Jerry Yee

Introduction

CKD patients are immunocompromised in CKD Stage 5 and ESRD; however, the degree of immunocompromise is less certain and documented in earlier stages. Nonetheless, CKD patients are immunized less frequently against influenza virus and *S. pneumoniae* than the general population. Influenza and pneumococcal vaccines may be co-administered. CKD patients should receive the following immunizations:

- a) Trivalent, *inactivated* influenza A/B (TIV) vaccine
- b) 23-valent polysaccharide pneumococcal (Pneumovax[®], PPV23) vaccine
- c) Hepatitis B virus (HBV) 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 lesser rates of seroconversion. In CKD Stage 5, antigen presenting cell and CD4 cell defects occur. 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. Hepatitis C virus (HCV) positive patients can be safely immunized against HBV. Lastly, booster vaccinations with tetanus toxoid, diphtheria, and acellular pertussis vaccines (Tdap) may be administered alone or co-administered with any of the vaccines listed below.

HEPATITIS B VACCINES: DOSES AND SCHEDULES

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

Abbreviations: IM, intramuscular.

[†]Special formulation (Recombivax HB Dialysis Formulation[®])

COMMENTS

- HBV immunization: evaluate antibody titer 2 mo after last dose.
- If antibody titer <10 mIU/mL, repeat entire dosing series and determine antibody response after 1–4 mo.
- Combined hepatitis A/B vaccine (Twinrix[®]) may be administered as a 3-dose series: 0, 1, and 6 mo.
- Healthcare workers who demonstrate an initial response to HBV immunization may be considered for a single booster dose after 5 years (Not FDA or NKF guideline).

Influenza Virus

United States Renal Data System data revealed that Medicare patients with chronic kidney disease (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 in order to decrease morbidity and mortality related to influenza. TIV immunization is now comprised of 2 “A” [one is H1N1] and 1 “B” virus strains and may be co-administered with pneumococcal vaccine. 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®).

Varicella zoster

Varicella zoster (VZ) re-activation or infection may be precipitated by the immunosuppression that follows organ transplantation. VZ immunization is available as two live, attenuated virus vaccines (Zostavax®, Varivax®). These may be administered in CKD patients. Patients undergoing consideration as organ transplant recipients should, where applicable, receive VZ immunizations pre-transplantation.

Vaccines

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

S. pneumoniae

Pneumovax® 23 Single 0.5-mL (25 mcg) IM (deltoid) injection.
Alternative: subcutaneous injection is permitted.

Revaccination with a single dose may be considered 5 years after the last dose in persons ≥ 65 y.o. who were <65 y.o. at the time of initial vaccination.

Tetanus, diphtheria (Td); Tetanus, diphtheria and pertussis (Tdap)

Td Dose 1 of initial series: 0.5-mL IM injection, upper arm
 Doses 2 and 3: 4–8 wk between doses 1 and 2
 and 6–12 mo between doses 2 and 3
 Booster doses: 0.5-mL IM injection every
 10 years after initial series
Tdap One dose is recommended for ages 19–64 y.o.

Trivalent Inactivated Influenza Vaccine

TIV Single annual dose IM

COMMENTS

- Intranasal live, *attenuated* influenza virus vaccine (FluMist®) is not FDA-approved for CKD patients.
- Oseltamivir phosphate (Tamiflu®) and zanamivir (Relenza®) neuraminidase inhibitors are not FDA-approved for CKD patients.
- HBV vaccines are contraindicated in persons with yeast allergy.
- Pneumococcal polysaccharide vaccine (Pneumovax® 23): persons without CKD and ≥ 65 y.o. should receive a 1-time revaccination, if < 65 y.o. at time of the initial vaccination and not re-vaccinated during the previous 5 years.

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Introduction

Anticipation of the need to initiate kidney replacement therapy (KRT) is paramount. Nearly 43% of CKD Stage 5/ESRD patients have no pre-ESRD evaluation by a nephrologist and often begin KRT in-hospital via a hemodialysis (HD) catheter. In these cases, healthcare expenditures during the initial 3 months of ESRD therapy increase by an average of \$30,000 per patient. To prevent this untoward clinical scenario, advanced CKD Stage 4 patients should be referred to a vascular access surgeon at $eGFR < 20 \text{ mL/min}/1.73 \text{ m}^2$ for timely planning of appropriate HD vascular access or peritoneal dialysis (PD) catheter placement.

In the US, lack of timely (early) vascular access planning, type of medical care prior to onset of ESRD, and socioeconomic factors result in a disproportionately high proportion of patients beginning KRT with in-hospital HD via temporary, non-tunneled, non-cuffed HD catheters that are associated with significant and costly morbidity (infections, venous stenosis) and mortality. To offset this trend, in 1997 the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI™) Clinical Practice Guidelines recommended earlier referral of CKD patients to nephrologists to facilitate vascular access evaluation and construction to optimize clinical outcomes and costs.

Timing of Kidney Replacement Therapy

The decision to treat patients with CKD by KRT as kidney transplantation, peritoneal dialysis, or hemodialysis should be made collaboratively by patients and their healthcare team. KRT is an expensive government entitlement program: minimum annual per patient cost, $\sim \$36,000$; annual average cost $\sim \$77,000$. Recent data reveal that starting KRT early does not increase patient survival. Although CKD Stage 5 begins at $eGFR < 15 \text{ mL/min}/1.73 \text{ m}^2$, KRT does not have to begin then, if the patient is well.

