

VHA/DoD CLINICAL PRACTICE GUIDELINE FOR THE
MANAGEMENT OF **CHRONIC KIDNEY DISEASE AND**
PRE-ESKD IN THE PRIMARY CARE SETTING

Veterans Health Administration
Department of Defense

Prepared by:

**THE MANAGEMENT OF KIDNEY FAILURE
Working Group**

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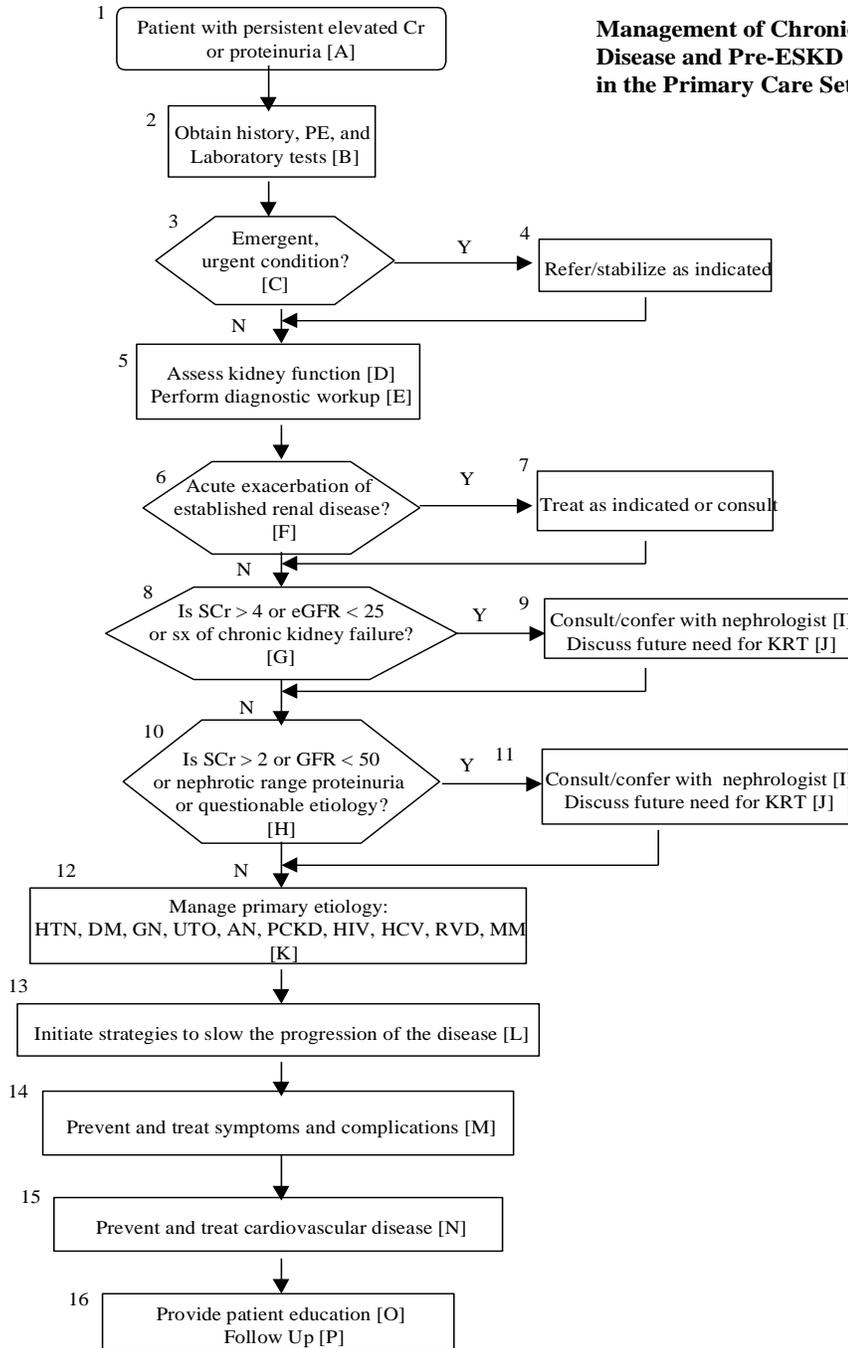
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ALGORITHM

Management of Chronic Kidney Disease and Pre-ESKD in the Primary Care Setting



KRT—Kidney Replacement Therapy; GN—Glomerulonephritis; UTO—Urinary Tract Obstruction; AN—Analgesic Nephropathy; PCKD—Polycystic Kidney Disease; HIV—Human Immunodeficiency Virus; HCV—Hepatitis C Virus; RVD—Renovascular Disease; MM—Multiple Myeloma.

VHA/DoD CLINICAL PRACTICE GUIDELINE FOR THE
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PRE-ESKD IN THE PRIMARY CARE SETTING

GOALS

THE PURPOSE OF THIS GUIDELINE IS TO:

- Identify patients at risk for progression of kidney disease or patients with reversible conditions
- Promote the recognition of abnormal kidney function
- Slow the progression of kidney disease
- Prevent or treat metabolic, hematologic, and cardiovascular abnormalities
- Describe the referral points to specialty care
- Encourage the preparation of the patient for end stage kidney disease (access) at an appropriate time

VHA/DoD CLINICAL PRACTICE GUIDELINE FOR THE
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ANNOTATIONS

A. Patient with Persistent Elevated Creatinine or Proteinuria (above Normal Limits)

DEFINITION

This guideline should be used for patients in need of further diagnostic work-up, treatment and follow-up. These patients present to primary care and are found to have:

- Persistent elevated serum creatinine—serum creatinine (SCr) level above the upper limit of normal for the laboratory on two consecutive tests

and/or
- Proteinuria (> 1+) on dipstick, confirmed on two tests.

ANNOTATION

This guideline applies to patients presenting with proteinuria or elevated serum creatinine and to patients being followed for chronic kidney disease. The presence of proteinuria may indicate kidney disease even with a normal serum creatinine. Kidney insufficiency is the asymptomatic stage of reduced kidney function with serum creatinine elevated above normal. Any of these patients has a potentially serious kidney disease that might progress to kidney failure.

Note: Pure hematuria is usually a urologic problem. If a referral is needed after the initial workup by primary care, it should be to urology and not nephrology.

DISCUSSION

Kidney failure leads to significant disability and health care costs. Early identification and treatment of at-risk patients may slow or prevent kidney failure. Most of these patients will be seen first by primary care providers who can evaluate and treat patients independently or in consultation with a nephrologist. Patients with more advanced kidney failure should be seen by a nephrologist who can help the primary care provider educate and prepare the patient for dialysis or kidney transplantation. Proper application of this guideline should improve health and reduce complications and costs in this patient population.

B. Obtain History, Physical Examination and Laboratory Tests

OBJECTIVE

To identify the clinical markers that indicate kidney disease and to outline basic diagnostic testing required in all patients.

ANNOTATION

History, physical exam, and basic laboratory evaluation remain the cornerstone for diagnosis in patients presenting with kidney disease.