The number of comorbidities that a patient has must be taken into consideration before initiating KRT. Patients > 75 y.o., particularly, if male, with multiple comorbidities managed conservatively fare just as well as those on dialysis because death versus dialysis is a competing survival risk. Therefore, conservative management, when chosen, focuses the shift from simply attempting to prolong life to providing quality of life and alleviation of symptoms. This includes optimization of all parameters associated with CKD care (*see CHECKLIST*).

Education

An informed patient fares better than the non-informed one. CKD education entails information of various kidney replacement therapies: transplantation, PD, in-center HD, and home HD. Physical conditions such as vision and manual dexterity, motivational level to actively participate in care, and family/social circumstances all play roles in the decision-making process. CKD educational materials are widely distributed over the Internet. Patient advocacy groups have authored numerous, helpful informational materials written at an appropriate reading level (*see CKD WEBSITES OF INTEREST*). When adequately informed about ESRD modalities, 38% of CKD Stage 5 patients choose PD in comparison to 5% of patients who had not received more intensive ESRD-modality training. The provision of dedicated CKD education classes for patients and families, in conjunction with CKD clinics, has resulted in improved clinical outcomes, particularly in ESRD-modality training, vascular access placement, BP control, and anemia of CKD.

Peritoneal Dialysis

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. Peritoneal dialysis as a modality option was discussed with 61% of patients before initiation of dialysis. 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. BP and P 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 patients and/or volume-dependent HTN. Contraindications to PD include extreme obesity, multiple abdominal surgeries, and recurrent peritonitis. Complications of PD catheters include peritonitis, catheter malfunction, and failure of PD due to membrane loss/fibrosis. Peritonitis can be treated with intra-peritoneal or *iv* antibiotics and may require catheter exchange. Catheter removal is absolutely indicated when pseudomonal, MRSA, or fungal peritonitis occurs.

Hemodialysis

About 92% of the incident dialysis patients in the United States undergo conventional HD, typically carried out thrice-weekly in a designated HD unit, *i.e.*, 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 the home environment, 5–6 sessions weekly for 2.5–3 h. Control of BP and phosphorus are superior with PD, nocturnal PD, and home HD compared to conventional thrice-weekly HD.

Optimal HD requires a well-functioning vascular access and this can be provided via an autogenous AVF (arteriovenous fistulas), bioprosthetic AVG (arteriovenous grafts), or HD catheters. The AVF is the best HD vascular access and most closely satisfies the requirement for adequate blood flow delivery to the dialysis machine, and has the lowest maintenance cost among all vascular access types. Notably, the failure of access function limits the ***delivered dose of dialysis***, a major survival determinant.

Vascular Access Planning and Construction

Key issues include timely nephrology referral; vein preservation; vascular access creation planning; timely referral to a surgeon specialized in access construction; post-construction follow-up; and appropriate intervention(s). Protection of superficial hand and forearm veins, particularly of the non-dominant arm, is critical in CKD patients. The dorsum of the hand should be used for peripheral lines and blood draws. The patient should be evaluated by venous mapping, preferably by ultrasound duplex scanning of the non-dominant arm (non-hand writing); if unsuitable, the dominant arm may be used for access creation. The patient and healthcare workers must know the intended surgery site. Therefore, vein preservation during hospitalizations and outpatient care must occur. Subclavian vein catheter placement(s) and PICC lines are discouraged and are associated with high central vein stenosis rates, and their use may preclude access creation(s). Cardiac AICD and pacemaker placements should be contralateral to the *planned* vascular access arm. Educational programs reinforcing the above should be provided to patients, their families and healthcare providers.

Preparation of the HD patient includes surgical vascular access construction. An AVF, typically created from a native artery and vein in the distal non-dominant upper extremity, is the optimal HD vascular access. Placement of an AVF should precede the time of anticipated HD by 6 months, to ensure sufficient fistula *maturational* before HD needle cannulation. When AVF creation is not feasible, AVG construction should proceed 3–6 weeks before anticipated HD.

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MEDICATION-RELATED PROBLEMS by Carol Moore

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 AKI/ARF or in 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.

Crystalluric 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 Ca-P 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 AKI/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-d 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 h before, during and 12 h after contrast administration.
- **Drugs:** stop diuretics (if feasible), NSAIDs, and metformin >48 h pre-contrast delivery.
- **Radiocontrast medium:** isosmolar radiocontrast (iodixanol, Visipaque®, 290 mOsm/kg) has reduced the risk of AKI/ARF in higher risk patients, *i.e.*, diabetes.
- **Diabetes:** glycemic control should be achieved prior to acute contrast delivery, *e.g.*, 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.

Gadolinium (Gd): Gd-based contrast agent (GBCA) procedures, *e.g.*, 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 at 1–4% in advanced CKD. Alternatives to Gd-based imaging studies should be aggressively sought in CKD Stages 4 and 5 and ESRD patients.

Three GBCA, gadopentetate dimeglumine (Magnevit™), gadodiamide (Omniscan®), and gadoversetamide (Optimark®) are contraindicated for patients with acute kidney injury (AKI) or severe CKD because NSF risk is deemed higher in these individuals. 4 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 GBCA administration and to monitor kidney function post-receipt of Gd-chelates. Serial hemodialyses to remove GBCA rapidly may be required in CKD Stages 4 and 5 patients and ESRD patients.

NB: *Gadodiamide and gadoversetamide may cause spurious hypocalcemia by interfering with total serum calcium assays. Avoid 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-RAS 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.
- ARAs: Spironolactone (Aldactone[®]) and eplerenone (Inspira[®]).

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 advised 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 ($K, 5.0\text{--}5.5$ mEq/L) usually requires no treatment, and dietary potassium restriction is the primary therapy.

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, but are not recommended for $eGFR <25 \text{ mL/min}/1.73 \text{ m}^2$
- GLP-1 receptor agonists: exenatide (Byetta[®]) is contraindicated for $eGFR <30 \text{ mL/min}/1.73 \text{ m}^2$; 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 $\text{GFR} <10 \text{ mL/min}/1.73 \text{ m}^2$.

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

- Metformin is contraindicated, if $\text{GFR} <50 \text{ mL/min}/1.73 \text{ m}^2$, *i.e.*, $\text{SCr} \geq 1.5 \text{ mg/dL}$ in males or 1.4 mg/dL in females in CKD or AKI.
- Stop metformin before iodinated radiocontrast delivery and hold for 48 h post-procedure. Restart drug after kidney function returns to baseline.

Mitochondrial damage: nucleoside analogs, *eg*, zalcitabine (ddC, Hivid[®]), didanosine (ddI, 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 and 5.
- Meperidine hydrochloride (Demerol[®]) metabolite, nor-meperidine, accumulates and can induce seizures; contraindicated in advanced CKD.

Neuropathy:

- Colchicine (Colcrys[®]): 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 (Macrodantin[®]): 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 Carol Moore

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 wk.

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 wk.

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)

Begin ESA treatment of Anemia of CKD at Hb <10 g/dL, if there is no iron deficiency.

The FDA target Hb range is 10–12 g/dL. 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 Hb <10 g/dL**

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

CKD: 40–100 mcg subcutaneously every 1–4 wk (0.45 mcg/kg/q wk)

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

Consult nephrologist for assistance in appropriate dosing.

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Epoetin alfa (recombinant human erythropoietin; Epogen®)

Indication: Anemia of CKD; **begin therapy at Hb <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 wk (50–100 Units/kg/wk)

Consult nephrologist for assistance in appropriate dosing.

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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 (ESRD: >200 ng/mL). Consult a nephrologist for assistance in appropriate dosing of parenteral iron and ESAs, which should not be initiated until the Hb is <10 g/dL.

Oral formulations

These agents should only be taken on an empty stomach. Take oral iron 2 h before or 4 h after antacids and at least 1 h 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 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 wt. (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%.

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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 min.
- Standard dilution for infusion is 125mg iron in 100 mL normal saline.
- Delivery rate not to exceed 250 mg iron over 60 min.
- Product is FDA approved in ESRD as a 125-mg dose *iv*.

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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 min
- Standard dilution for infusion is 100 mg iron in 100 mL normal saline
- Delivery rate not to exceed 150 mg iron over 60 min, *i.e.*, 300 mg/2-h
- Product is FDA-approved for CKD Stages 3–5, including ESRD

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Ferumoxytol (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 510mg 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 \geq 17 seconds.
- Delivery rate not to exceed 30 mg per second.
- Product is FDA-approved for CKD Stages 3–5, including ESRD.
- Ferumoxytol may affect the diagnostic ability of MRI for up to 3 mo. Gd-based studies should be conducted prior to ferumoxytol administration

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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 dose exceeds 9 GelCaps.

- FDA approved for CKD Stage 5

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 hydrochloride (Renagel®)

Sevelamer carbonate (Renvela®)

Indication: P-binder therapy in CKD

Renagel® Tablet: 400 mg or 800 mg tablets

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.

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- 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.

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- FDA-approved for CKD Stage 5.

COMMENTS

- Do not take Ca-based P-binders with iron salts or NaHCO₃.
- Calcium carbonate is not FDA-approved for use as a P-binder.
- Dietary and prescribed elemental Ca should not exceed 2000 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 >1500 mg, Corr Ca >10.2 mg/dL, or P >4.6 mg/dL.

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 and once monthly × 8, if 25(OH)D <15 ng/mL and 50,000 IU once monthly × 6, if 25(OH)D is 15–30 ng/mL unless Corr 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 mo, 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, 2000 IU, 1750 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. Vitamin D3 1750 IU once daily ≈ Vitamin D2 50,000 IU monthly).

Active Vitamin D Sterols

Active vitamin D sterols should only be initiated when 25(OH)D level is >30 ng/mL, with elevated iPTH. 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 (**see Comments, p. 35**).

Calcitriol [$1\alpha,25(\text{OH})_2\text{D}3$; 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 Corr Ca and P every 2 wk initially.

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

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Doxercalciferol [$1\alpha(\text{OH})\text{D}2$; 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 >70 pg/mL: 1.0 mcg once daily with increases of 0.5 mcg and monitoring of serum Corr Ca and P every 2 wk initially.