History

- Chronic medical problems:
Diabetes, hypertension, prior kidney disease, collagen vascular disease, hepatitis, HIV, kidney stones, prostate disease

- Attention to symptoms associated with kidney disease such as:
 - Decreased attentiveness
 - Nausea/vomiting, anorexia, weight change
 - Dyspnea, orthopnea, leg swelling
 - Fatigue, muscle cramps, restless legs, peripheral neuropathy
 - Pruritus
 - Urinary urgency, frequency, nocturia, dysuria.
- Medications/over the counter products (NSAIDs, ACEIs, angiotensin receptor blockers, diuretics, analgesics, antibiotics, antiviral agents, lithium)
- Family history of kidney disease (Polycystic Kidney Disease-PCKD)

Physical Examination

- Height, weight
- Vital signs including orthostatic blood pressure
- Volume assessment (rales, jugular venous distention, peripheral edema, cardiac heave/gallop/rub)
- Vascular exam (pulses, bruits)
- Abdominal findings (mass, bruit, palpable bladder, flank tenderness)
- Digital rectal exam (prostate) in men
- Neurological exam
- Integument (rash, stigmata of embolic disease or ischemia)
- Joints (arthritis).

Basic Laboratory Evaluation

- Na, K, Cl, CO₂, BUN, SCr, glucose, Ca, PO₄, alb, total protein, cholesterol
- Urinalysis and review of urinary sediment
- Complete blood count (CBC) with differential.

REFERENCES

Dolson, 1998; Canadian Society of Nephrology Guidelines, 1998

C. Emergent, Urgent Condition?

OBJECTIVE

To identify patients with acute (potentially reversible) kidney disease or life-threatening conditions who require immediate attention.

ANNOTATION

Rapidly increasing SCr (25% increase over days) requires urgent investigation.

The initial evaluation should determine whether a patient has manifestations of kidney disease that require emergent or urgent intervention such as:

- fluid overload, especially pulmonary edema
- hyperkalemia
- metabolic acidosis

- pericarditis
- encephalopathy
- uremic symptoms such as nausea, vomiting and anorexia.

Acute kidney dysfunction is frequently reversible. Patients with any acute component require prompt medical intervention.

The most common causes of acute kidney dysfunction include:

- volume depletion
- severe heart failure
- urinary tract obstruction
- acute tubular necrosis (ATN)
- acute interstitial nephritis
- acute pyelonephritis
- acute glomerulonephritis
- atheroembolic disease.

DISCUSSION

Information about the patient's recent baseline creatinine levels and urinalysis results is necessary to determine the acuity of the kidney process. Clues to the diagnosis of these conditions can be obtained by careful evaluation of the presenting history, physical and screening laboratory evaluation. Since each condition requires specific treatment to reverse the kidney failure and/or slow the deterioration of kidney function, every effort should be made to ensure that the patient receives timely care for these conditions. Clues to the diagnosis of specific acute processes include:

1. **VOLUME DEPLETION** is frequently accompanied by a history of anorexia, vomiting, diarrhea, diuretic use or blood loss. Physical examination may show tachycardia, hypotension or postural changes in pulse and blood pressure. The laboratory demonstrates elevated BUN and creatinine levels, often with BUN elevated out of proportion to Cr. The urine is typically concentrated, i.e. specific gravity > 1.015 and urine osmolality > 350 mosm/kg H₂O. The urine sodium concentration in a spot urine is typically < 20 mmol/L. Using values measured in a spot urine sample one can measure the fractional excretion of sodium ((FE_{Na}) %).

$$(FE_{Na}) = \frac{[U_{Na}/P_{Na}]}{[U_{Cr}/P_{Cr}]} \times 100$$

Typically in patients with volume depletion, the FE_{Na} < 1%.

2. **SEVERE CONGESTIVE HEART FAILURE** is usually diagnosed based on the history and physical examination. Urinary findings are usually similar to those in volume depletion.
3. **URINARY TRACT OBSTRUCTION** can be accompanied by symptoms of flank pain, hesitancy, urgency, post-void dribbling, dysuria, hematuria or decreased urinary output. The physical exam may reveal a palpable bladder. The diagnosis is typically made by demonstrating hydronephrosis on kidney ultrasound. Check for a large post void residual urinary volume using catheterization or bladder scan.
4. **ACUTE TUBULAR NECROSIS (ATN)** is frequently associated with hypotension, infection, surgery or exposure to nephrotoxic agents. FE_{Na} is usually > 2% although this may be variable. Muddy brown casts may be present in the urine.
5. **ACUTE INTERSTITIAL NEPHRITIS** is often drug related. Patients may also have fever, rash, history of arthralgias, eosinophilia, and sterile pyuria or eosinophiluria. Non-nephrotic proteinuria is frequently present. Nephrotic syndrome may be seen in patients with acute interstitial nephritis due to NSAIDs.

6. ACUTE PYELONEPHRITIS is accompanied by symptoms related to infection including fever and CVA tenderness. The urinalysis shows white blood cells, red cells and sometimes white blood cell casts. Urine cultures are positive.
7. ACUTE GLOMERULONEPHRITIS may be accompanied by the history and findings of sudden onset of edema, hypertension, hematuria and flank pain. The urinalysis shows proteinuria, RBCs, and may show red blood cell casts or dysmorphic red cells.
8. ATHEROEMBOLIC DISEASE is commonly seen following arteriography, vascular or cardiac surgical procedures, or in patients on anticoagulant or thrombolytic therapy. The physical exam may show livedo reticularis, ischemia of distal extremities, and retinal plaques. Urinalysis may show eosinophiluria.

REFERENCES

Brady et al., 1996; Lieberthal and Levinsky, 1992

EVIDENCE

QE=III

SR=A

D. Assess Kidney Function

OBJECTIVE

To determine the current level of kidney function.

ANNOTATION

Assessment of kidney function involves estimation of the Cl_{cr} using S_{Cr} and quantitation of proteinuria.

Cl_{cr} can be estimated by using the Cockcroft-Gault formula (Toto, 1997; Cockcroft, 1976):

For males: $(140 - \text{age}) / \text{Scr (mg/dL)} \times \text{wt (kg)} / 72$ For females x by 0.85

The 24-hour urine collection for creatinine clearance approximates the glomerular filtration rate (GFR). It is less accurate than the formula, however, and more difficult to perform.

For quantitation of proteinuria use a spot urine protein/creatinine ratio.

DISCUSSION:

The serum creatinine does not rise above the normal range until the creatinine clearance rate has already declined to less than half of normal (50 ml/min). For every 50-percent reduction in glomerular filtration rate (GFR) (approximated by the estimated GFR), the serum creatinine concentration approximately doubles. It should be recognized that since serum creatinine is determined both by kidney function and muscle mass, patients with low serum creatinine and low muscle mass may have significant impairment of kidney function. Conversely patients with high muscle mass may have serum creatinines above normal without impairment of kidney function.