CKD Stage 4: iPTH >110 pg/mL: 1.0 mcg once daily with increases of 0.5 mcg and monitoring of serum Corr Ca and P every 2 wk 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 Corr Ca and P every 2 wk initially.

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Paricalcitol [19-nor-1 α -OH₂D2; 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 ≤500 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 wk.
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 Corr Ca and P every 2 wk.

CKD Stage 5: If iPTH >150 pg/mL: Initiate 1–2 mcg per HD (titrated to goal iPTH, maximum dose 15 mcg per HD treatment) with monitoring of serum Corr Ca and P every 2 wk, initially.

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Calcimimetics

Cinacalcet (Sensipar®)

Indication: Treatment of SHPT in ESRD.

Tablet: 30, 60, and 90 mg tablet.

Maximum daily dose: 180 mg.

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

- a) Initiate cautiously in patients with Ca <8.4 mg/dL.
- b) Monitor frequently for hypocalcemia during therapy.
- c) PTH should only be drawn >8 h after dose is taken.

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Renal-Formulated Multivitamins (MVs)

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 mg elemental iron).

Niferex® for CKD: 1 capsule once daily.

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

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

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<http://www.fda.gov/Drugs/DrugSafety/ucm223966.htm>; Accessed 1/10/2011
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DIAGNOSTIC CODING PRINCIPLES by Jerry Yee

Introduction

Coding errors are frequent in CKD. For patients with GFRs <60 mL/min/1.73 m² (CKD Stage 3), the sensitivity and specificity of kidney disease diagnostic codes are 11% and 96%, respectively. Sensitivity increases to 14% in diabetic, hypertensive patients >60 y.o. with CVD. Since CKD is associated with multiple comorbid conditions, most CKD patients can be assigned multiple ICD-9-CM codes: anemia of CKD (285.21), benign HTN with CKD (403.1x), proteinuria (791.0), dyslipidemia (272.x), metabolic acidosis (276.2), and renal edema formation (276.6), without heart failure.

Diagnoses must be first established and documented for appropriate coding and billing. For example, a CKD Stage 4 patient might have CKD-MBD, with associated bone disease, *eg*, renal osteodystrophy (588.0), vascular calcification, hypovitaminosis D (268.9), and secondary hyperparathyroidism of renal origin (588.81). However, to code all of these problems, an appropriate combination of abnormal radiographs, DEXA scans or bone biopsy, elevated bone-specific alkaline phosphatase or PTH, and low vitamin D levels would be required. Code only “what you know” and “what you can document.”

Classification

Kidney diseases are found in the ICD-9-Clinical Modification Tabular Index under **Section 10: Diseases of the Genitourinary System** (580–629), principally as codes 580–589. Hypertensive disorders are defined as codes 401–405 in **Section 7: Diseases of the Circulatory System** (390–459). Complicating features of CKD such as acid-base, fluid and electrolyte disorders are primarily found as codes 275–276 in **Section 3: Endocrine, Nutritional and Metabolic Diseases and Immunity Disorders** (240–279). Notably, this section includes codes for diabetic kidney disease, with additional specification by the level of glycemic control (250.4x).

Approach to Diagnostic Coding in CKD

Diagnostic coding of CKD typically follows one of these patterns: a) diabetic kidney disease; b) hypertensive kidney disease; c) glomerular diseases, primary or secondary; d) vascular disorders (renal artery disease, microangiopathy); e) tubular and interstitial disorders (urinary tract infection, stones, urinary tract outlet obstruction, drug toxicity); f) cystic diseases; g) acute kidney injury; and h) kidney transplantation-related problems.

Coding should be applied as specifically as possible, with appropriate utilization of 4th and 5th digits. For example, codes are specific for types 1 and 2 diabetes and their complications. Diabetic complications are assigned 4th digits (250.*xx*), and the degree of glycemic control is assigned a 5th digit (250.*xx*).

Diagnoses of electrolyte disorders should be completely spelled out, *ie*, hyponatremia and hyperkalemia must **not be documented with shorthand forms or symbols**: **hyponatremia** must be used instead of ↓Na⁺ and **hyperkalemia** must be used instead of ↑K⁺. Lastly, symptoms and signs of CKD also have specific codes, *eg*, dysuria, hematuria, nocturia, tenesmus, *etc*.

CKD Codes

ICD-9-CM codes for CKD have been reclassified and parallel clinical stratification of CKD. Before 3 months, use the ARF code. After 3 months of kidney disease, a CKD Stage-specific code should be used. The invalid Code 585 has been replaced by CKD Stage-specific codes, 585.1–585.6 and 585.9 (*see Tables*).

Specifically, code 585.5 denotes CKD Stage 5, but not ESRD (585.6) or CKD, unspecified (585.9). If CKD results from systemic illness, that disorder is coded first. For example, a hypertensive SLE patient with diffuse proliferative glomerulonephritis of 5 months duration and laboratory findings: SCr >2.5 mg/dL, GFR 43 mL/min/1.73 m², BP 153/90 mmHg, iPTH 220 pg/mL, 25(OH)D 18 ng/mL, Hct 29%, and UPC 5.3, is coded as follows.

- **Systemic disorder:** SLE (710.0); *Etiology*, proliferative glomerulonephritis (581.0) and CKD Stage 3 (585.3).
- **Complications:** benign HTN of CKD (403.1x), secondary hyperparathyroidism of renal origin (588.81), hypovitaminosis D, unspecified (268.9), anemia of CKD (285.21), and proteinuria (791.0).