Patients with a serum creatinine level above the normal range but under 2.0 mg/dL have significant kidney disease but are less likely to have electrolyte disturbances, anemia, or bone disease than those with a creatinine level of ≥ 2.0 mg/dL.

GFR was classically assessed by measurement of creatinine clearance using 24-hour urine collection. Estimation of GFR by this method is, however, associated with many problems. Inaccuracies in the urine collection, resulting in

either over-collection or under-collection of the 24-hour urine volume may result in overestimation or underestimation, respectively, of creatinine clearance. In addition, creatinine is an imperfect marker of kidney function. Under normal circumstances, approximately 10% of urine creatinine is excreted by tubular secretion rather than glomerular filtration. In patients with kidney insufficiency, the percentage of tubular secretion increases to as much as 30 to 50%. As a result, creatinine clearance significantly overestimates GFR in patients with moderate to advanced kidney insufficiency.

Given these drawbacks to measurement of creatinine clearance by 24-hour urine collection, creatinine clearance—and hence GFR—should be estimated by using the Cockcroft-Gault formula (Toto, 1997; Cockcroft, 1976).

Several other methods have been validated for the measurement of GFR. Cimetidine inhibits tubular secretion of creatinine. GFR can be assessed by means of 2-hour creatinine clearance following cimetidine administration (Olsen et al., 1989; Walser, 1998; Mitch and Walser, 2000). The dosage of cimetidine has varied widely in the 12 reported studies: a suggested dose is 900 mg at bedtime the night before the test and 900 mg the morning of the test. Most reports find no side effects of giving cimetidine in this manner, even in severe chronic kidney insufficiency (CKI). A water load of four glasses (1 L) of water or clear liquids should be ingested about one hour before the test. Three accurately timed urine collections are obtained, about 35 minutes long, and a single serum sample for Cr analysis is drawn, sometime during the test. GFR is the average over the three periods of Cr excretion rate divided by serum Cr concentration. Correction of GFR for body size is unnecessary when following individual patients. In some patients, urine flow may be too low to obtain accurate urine collections, despite the water load. Further water loading doesn't help and may lead to water intoxication. The test is best repeated with the patient recumbent during the urine collections. It is important to note that cimetidine administration increases serum Cr for several days, even though it has no effect on GFR.

GFR can also be measured using iothalamate as a marker that is filtered at the glomerulus and not significantly secreted or reabsorbed by the kidney tubule. Although iothalamate clearances provide a highly accurate assessment of GFR, the cost and inconvenience of this test do not warrant its routine clinical use.

Several studies have demonstrated a close correlation between the spot urine protein/creatinine and 24 hour urine protein collection. This correlation is near unity with a relatively narrow standard deviation until daily protein excretion exceeds 3.5 g/dL in diabetic patients, and even then it distinguishes patients with nephrotic syndrome from those without (Rodby, 1995). The correlation is most accurate when testing the first morning voided urine, e.g., a urine protein/creatinine ratio of 1.0 g/g is equivalent to a 24-hr urine protein excretion rate of 1 g; a ratio of 0.3 g/g would be the equivalent of 300 mg/24 hours, etc.

For the above reasons this panel advocates the estimation of creatinine clearance from serum creatinine concentrations using the Cockcroft-Gault formula and the estimation of protein excretion using the protein/creatinine ratio in the first a.m. voided urine for screening and follow-up therapy, unless the urine protein/creatinine is above 3.5.

REFERENCES

Toto et al, 1997; Cockcroft et al., 1976; Olsen et al., 1989; Walser, 1998; Mitch and Walser, 2000; Rodby et al., 1995

EVIDENCE

QE=II
SR=B

E. Perform Diagnostic Work-up

OBJECTIVE

To establish the etiology of kidney disease.

ANNOTATION

Perform specific lab tests or special studies to define the cause of:

- Persistently elevated creatinine
- Persistent proteinuria

The complete history and physical must precede and guide the diagnostic work-up. Additional tests and imaging studies should be considered if indicated.

Diagnostic tests:

- Urinalysis
- Quantitate Proteinuria
- Complete Blood Count
- Na, K, Cl, CO₂, BUN, SCr, glucose, Ca, PO₄, alb, total protein
- Estimated GFR
- Cholesterol

- Kidney ultrasound should be ordered
 - To evaluate for urinary tract obstruction
 - To estimate the size of the kidney
 - To evaluate for polycystic kidney disease.

The urinalysis reagent dipstick for protein and blood gives the important initial information regarding the type of disease that may be causing kidney disease or proteinuria. (Table 1)

The degree of proteinuria further defines the cause of the persistent elevated creatinine and/or the cause of the abnormal proteinuria. (Table 2)

An etiologic evaluation should be guided by history and physical, urinary sediment and degree of proteinuria. (See Appendix 1, Etiologic Evaluation)

A guide to specialized laboratory studies for the diagnosis of kidney disease can be found in Appendix 2.

Table 1. Urine Dipstick: Interpretation

PROTEIN	BLOOD	CONSIDER
Negative	Negative	False negative R/O microalbuminuria R/O multiple myeloma and other paraproteinuria Pre-kidney cause Post-kidney cause Ischemic nephropathy
Positive	Negative	R/O false positive, benign or orthostatic proteinuria Consider HTN, nephrosclerosis, diabetes, tubulo-interstitial diseases, PCKD, GN, etc. Quantitate protein
Positive	Positive	UTI, pyelonephritis, RPGN, GN, HIV vasculitis, pulmonary-kidney syndrome, HUS, TTP, malignant HTN, nephrotic syndrome, nephrolithiasis with obstruction, atypical DM, cystic kidney disease

UTI: Urinary Tract Infection; RPGN: Rapidly Progressive Glomerulonephritis; HUS: Hemolytic Uremic Syndrome; TTP: Thrombotic Thrombocytopenic Purpura

Table 2. Evaluation Of Proteinuria

<p>a. Spot protein creatinine ratio estimates 24 hour excretion of protein in grams/24 hr. To perform the test, a random urine sample is submitted to the laboratory for protein concentration (in mg/dL) and creatinine concentration (in mg/dL). The protein concentration is divided by the creatinine concentration, and the unit-less number is the estimated daily protein excretion in gm/24 hrs. An abnormal ratio is > 0.15, which estimates a 24 hour protein excretion of > 150 mg/day (> 0.15 gm/day). Many nephrologists recommend using protein:creatinine ratios to quantify protein excretion instead of a 24 hour urine collection.</p>												
<p>b. Further define cause based on degree of proteinuria</p> <table border="0"> <tr> <td>normal:</td> <td>< 150 mg/24hr</td> </tr> <tr> <td>microalbuminuria:</td> <td>30-300 mg/24 (specifically albumin; usually measured in diabetics)</td> </tr> <tr> <td>trace proteinuria:</td> <td>150 to 500 mg/24 hr</td> </tr> <tr> <td>mild proteinuria:</td> <td>500 mg to 1 g/24 hr</td> </tr> <tr> <td>moderate proteinuria:</td> <td>1-3 g/24 hr</td> </tr> <tr> <td>nephrotic range proteinuria:</td> <td>> 3 g/24 hr</td> </tr> </table>	normal:	< 150 mg/24hr	microalbuminuria:	30-300 mg/24 (specifically albumin; usually measured in diabetics)	trace proteinuria:	150 to 500 mg/24 hr	mild proteinuria:	500 mg to 1 g/24 hr	moderate proteinuria:	1-3 g/24 hr	nephrotic range proteinuria:	> 3 g/24 hr
normal:	< 150 mg/24hr											
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mild proteinuria:	500 mg to 1 g/24 hr											
moderate proteinuria:	1-3 g/24 hr											
nephrotic range proteinuria:	> 3 g/24 hr											
<p>c. Types of proteinuria</p> <ol style="list-style-type: none"> 1. Overflow proteinuria: Trace or negative dipstick protein but disproportionate larger amount on 24 hr. test. Its presence suggests: light-chain, paraproteinemia, lymphoproliferative process, or hemolysis (only if dip also blood +). 2. Tubular protein: 500 mg – 2000 mg/24 hours. Differentiate from glomerular causes by UPEP +/- IEP UPEP: albumin > globulin suggests glomerular proteinuria globulin > albumin suggests light chains or paraproteinemia Some common causes include analgesic nephropathy, focal glomerular sclerosis (recurrent UTI, reflux), collagen vascular diseases (Sjogren’s syndrome, lupus), hepatitis, HIV, PCKD, heavy metal toxicity, interstitial nephritis (drugs or infectious), granulomatous diseases, etc. 3. Glomerular protein, suggested by moderate to heavy proteinuria. Suggests a more serious disorder. Significant glomerular damage with proteinuria of >3 grams: refer to nephrologist. R/O diabetes progression, hepatitis, HIV, vasculitis, malignancy, GN, etc. 4. Massive proteinuria (> 6 gm/24 hours) Focus H & P to rule out HIV, hepatitis-associated nephropathy (HAN), severe focal glomerulosclerosis, etc. Refer to nephrologist. 												

UPEP—Urine Protein Electrophoresis; IEP—Immuno-Electrophoresis

REFERENCES

Fairley 1993; Scherberich, 1990

EVIDENCE

QE=3DII-3

SR=A

F. Is There an Acute Exacerbation of Established Kidney Disease?

OBJECTIVE

To identify acute deterioration of kidney function in a patient with established kidney disease.

ANNOTATION

Patients with established chronic kidney disease might also develop acute kidney failure due to a new illness, or as a complication of therapy. Any worsening of kidney function, especially if it occurs over a short time period, should be considered acute kidney failure, and evaluated promptly. Only after acute kidney failure is ruled out can deterioration in kidney function be ascribed to progression of the patient's underlying chronic disease.

Common causes of acute deterioration in kidney function include:

- medications (ACEI, NSAIDs, ARBs and many others)
- volume depletion
- urinary tract obstruction or infection
- radiographic contrast
- worsening congestive heart failure
- kidney vascular disease (aortic dissection, cholesterol embolization)
- sepsis
- rhabdomyolysis or hemolysis.

G. Is Scr > 4 mg/dL or Cr Cl < 25 or Symptoms of Chronic Kidney Failure?

OBJECTIVE

To ensure that all patients who might benefit from kidney replacement therapy will have the options presented to them in a timely manner to permit adequate preparation for kidney replacement therapy (KRT).

DISCUSSION

The vast majority of patients with moderate to severe kidney insufficiency will progress to end stage kidney disease (ESKD) requiring KRT and should be referred to the nephrologist. Referral to the nephrologist at this time will facilitate the preparation of the patient for the KRT including transplantation. The latest time to refer a patient with pre-ESKD to the nephrologist should be when the creatinine is 4.0 mg/dL or the creatinine clearance is 25 ml/min. Referral should occur at least six months to one year prior to the anticipated start of dialysis. The anticipated start of dialysis can be predicted by plotting the reciprocal of SCr against time (Mitch & Walser, 2000).

Early referral to nephrology and predialysis education have been associated with:

- improved vocational outcomes
- delay in the need to initiate ESKD therapy
- increased proportion of patients initiating dialysis who have permanent dialysis access, particularly arterio-venous (A-V) fistula (which has a much longer useful life)
- a difference in modality selection (i.e. increased likelihood of selecting PD)
- reduced need for urgent dialysis
- reduced hospital length of stay
- better metabolic parameters.

Referrals that occur very late in the course of kidney disease, so that patients require urgent initiation (within 1 month) of dialysis, have been associated with the following adverse events:

- severe metabolic abnormalities at the time of dialysis initiation (acidosis, hyperphosphatemia, anemia, hypoalbuminemia)
- severe hypertension and volume overload
- higher initial hospitalization rate and costs of initiation of dialysis
- low prevalence of permanent access and greater use of central vein catheterization for access
- increased one-year mortality rate
- decreased patient participation in the development of their dialysis treatment plan
- delayed referral for transplantation.

REFERENCES

Campbell et al., 1989; Jungers et al., 1993; Ragson et al., 1993; Binik, et al., 1993; Levin et al., 1999; Hayslip & Suttle, 1995; Arora et al., 1999; Mitch & Walser, 2000

EVIDENCE

QE=II

SR=A

H. Is Serum Cr \geq 2.0 mg/dL (\geq 1.5 female) or GFR \leq 50 ml/min or Nephrotic Range Proteinuria or Questionable Etiology of Kidney Disease

OBJECTIVE

To identify individuals with kidney disease who are at risk for progression, who require further diagnostic procedures, or who will benefit from early consultation with the nephrologist.

ANNOTATION

All patients with established kidney disease are at risk for progression and may require interventions to slow the progression, prevent complications, and reduce symptoms. The primary care provider should institute these interventions. Severity of the kidney function indicated by Scr \geq 2.0 mg/dL (or GFR \leq 50 ml/min) is usually associated with progression of the kidney disease; therefore a nephrologist can assist the primary care provider in managing the disease and its associated complications.

In patients with nephrotic range proteinuria or kidney disease of unknown etiology the nephrologist will make the diagnosis and recommend treatment. Kidney biopsy may be recommended to determine the histopathology of the kidney disease.

DISCUSSION

Interventions aimed at slowing progression of chronic kidney disease and the evaluation and management of associated complications should begin early. The goals of these interventions are multiple, including delaying, preventing or even reversing the progression of the disease.

Retrospective studies indicate that kidney osteodystrophy may begin at an estimated Glomerular Filtration Rate (eGFR) of 40-50 ml/min, anemia of kidney disease may begin at 30-40 ml/min, and malnutrition may develop at 30-40 ml/min. The National Institutes of Health (Morbidity and Mortality of Renal Dialysis, 1994) has recommended that patients be referred to a nephrologist for initial consultation at a serum creatinine of 1.5 mg/dl for women and 2.0 for men.