Hypertension Codes

Codes for HTN are grouped as 401–405. When documenting HTN, the adjective “benign” or “malignant” should always precede the diagnosis of HTN. Primary (essential or benign) HTN without CKD is coded 401.9. However, if high BP is the cause of CKD, benign HTN of CKD often termed “hypertensive nephrosclerosis” (403.1x) is coded first followed by a CKD Stage-specific code. For example, an individual with HTN for 20 years, GFR 50 mL/min/1.73 m², and microalbuminuria should be assigned codes 403.10, 585.3, and 791.0. If HTN follows the onset of diabetic CKD and is not “malignant” (asymptomatic, not requiring hospitalization or associated with acute target organ damage), then the code for “benign” hypertension associated with CKD Stages 1–5 but not ESRD (403.10) should follow coding of the primary disorder *with* a CKD Stage code (eg, 250.40, 403.10, and 585.x). In this case, the diabetic nephropathy code (250.4x) is followed by the benign HTN of CKD code (403.10), and the CKD stage code (585.x).

Hypertensive nephrosclerosis cannot be coded concurrent with primary hypertension (401.9) or secondary hypertension (405.0–405.9). Generalized or regional atherosclerosis often accompanies hypertension and these disorders can also be coded when actively managed. However, coding here may be more appropriately coded as unspecified hypertension, with CKD (403.90, 403.91).

CKD Complication Codes

This section describes under-coding of CKD-associated complications. Mineral, electrolyte and acid-base disturbances of CKD are often diagnosed and managed, but not coded.

Hypotonicity/hyponatremia, hypertonicity/hypernatremia, dyskalemias, dyscalcemias, phosphorus disorders, and acid-base disturbances should be coded when present, appropriately documented and addressed in the treatment plan (*see above*). Hyperuricemia is coded as abnormal blood chemistry (790.6) and is frequent in CKD, but it does not define gout (274.0–274.9) or uric acid stone disease (274.11).

CKD Code Omissions

Coding omissions are frequent in CKD. For example, the codes for hypertensive heart and CKD (404.x) are underutilized. In addition, all UTIs (599.0) should be coded concurrently with organism-specific codes (*eg. E. coli* 482.2). Lastly, parenchymal abnormalities such as cysts (acquired 593.2; congenital 753.10, 753.11; ADPKD 753.13) or agenesis/dysgenesis (753.0) and dysplasia (753.15) have specific codes, but are often not coded at all.

COMMENTS

- Evaluation and Management coding of CKD should be internally reviewed at each institution and with respective healthcare payors.
- ICD-9-CM will eventually be phased out in the United States.
- ICD-10-CM is a more complicated system that is substantially more robust in its descriptive capabilities.
- The codes described in this section will no longer be applicable at the time of ICD-10-CM implementation.

REFERENCES

H Quan, et al. Med Care 43: 1130, 2005

CHRONIC KIDNEY DISEASE DIAGNOSTIC CODES

Disorder	Code	Comment
Acute Renal Failure (ARF, AKI)	584.9	Excludes any CKD Code
CKD, Stages 1–5	585.x	x = 1–5 for CKD Stages 1–5
CKD at end-stage renal disease (ESRD)	585.6	Chronic kidney replacement therapy initiated, eg, HD, CAPD, kidney transplantation (add V42.0)
CKD, UNSP	585.9	CKD, w/o established etiology. Excludes ARF (584.9)
Kidney failure, UNSP (not from pregnancy, HTN)	586	Acuity/chronicity and etiology of kidney failure are unknown
Renal sclerosis, UNSP	587	Implies small kidneys
Impaired kidney function, NOS	588.9	See kidney failure, UNSP (586)
Small kidney, unilateral	589.0	By confirmatory imaging study
Small kidneys, bilateral	589.1	By confirmatory imaging study
Small kidney, NOS	589.9	By confirmatory imaging study
Anemia of CKD	285.21	EPO Level Not Recommended
Anemia of other chronic disease	285.29	Excludes anemia of CKD (285.21) and anemia of malignancy (285.22)
Anemia, iron deficiency	280.9	In CKD, iron deficiency is TSAT <20% and/or ferritin <100 ng/mL
Nephrotic s. (nephrosis), from systemic disorder	581.81	Code first underlying disease, eg, type 2 diabetes mellitus (250.4 x)
Nephrotic s. (nephrosis), NOS	581.9	Albuminuria/proteinuria, hypercholesterolemia and edema
Renal osteodystrophy (ROD)	588.0	CKD-MBD manifested as osteitis, osteomalacia, osteoporosis, sclerosis
Secondary HPT, renal origin	588.81	iPTH >70 pg/mL at any CKD Stage
Other specified disorder	588.89	Result of impaired function
Vitamin D deficiency, UNSP	268.9	25(OH)D level <30 ng/mL
Diabetes, Type 1 w/ CKD, Controlled glycemia	250.41	Add CKD Stage-specific code (585. x)
DM, Type 1 w/ CKD and uncontrolled glycemia	250.43	Add CKD Stage-specific code (585. x)
DM, Type 2 w/ CKD and controlled glycemia	250.40	Add CKD Stage-specific code (585. x)
DM, Type 2 w/ CKD and uncontrolled glycemia	250.42	Add CKD Stage-specific code (585. x)
Dyslipidemia	272.x	x = 0 cholesterol; 1 triglyceride; 2 mixed (cholesterol and triglyceride)
Glucose, elevation; hyperglycemia	790.2 x	x = 1 fasting glucose; 9 non-fasting glucose, NOS

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; HTN, hypertension; PKD, polycystic kidney disease; NOS, not otherwise specified; ULN, upper limit normal; UNSP, unspecified.