Kidney biopsy may be recommended to determine the histopathology causing nephrotic range proteinuria in the non-diabetic adult. In one study of 28 adults with nephrotic syndrome, knowledge of histopathology altered management in 24, or 86%, of cases (Richards et al., 1994). While kidney biopsy is not routinely recommended for diagnosis of diabetic nephropathy, it may be required if the clinical course in an individual patient is not clearly consistent with diabetic glomerulopathy (absence of retinopathy especially in the presence of nephrotic range proteinuria, abrupt onset of proteinuria and short duration of diabetes). In one prospective series 23% of diabetics with proteinuria had non-diabetic glomerular diseases (Parving et al., 1992).

REFERENCES

Morbidity and Mortality of Renal Dialysis, 1994; Richards et al., 1994; Parving et al., 1992

EVIDENCE

QE=II-2
SR=B

I. Consult/Confer with Nephrologist

OBJECTIVE

To obtain the assistance of a specialist for either diagnostic or management issues.

ANNOTATION

Referral to a nephrologist may be helpful to the primary care provider to:

- Assist with diagnosis of the cause of kidney disease, including kidney biopsy
- Assist in ruling out reversible causes of elevated creatinine such as urinary tract obstruction
- Reinforce the need for aggressive blood pressure control and dietary management to slow the progression of the disease
- Jointly manage various complications of kidney insufficiency such as:
 - electrolyte disorders
 - secondary hyperparathyroidism
 - anemia secondary to erythropoietin deficiency
 - metabolic acidosis

J. Discuss Future Need for KRT

OBJECTIVE

To prepare the patient, in a timely and effective manner, for eventual KRT.

ANNOTATION

Counseling by Primary Care

- Development of ESKD is emotionally traumatic for most patients
- Patients who learn to accept ESKD have better compliance and better outcomes

- Advantages of early discussion about ESKD and KRT options:
 - Assists in emotionally preparing patient for lifestyle changes
 - Trust and continuity established by primary care aids nephrologist
 - Allows time for preparation and consideration of home dialysis and LRD transplant
- Simple steps that can be taken in the primary care setting:
 - General discussion about progression of kidney disease to ESKD
 - Explanation of why patient needs to see nephrologist
 - Reinforce and review information provided to patient by nephrologist
 - Discuss in general terms principles of dialysis (HD and PD) and transplantation
 - Maintain consistency of information between primary care and nephrologist.

Indications for Initiation of Kidney Replacement Therapy

The indications for the initiation of dialysis are controversial. Some authors advocate early initiation of dialysis, prior to the development of symptoms, based on the assessment of GFR (NKF-DOQI Peritoneal Dialysis Guidelines, 2001). They contend that early uremia is associated with impaired nutritional intake and progressive malnutrition, and advocate the initiation of kidney replacement therapy with “incremental” dialysis, progressively increasing the dose of dialysis as residual kidney function declines. In contrast, other experts advocate the use of aggressive protein restriction with supplementation of essential amino acids to postpone the development of uremic symptoms, contending that nutritional status can be maintained with this approach (Walser & Hill, 1999; Walser et al., 1999).

In light of the above controversy, Table 3 can be used to guide initiation of kidney replacement therapy after attempts have been made to optimize dietary protein and caloric intake.

Table 3. Indications For Initiation Of Kidney Replacement Therapy

Absolute Indications for Dialysis	Relative Indications for Dialysis
Advanced uremia Uremic pericarditis Uremic encephalopathy Uremic pancreatitis	Estimated GFR < 10 mL/min/1.73m ² (Kt/V urea < 2.0), unless: Lean body mass is stable or increasing and nPNA > 0.8 g/kg/day
Metabolic disturbances refractory to medical management Hyperkalemia Metabolic acidosis	Estimated GFR of 10-20 mL/min/1.73m ² with signs of malnutrition (nPNA < 0.8 g/kg/day or loss of lean body mass)
Uremic symptoms not amenable to dietary modification Severe nausea and vomiting Anorexia with weight loss Uremic encephalopathy Neuropathy	
Refractory volume overload Congestive heart failure Pulmonary edema Peripheral edema with skin breakdown	Moderately severe to severe volume overload

NPNA—Normalized Protein Nitrogen Appearance Rate

DISCUSSION

Development of end stage kidney disease (ESKD) along with the need for kidney replacement therapy is an emotionally traumatic experience for most patients. Psychologic acceptance of ESKD and dialysis is an important factor contributing to the success of treatment. Patients who are emotionally and intellectually prepared for ESKD are typically more compliant with therapy and predictably have improved well being and outcome. Early discussion of ESKD options (hemodialysis, peritoneal dialysis, and kidney transplantation) not only prepares patients for inevitable lifestyle changes, but also opens the possibility for early decisions regarding the modality of ESKD therapy. Patients who are interested in transplantation may be given the opportunity to seek a potential living donor leading to successful transplantation prior to the initiation of dialysis. Patients interested in home dialysis (either hemo or peritoneal) can be provided an opportunity to learn about the techniques and make the necessary arrangements prior to initiation of dialysis. Several simple measures can be taken by the primary care provider to ease patients with chronic kidney disease along the path toward kidney replacement therapy.

Patients with progressive kidney disease should receive counseling by the primary care provider concerning the available kidney replacement therapy options, including a supplemented very low protein diet. While primary care providers are not expected to discuss dialysis or transplantation options in detail with patients, even a very general discussion about ESKD treatment options prepares the patient for future detailed discussion with the nephrologist. Patients who have developed trust and continuity with their primary care providers greatly benefit from this preliminary overview, and are better prepared for a consultation with the nephrologist.

It is vital that patients with CKF progressing toward ESKD receive consistent information from all care providers. A basic understanding of the ESKD treatment options, and an appreciation of the distinction between the slowing of progression of disease versus a reversal of disease process are vital. Many patients develop a mistaken belief that kidney damage can be reversed, or that the kidney disease will “go away” making dialysis or transplant unnecessary. The restoration of lost function is not medically possible, and this needs to be consistently and clearly conveyed to patients. Avoiding misconceptions about the disease process enhances treatment acceptance both in the short and long term.

Specific recommendations for patients choosing hemodialysis:

- Planning for vascular access should occur well before the need for dialysis.
- No blood should be drawn from the non-dominant arm.
- Forearm exercises should be used to build up the muscles and thereby increase the size of the veins in the forearm.
- At the latest, patients should be referred for AV fistula surgery when the estimated Glomerular Filtration Rate (eGFR) is < 20mL/min by Cockcroft formula (see Annotation D, above) in diabetics, and when eGFR < 15mL/min in nondiabetics.
- A native AV fistula should be the preferred access for hemodialysis.
- A PTFE graft should be placed only if the patient comes for chronic dialysis as an emergency and has poor veins or after failure of the AV fistula at wrist and elbow.

Types of permanent vascular access for hemodialysis

- Native vessel arteriovenous (AV) fistula in the arm, either above the wrist (Brescia-Cimino fistula) or one created at the anatomical snuff box
- Native vessel AV fistula at the elbow, involving the brachial artery and either the elbow perforating vein, the cephalic vein, or the basilic vein

- Polytetrafluoroethylene (PTFE) bridge graft: either in the forearm, upper arm, or thigh
- Two year survival rate of a PTFE graft is only 30-40%, and these grafts have a useful life only one-third to one-tenth that of a native vein fistula. Other studies show that a large proportion of the hospitalization costs encountered in Medicare's end-stage kidney disease (ESKD) program are associated with the frequent interventions and high failure rates of the PTFE grafts.

REFERENCES

NKF-DOQI, 2001; Walser & Hill, 1999; Walser et al., 1999; Hakim & Himmelfarb, 1998; Brouwer, 1999; Gade et al., 1995; Chazan et al., 1995; Sparks et al., 1997; Feldman et al., 1996; Bell et al, 1998; Sands & Miranda, 1997; Shinaberger et al., 1999; Cockcroft & Gault 1976

K. Manage Primary Etiology of Kidney Disease: DM, HTN, GN, UTO, Analgesic Nephropathy, PCKD, HIV-AN, HCV, RVD, MM or Other

OBJECTIVE

To treat the primary cause(s) of kidney disease.

ANNOTATION

Treatment of the underlying disorder leading to kidney disease may delay, prevent or reverse the progression of kidney insufficiency. In the majority of cases the etiology of the kidney disease has previously been determined (see Box 5 or 11).

1. Hypertension: See VA/DoD Hypertension Guideline
2. Diabetes Mellitus: See VA/DoD Diabetes Guideline
3. Glomerulonephritis (GN)

GN includes multiple diseases, each of which may require different treatments. The nephrologist will determine the specific treatment of GN.

4. Polycystic Kidney Disease (PCKD)

Because of the systemic nature of polycystic kidney disease (PCKD) and its detailed implications for patient and family counseling, a diagnosis of PCKD should prompt a referral to nephrology, at least for initial evaluation and recommendation. Although there is no specific treatment, periodic follow-up by a nephrologist is recommended. Nephrology consultation should be sought for any PKD patient with UTI, for appropriate antibiotic selection.

5. Urinary Tract Obstruction

The treatment of urinary tract obstruction is relief of the obstruction, which may require referral to a urologist. The patient with UTO may also have infection, which should be treated.

Patients should receive follow-up after diagnosis and relief of urinary obstruction to determine whether kidney function has normalized. Serum creatinine may require several weeks to reach a steady state, and may never return to normal. Should kidney failure not resolve within weeks, alternative causes for kidney dysfunction, or new acute kidney failure should be considered. Nephrology should be consulted if serum creatinine remains greater than 2 mg/dL.

6. Analgesic Nephropathy

Analgesic Nephropathy is caused by chronic use of NSAIDS (e.g. indomethacin, fenoprofen, naprosyn, ibuprofen etc.) or abuse of combination analgesics (e.g. aspirin, acetaminophen). Cessation of the offending agent(s) may improve kidney function.

7. HIV-Associated Nephropathy (HIV-AN) and HCV-Related Kidney Disease

Evidence of kidney abnormalities (elevated serum creatinine, proteinuria and/or hematuria) in HIV infected individuals should prompt early evaluation by the nephrologist. The spectrum of kidney disease seen in HIV positive patients includes HIV-AN, immune-complex mediated glomerulonephritis and acute kidney failure syndromes. Kidney biopsy may be required to determine the etiology of the kidney failure.

Management of HIV-AN may include the use of anti-retroviral medications and angiotensin converting enzyme inhibitors. Use of corticosteroids is controversial. Testing for both HBV and HCV should be performed in HIV positive individuals with kidney disease.

Evidence of kidney disease in HCV-positive individuals requires early nephrologic consultation. Kidney disease may exist in the absence of active hepatitis. The most common kidney disease found in these patients is membranous proliferative glomerulonephritis (MPGN), which may be associated with cryoglobulinemia. Testing for complement levels and the presence of cryoglobulins may be initiated prior to referral. Kidney biopsy may be required in many cases to confirm the etiology of the kidney disease. Treatment of this entity may include alpha interferon and ribavirin and should only be administered after consultation with a kidney specialist.

REFERENCES

Burns et al., 1997; Rao, 1998; Kimmel et al., 1998; Johnson et al., 1994

8. Renovascular Disease (RVD)

The indications for the treatment of kidney artery stenosis associated with CKI are controversial (Greco & Breyer, 1996; Rimmer & Genari, 1993; Caps et al, 1998). Although there is some evidence that intervention with surgery or angioplasty may reverse or stabilize kidney function, the natural history of untreated atherosclerotic kidney artery stenosis is not well characterized. In the absence of randomized controlled studies, patients with known kidney artery stenosis should be referred to a nephrologist if they have hypertension that is difficult to control, or if they experience an increase in Cr of > 25% in less than six months (Dean et al, 1991).

The patient with bilateral kidney artery stenosis is at risk for development of worsening kidney function or hyperkalemia with the use of ACE-I (Hricik et al., 1983) or angiotensin receptor blockers. Although these drugs may be used safely in most patients with unilateral kidney artery stenosis, such patients require careful monitoring. Serum creatinine and potassium should be determined within 2-4 weeks of initiating therapy or increasing dosage. ACEI have been found to be effective in ameliorating diabetic (The GHISEN Group 1997) and non-diabetic kidney disease when proteinuria is present (The GHISEN Group 1997). They should be used cautiously in patients with suspected renovascular disease including patients with unilateral, bilateral or small vessel disease i.e. ischemic nephropathy because angiotensin II is very important in maintaining GFR when vascular perfusion is impaired. Usually these patients exhibit progressive kidney failure but scant proteinuria.

REFERENCES

Greco & Breyer, 1996; Rimmer & Gennari, 1993; Caps et al., 1998; Dean et al., 1991; Hricik et al., 1983; The GHISEN Group, 1997

EVIDENCE

Referral to nephrology:

Dean et al., 1991

QE=II-3

SR=C

Use of ACE-1 or angiotensin receptor blockers:

Hricik et al., 1983

QE =II-3

SR=A

9. Multiple Myeloma With Monoclonal Immunoglobulin Light Chain-Related Kidney Diseases

Elevated serum creatinine may be the initial presentation in patients with multiple myeloma or other paraproteinemias. Disease entities associated with monoclonal gammopathies include multiple myeloma, undefined plasma cell dyscrasia, AL amyloidosis, chronic lymphocytic leukemia. Management of monoclonal light chain-related kidney disease requires abolishing the production of immunoglobulin light chains. Special attention should be given to avoidance of all nephrotoxics like NSAIDs, radiocontrast dye, and dehydration.

REFERENCE

Sanders & Herrera, 1993

EVIDENCE:

QE=III

SR=B

L. Initiate Strategies to Slow the Progression of the Disease

OBJECTIVE

To retard the progression of kidney disease by the use of non-invasive interventions.

ANNOTATION

The strategies to slow the progression of the disease include:

- Control of hypertension
- Use of ACE-I
- Protein restriction
- Control of hyperglycemia in diabetics.