CHRONIC KIDNEY DISEASE DIAGNOSTIC CODES

Disorder	Code	Comment
Benign/Essential HTN w/ No CKD	401.9	Normal GFR w/ No Proteinuria and No Hematuria
Malignant HTN CKD, Stages 1–4 or UNSP	403.00	Add CKD Stage-specific code (585. x)
Malignant HTN CKD, Stage 5 or ESRD	403.01	Add CKD Stage-specific code (585. x)
Benign HTN CKD, Stages 1–4 or UNSP	403.10	Add CKD Stage-specific code (585. x)
Benign HTN CKD Stage 5 or ESRD	403.11	Add CKD Stage-specific code (585. x)
UNSP HTN CKD, Stages 1–4	403.90	Add CKD Stage-specific code (585. x); unknown, if malignant or benign
UNSP HTN CKD, Stage 5 or ESRD	403.91	Add CKD Stage-specific code (585. x); unknown, if malignant or benign
Hypertensive heart and kidney disease	404. xx	Add CKD Stage-specific code (585. x); refer to ICD-9-CM (Section 404)
Benign renovascular HTN	405.11	Diagnosis established by imaging study. Excludes 405.19.
UNSP HTN, secondary	405.9	Excludes essential HTN (401.9)
Benign HTN, secondary, not renovascular	405.19	Include with diabetes and CKD Stages 1–5 and ESRD, Excludes 403. xx . Excludes renovascular origin (405.11).
Hyperaldosteronism, UNSP	255.10	
HTN, w/o a formal, prior diagnosis of HTN	796.2	Incidental or transient finding; use for "white coat" HTN
Infectious Pyelonephritis	590. x	x = chronic disorder; 1 acute
Other specified pathological kidney lesion/abnormality	583.89	Glomerulonephritis or interstitial nephritis not specified elsewhere
Cystic kidney disease, acquired	593.2	Excludes codes 753.1, 753.13
Cystic kidney disease, NOS	753.10	Excludes codes 593.2, 753.13
ADPKD, PKD	753.13	Excludes codes 593.2, 753.10
Calculus (Stone), Kidney; Nephrolithiasis	592.0	Excludes stone in bladder, pelvis and/or ureters
Calculus, ureter	592.1	Includes stone in pelvis or ureter
Calculus, uric acid	274.11	Excludes 592.0
Renal colic	788.0	Symptom code
Hyperuricemia	790.6	Abnormal blood chemistry

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; HTN, hypertension; PKD, polycystic kidney disease; NOS, not otherwise specified; ULN, upper limit normal; UNSP, unspecified.

CHRONIC KIDNEY DISEASE DIAGNOSTIC CODES

DISORDER	CODE	COMMENT
DISORDER OF MAGNESIUM	275.2	HYPOTHYROIDISM OR HYPERMAGNESEMIA
Phosphorus/phosphate	275.3	Hypo- or hyperphosphatemia
Calcium	275.4x	x = 1 hypocalcemia; 2 hypercalcemia
Potassium	276. x	x = 7 hyperkalemia; 8 hypokalemia
Sodium	276. x	x = 0 hypernatremia; 1 hyponatremia
Chloride	276.9	Hypo- or hyperchloremia
Acidosis	276.2	Metabolic and/or respiratory
Alkalosis	276.3	Metabolic and/or respiratory
Acid-Base disorder, mixed	276.4	Acidosis and/or alkalosis
Volume depletion, UNSP	276.50	Salt and/or water Loss, w/ or w/o dehydration
Dehydration (complication/comorbid condition)	276.51	Perform "orthostatic vital signs" for payment; see volume depletion (276.50, 276.52)
Hypovolemia, volume depletion	276.52	Volume depletion w/ or w/o dehydration
Edema, renal origin without heart failure	276.6	Excludes edema from heart- and/or liver disorder, eg, cirrhosis (782.3)
Edema, non-renal origin	782.3	Edema from heart failure or cirrhosis
Hypotension, orthostatic	458.0	Excludes hypotension (458.9)
Hypotension, low BP	458.9	Excludes volume depletion (276.50)
UTI UNSP; Non-Candida species	599.0	Clinical or Lab Diagnosis
Urinary tract obstruction, UNSP	599.60	Code 599.6 is invalid; Excludes BPH w/ obstruction (600.01)
Hematuria, UNSP	599.70	Symptom, positive dipstick
Hematuria, gross	599.71	Patient-related symptom
Hematuria, microscopic	599.72	Hematuria confirmed by microscopy
Urinary retention, NOS	788.20	Symptom code
Incomplete bladder emptying	788.21	Symptom code
Urinary symptoms	788.4x	x = 1 frequency; 2 polyuria; 3 nocturia
Urinalysis, abnormal dipstick or microscopic evaluation	791. x	x = 0 protein; 2 hemoglobinuria; 5 glucose; 6 ketones; and 7 cells or casts; Excludes hematuria (599.7)

Abbreviations: **ADPKD**, autosomal dominant polycystic kidney disease; **HTN**, hypertension; **PKD**, polycystic kidney disease; **NOS**, not otherwise specified; **ULN**, upper limit normal; **UNSP**, unspecified.