1. Control of hypertension

In patients with chronic kidney disease, progressive glomerulosclerosis results in a progressive loss of kidney function, even when the initial kidney insult has been removed. Vigorous control of hypertension reduces the glomerular capillary pressure and slows the progression of glomerulosclerosis. The goal blood pressure should be < 125/75 or mean arterial pressure less than 92 for patients with proteinuria and 130/85 in patients without proteinuria. ACE-I or ARB is the preferred antihypertensive agents (Pitt B, 1997).

2. Use of ACE-I

ACE-I has beneficial effects in patients with diabetic nephropathy and other kidney diseases. These drugs slow progression independent of their effect on blood pressure. ARBs are a new class of drugs, which may be used in patients who are intolerant of ACE-I (Pitt B, 1997). Studies on their effect are in progress.

ACE-I reduces proteinuria, an effect that may—in itself—be renoprotective. These agents reduce proteinuria at any given level of blood pressure reduction more than other antihypertensive drugs. Risks associated with use of these drugs include dangerous hyperkalemia and acute kidney failure when they are used in situations associated with decreased glomerular filtration pressure such as dehydration or kidney artery stenosis (Wynckel, 1998; Cronin, 2000). Careful monitoring of potassium levels and serum creatinine is warranted. (See Appendix 4)

3. Protein restriction

Protein restriction appears to slow the progression of kidney insufficiency and decrease symptoms and signs of kidney insufficiency. Furthermore, some deferral of dialysis is achieved simply by reduction of symptoms and the severity of azotemia at any given level of kidney function.

The benefit of a low protein diet in slowing progression is controversial. Clinical trials suggest that dietary protein restriction may slow the progression of kidney disease.

A low protein diet (0.6 g/kg) without supplements may be less effective than a very low protein diet (0.3 g/kg) supplemented by essential amino acid (or ketoacid) tablets, 10 g/day in divided doses with meals (Di Landro, 1990), but raises additional problems of compliance and cost.

Protein restriction also reduces proteinuria. In nephrotic patients, a progressive fall in proteinuria and rise in serum albumin may occur over several months, especially if CKI is not severe (Walser et al., 1996). This response was seen to a very low protein diet (0.3 g/kg) supplemented by essential amino acids (10-20 g/day in divided doses with meals), but not to a conventional low protein diet ((0.6 g/kg).

4. Control of hyperglycemia in diabetics

Refer to module G in the VA/DoD Diabetic Mellitus Guideline.

REFERENCES

Wynkel, 1998; Cronin, 2000; Di Landro, 1990; Walser, 1996; Levey et al., 1999; Kasiske et al., 1998; Klahr et al., 1994; Giatras et al., 1997; Peterson et al., 1995; The Diabetes Control and Complications Trial Research Group (DCCT), 1993; Lewis et al., 1999; The DCCT, 2000; Vijan et al., 1997

EVIDENCE

QE=I
SR=A

M. Prevent and Treat Symptoms and Complications (Metabolic Abnormalities, Hematologic Abnormalities, Volume Overload, and Nutrition)

OBJECTIVE

To maintain normal metabolic levels and homeostasis in patients with kidney disease.

ANNOTATION

There are numerous complications and symptoms that may require treatment. The common metabolic and hematologic abnormalities are addressed here.

1. Metabolic Abnormalities

Disorders of Potassium Balance

Disorders of K homeostasis (both high and low K levels) may result in preventable morbidity and mortality. K levels should be checked periodically in patients with kidney disease. (See Table 3)

Hyperkalemia is a common disorder in patients with kidney disease, especially when the GFR falls below 20 ml/min. Hyperkalemia may occur as a result of impaired tubular secretion of K in patients with mild chronic kidney insufficiency (CKI). It is more prevalent among diabetics with type 4 Kidney Tubular Acidosis and is frequently exacerbated by the use of certain drugs such as ACE-I, ARBs, NSAIDS, trimethoprim and non selective beta blockers. Other contributing conditions include volume depletion leading to poor urine flow, severe hyperglycemia and starvation. Especially in diabetics, poor oral food intake (e.g. preoperative periods) resulting in low serum insulin levels may cause or exacerbate hyperkalemia (Allon, 1995). High intake of certain food items (see Table 5 below) can also lead to hyperkalemia in patients with impaired kidney function. Referral to a dietitian for a K restricted diet is useful.

K > 6.5

Elevation of K above 6.5 meq/L is a medical emergency and needs immediate attention to prevent life threatening cardiac arrhythmia.

K 5.5 - 6.5 mEq/L

A more conservative approach is generally acceptable if a rapidly reversible cause is identified (e.g. oral K supplementation) and the patient is symptomatic, without EKG manifestations of hyperkalemia. Discontinuation of offending drugs, adequate nutrition, moderate K restriction and/or correction of prekidney azotemia or metabolic acidosis with sodium bicarbonate is frequently sufficient. Persistent hyperkalemia may require a more stringent dietary limitation although very low K diets (less than 40 meq/L/day) may lead to protein malnutrition. If the cause for hyperkalemia is not readily identifiable and the elevation in serum K is mild, other measures can be instituted in the outpatient setting. Liberalization of sodium intake, loop diuretics and thiazides may be used in selected patients although their side effects (volume depletion, hyperuricemia, etc.) must be taken into account. Another option includes the use of sodium polystyrene sulfonate (SPS) or Kayexalate[®]. The usual dose for SPS is 30 grams given with 100 mL of a 20% sorbitol solution. This can be repeated every 4 to 6 hours as needed. Lower doses (5 to 10 grams with meals) can be used to control chronic mild hyperkalemia (Rose, 1999). Fludrocortisone, a potent mineralocorticoid may be used in patients with type 4 RTA (De Fronzo, 1980). Refractory hyperkalemia should prompt a referral to a nephrologist.

Table 5. Potassium Content Of Foods (Gennari, 1998)

Highest content (>25 mEq/100 g)	Dried figs, molasses, seaweed
Very high content (>12.5 mEq/100 g)	Dried fruit (dates, prunes) nuts, avocados, bran cereals, wheat germ, lima beans
High content (>6.2 mEq/100 g)	Vegetables: spinach, tomatoes, broccoli, winter squash, beets, carrots, cauliflower, potatoes Fruits: bananas, cantaloupes, kiwi, oranges, mango Meat: ground beef, steak, pork, veal, lamb

Since the cause of hyperkalemia may be multifactorial and may differ from patient to patient, the choice of treatment of mild-to-moderate hyperkalemia may require different combinations of the recommendations.

After therapy is instituted, a follow-up potassium level should be performed within one week to ensure effectiveness of therapy and identify any need for further modification of the treatment regimen.

Hypokalemia $K < 3.5$

Hypokalemia may occur as a result of diuretic therapy or kidney disease and may cause cardiac arrhythmia and muscle weakness. A fall in serum K of 1 mEq/L reflects a loss of about 200-400 mEq in total body K. Replacement by foods high in K (see Table 5 above) is usually less effective than administration of oral potassium chloride (KCl). Slow release tablets or capsules can be used, in the following dosage: (a) for prevention of hypokalemia, KCl 8-20 mEq/day; (b) for treatment of potassium depletion, KCl 40-100 mEq/day.