CKD WEBSITES OF INTEREST

American Association of Kidney Patients: <http://www.aakp.org/>

American Kidney Fund: <http://www.kidneyfund.org/kidney-health/>

American Society of Nephrology: <http://asn-online.org>

American Society of Hypertension:

http://www.ash-us.org/patient_edu/pdffiles/BloodPressureHealthEnglish.pdf

http://www.ash-us.org/patient_edu/pdffiles/BloodPressureHealthSpanish.pdf

American Society of Pediatric Nephrology: <http://aspneph.com>

Centers for Medicare and Medicaid Services:

<http://www.cms.hhs.gov/ICD9ProviderDiagnosticCodes/>

Dietary Approaches to Stop Hypertension (DASH): <http://dashdiet.org>

Greenfield Health Systems:

http://Ghsrenal.Com/CKD/HFHS_CKD_Guidelines_v6.0.pdf

Hypertension Online: <http://www.hypertensiononline.org/index.cfm>

Immunizations:

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

International Society of Nephrology:

<http://www.isn-online.org/isn/society/about/index.html>

Kidney Disease: Improving Global Outcomes (KDIGO™): <http://kdigo.org>

National Anemia Action Council: <http://www.anemia.org>

National Kidney Disease Education Program:

<http://kidney.niddk.nih.gov/kudiseases/pubs/proteinuria/index.htm>

<http://kidney.niddk.nih.gov/kudiseases/pubs/yourkidneys/>

National Kidney Foundation:

<http://www.kidney.org/professionals/ks/cmeprograms.cfm>

National Kidney Foundation: <http://kidney.org>

National Kidney Foundation of Michigan:

<http://www.kidney.org/site/index.cfm?ch=306>

Nephron Information Center: <http://www.nephron.com>

Renal Physicians Association: <http://www.renalmd.org/>

United States Renal Data System Coordinating Center: <http://www.usrds.org/>

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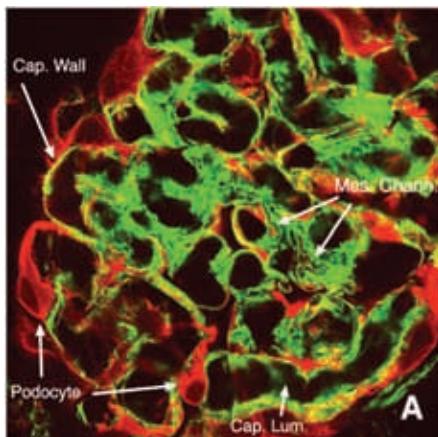
WEBSITE MANAGEMENT by Gerard Zasuwa

Updated editions of “**CHRONIC KIDNEY DISEASE (CKD): CLINICAL PRACTICE RECOMMENDATIONS FOR PRIMARY CARE PHYSICIANS AND HEALTHCARE PROVIDERS — A COLLABORATIVE APPROACH (EDITION 6.0)**” can be obtained from the Greenfield Health Systems website in Adobe portable document format (pdf).

GHSRENAL.COM/CKD/HFHS_CKD_GUIDELINES_V6.0.PDF
(Webmaster: Gerard Zasuwa)

PURCHASING INFORMATION

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Glomerulus III: Architecture — Pedro Cortes

IF LOST, PLEASE RETURN TO THE OWNER:

“... the ghosts of dead patients that haunt us do not ask why we did not employ the latest fad of clinical investigation. They ask us, why did you not test my urine?”

— SIR ROBERT GRIEVE HUTCHISON (1871–1960) —

CHRONIC KIDNEY DISEASE CHECKLIST

CKD IDENTIFICATION		RISK ASSESSMENT	RULE OUT AKI/ARF
<input type="checkbox"/> MDRD GFR <60 mL/min	<input type="checkbox"/> UPC >0.2	<input type="checkbox"/> Hypertension	<input type="checkbox"/> R/O obstruction
<input type="checkbox"/> UACR >30 mg/g	<input type="checkbox"/> Hematuria	<input type="checkbox"/> Diabetes	<input type="checkbox"/> R/O hypovolemia
<input type="checkbox"/> Kidney stones	<input type="checkbox"/> Structural defect	<input type="checkbox"/> Metabolic syndrome	<input type="checkbox"/> Heart failure
<input type="checkbox"/> Small kidney sizes		<input type="checkbox"/> Morbid obesity	<input type="checkbox"/> Hypotension
		<input type="checkbox"/> Elevated LDL-C	<input type="checkbox"/> Nephrotoxic drug
		<input type="checkbox"/> Heart failure	<input type="checkbox"/> NSAID, COX-1/2
		<input type="checkbox"/> Family History of CKD	<input type="checkbox"/> Rhabdomyolysis
		<input type="checkbox"/> Ethnicity	<input type="checkbox"/> Radiocontrast agent
CVD RISK REDUCTION		<input type="checkbox"/> Autoimmunity	<input type="checkbox"/> Phosphate cathartic
<input type="checkbox"/> Aspirin	<input type="checkbox"/> Beta blocker	<input type="checkbox"/> Environmental toxin	
<input type="checkbox"/> Smoking cessation	<input type="checkbox"/> Weight reduction	<input type="checkbox"/> Nephrotoxic drug	
		<input type="checkbox"/> Cigarette smoking	
		<input type="checkbox"/> Preeclampsia	<input type="checkbox"/> LDL-C <100
		<input type="checkbox"/> Recurrent UTIs	<input type="checkbox"/> Non-HDL-C <130 mg/dL
		<input type="checkbox"/> Prior Hx of AKI/ARF	<input type="checkbox"/> TG <150 mg/dL
			<input type="checkbox"/> ↑ LDL-C → statin
			<input type="checkbox"/> ↑ TG → gemfibrozil
DIABETES		PROTEINURIA	DYSLIPIDEMIA
<input type="checkbox"/> BP <130/80 mmHg	<input type="checkbox"/> ACEI or ARB	<input type="checkbox"/> ACEI or ARB	<input type="checkbox"/> LDL-C <100
<input type="checkbox"/> HbA1C <7% (eAG, 154)	<input type="checkbox"/> UACR <30 mg/g	<input type="checkbox"/> DRI or ARA	<input type="checkbox"/> Non-HDL-C <130 mg/dL
<input type="checkbox"/> Glipizide preferred		<input type="checkbox"/> BP optimized	<input type="checkbox"/> TG <150 mg/dL
		<input type="checkbox"/> NDHPCCB	<input type="checkbox"/> ↑ LDL-C → statin
		<input type="checkbox"/> ACEI + ARB	<input type="checkbox"/> ↑ TG → gemfibrozil
HYPERTENSION		RENAL NUTRITION	
<input type="checkbox"/> BP <130/80 mmHg	<input type="checkbox"/> Diuretic	<input type="checkbox"/> Pentoxyphylline	
<input type="checkbox"/> ACEI or ARB			
<input type="checkbox"/> JNV 7 Compelling Indication(s)	<input type="checkbox"/> U _{Na} <100 mEq/24-h	<input type="checkbox"/> Ca & P in normal range (at any iPTH level)	<input type="checkbox"/> Protein restriction
<input type="checkbox"/> UPC <0.2		<input type="checkbox"/> PTH 130–600 pg/mL	<input type="checkbox"/> Na & K restriction
		<input type="checkbox"/> Trend Alk Phos	<input type="checkbox"/> P Restriction
		<input type="checkbox"/> Extraskeletal calc'n	<input type="checkbox"/> Renal MVI
		<input type="checkbox"/> 25(OH)D ≥30	<input type="checkbox"/> Caloric restriction
			<input type="checkbox"/> Renal nutritionist
ANEMIA OF CKD		IMMUNIZATIONS	
<input type="checkbox"/> Hb 10–12 g/dL	<input type="checkbox"/> R/O blood loss	<input type="checkbox"/> ACEI or ARB	<input type="checkbox"/> HBV
<input type="checkbox"/> TSAT ≥20%	<input type="checkbox"/> UPC <0.2	<input type="checkbox"/> Active Vitamin D	<input type="checkbox"/> HBV Ab titer ≥10 IU/mL
<input type="checkbox"/> Ferritin ≥100 ng/mL		<input type="checkbox"/> P-binder Rx	<input type="checkbox"/> TIV, annual
<input type="checkbox"/> Vit B ₁₂ & Folate		<input type="checkbox"/> 25(OH)D ≥30	<input type="checkbox"/> Pneumovax, initial
<input type="checkbox"/> Iron therapy: po / iv	<input type="checkbox"/> Inflammation	<input type="checkbox"/> Vitamin D2 or D3	<input type="checkbox"/> Pneumovax, booster
<input type="checkbox"/> ESA treatment		<input type="checkbox"/> Active Vitamin D	<input type="checkbox"/> Tdap, booster
METABOLIC ACIDOSIS		LATE-STAGE CKD	
		<input type="checkbox"/> P-binder Rx	<input type="checkbox"/> Adjust drug dose(s)
		<input type="checkbox"/> HCO ₃ 22–26 mEq/L	<input type="checkbox"/> Protect access arm
		<input type="checkbox"/> NaHCO ₃ Rx	<input type="checkbox"/> Access evaluation
		<input type="checkbox"/> Protein restriction	<input type="checkbox"/> Consider transplant

Abbreviations: **Alk Phos**, alkaline phosphatase; **ARA**, aldosterone receptor antagonist; **DRI**, direct renin inhibitor; **eAG**, estimated average glucose; **ESA**, erythropoiesis-stimulating agent; **UACR**, urine albumin-to-creatinine ratio; **UPC**, urine protein-to-creatinine ratio; **TSAT**, transferrin saturation; **NDHPCCB**, non-dihydropyridine calcium channel blocker; **TIV**, trivalent inactivated influenza vaccine.

NEPHROLOGY CONSULTATION MAY BE CONSIDERED AT ANY STAGE OF CKD

NOTES



DIVISIONS OF NEPHROLOGY & HYPERTENSION
AND GENERAL INTERNAL MEDICINE