Severe hypokalemia, defined as serum K level below 3.0 mEq/L, may require intravenous K replacement, especially in patients on digoxin or if it is anticipated that K losses will continue (e.g. vomiting, diarrhea, etc.) In the patient with kidney disease, replacement should be approached with caution. High KCl doses must be used with more frequent measurements of the serum K. IV KCl replacement should be given no faster than 10 mEq per hour. It is preferable to replace K as a Cl salt as opposed to K-citrate or K-bicarbonate; one exception to this may be kidney tubular acidosis (the hypokalemic types) and chronic diarrheal states (Rose, 1999).

REFERENCES

Allon, 1995; Rose, 1999; DeFronzo, 1980; Gennari, 1998

EVIDENCE

QE=III

SR=A

Disorders of Calcium Metabolism

The goal of therapy is to normalize serum Ca to avoid development of kidney osteodystrophy as well as neuromuscular and cardiovascular complications.

Ca balance is altered in kidney disease patients. Low serum Ca is a salient feature of kidney disease and is a component of the syndrome of secondary hyperparathyroidism. Secondary hyperparathyroidism starts early in kidney patients, when serum creatinine levels are between 1.5 to 2.0 mg/dL (Malluche & Faugere, 1990). Low Ca levels result primarily from deficiency of 1,25-dihydroxyvitamin D₃; however, not all patients with hypocalcemia should be started on vitamin D preparations. Normocalcemia can be obtained in many patients by using measures other than vitamin D administration (see below).

Ca < 8.0 mg/dL

Hypocalcemia is rare in patients with kidney disease unless the GFR falls below 30 ml/min. Calcium may be low because of an associated hypoalbuminemia. A useful correction of calcium concentration for hypoalbuminemia is corrected Ca = Measured Ca + (4- serum albumin) x 0.8. Hypocalcemia is frequently the result of associated hyperphosphatemia and decreased levels of 1,25-dihydroxyvitamin D₃ levels. Along with hyperphosphatemia, hypocalcemia contributes to secondary hyperparathyroidism and kidney osteodystrophy. Treatment of hypocalcemia should be modified in response to PO₄ levels. In patients with a serum PO₄ above 4.5 mg/dL, we recommend the use of Ca based PO₄ binders. Calcium carbonate (1250 mg tablets containing 500 mg of elemental Ca) given as one to four tablets three times a day with meals is also effective. Calcium carbonate may also be administered as 420 mg tablets containing 168 mg of elemental calcium. Calcium acetate (667 mg tablets, two to four tablets a day with meals) is also effective, but is more expensive. This will frequently raise serum Ca (although not necessarily normalizing it) by lowering serum PO₄. In hypocalcemic patients with normal serum PO₄, calcium-carbonate or calcium-acetate can be given between meals (Hruska & Teitelbaum, 1995). The major side effect of these preparations is hypercalcemia.

Refractory hypocalcemia, especially in normophosphatemic patients, may require the use of calcitriol (1,25-dihydroxyvitamin D₃). This form of therapy is better instituted in consultation with the nephrologist, given the possibility that the patient may be suffering from “adynamic bone disease,” in which case vitamin D treatment may

be counterproductive (Hruska & Teitelbaum, 1995). Correction of hypocalcemia through nutritional means, such as the use of dairy products, frequently results in an elevation of serum PO_4 that is obviously undesirable.

REFERENCES

Hruska & Teitelbaum, 1995; Malluche & Faugere, 1990

EVIDENCE

QE=II

SR=A

Ca > 11mg/dL

Spontaneous hypercalcemia is infrequent in CKF patients, most often resulting from underlying conditions such as myeloma, sarcoidosis and neoplasms. More commonly, hypercalcemia in this population is iatrogenic, resulting from the use of calcium-containing PO_4 binders, either alone or in combination Vitamin D analogues. In patients treated with calcium carbonate or calcium acetate, temporary discontinuation or reduction of Ca-based binders usually results in normalization of serum Ca. It is important to remember that patients may be taking calcium carbonate (Tums[®]) to alleviate dyspepsia without recognizing them as a source of Ca. In patients not on exogenous calcium or vitamin D, the development of hypercalcemia should prompt the work-up for an underlying condition.

When the Ca x PO_4 product exceeds 70, there is a possibility of dangerous precipitation of Ca in non-osseous tissues. Use of Ca based PO_4 binders may transiently exacerbate the problem. Use of aluminum hydroxide (300 to 600 mg p.o. tid with meals) for periods not to exceed 7-10 days (to avoid Al^{3+} toxicity) may be necessary. When the Ca x PO_4 product falls below this dangerous level, calcium-carbonate or calcium-acetate may be started. RenaGel[®], a new polymeric resin that does not contain Ca may be used (Slatopolsky et al., 1999), but its high cost and recent introduction will probably limit its use to the Nephrology Service.

REFERENCES

Slatopolsky et al., 1999

EVIDENCE

QE=II

SR=A

Disorders of Phosphate Metabolism (Hyperphosphatemia is serum $\text{PO}_4 > 4.5 \text{ mg/dL}$)

Adequate control of serum phosphorus is important for preventing the development of secondary hyperparathyroidism and the occurrence of soft tissue calcifications. Hyperphosphatemia has been identified as an independent risk factor for mortality in hemodialysis patients.

Hyperphosphatemia is at the center of the pathogenesis of secondary hyperparathyroidism and kidney osteodystrophy (Hruska & Teitelbaum, 1995). As kidney disease progresses, retention of PO_4 leads to stimulation of parathyroid hormone (PTH) secretion resulting in high levels of osteoclastic and osteoblastic cell activity (high bone turnover), with increased deposition of extracellular bone matrix resulting in fibrosis. Measurement of serum PO_4 level and serum Ca level four times per year is recommended.

Healthy individuals ingest about 1 to 1.8 grams of phosphorus a day. Patients with kidney disease may require restriction to 0.8 to 1.2 grams of phosphorus a day. Use calcium carbonate or calcium acetate with meals (see treatment of hypocalcemia) when dietary restriction does not accomplish the target serum PO_4 level of less than 4.5 mg/L.

Aluminum hydroxide should be used sparingly and for short duration to avoid aluminum loading and toxicity. Citrate based compounds should not be administered concurrently with aluminum based binders because they increase aluminum absorption in the gut, and may cause aluminum intoxication.

REFERENCE

Hruska & Teitelbaum, 1995

EVIDENCE

QE=II

SR=A

Hypoalbuminemia (Serum Albumin Less Than 3.5 g/dL)

Malnutrition in patients with kidney failure is common. Mortality in dialysis patients correlates inversely with albumin levels (Lew et al., 1996, USRDS, 1999). Early referral to a nutritionist is indicated in all patients with compromised kidney function. Preferably patients should see a nutritionist at least twice a year and more frequently when they reach pre-ESKD levels of GFR (< 20 ml/min). Protein intake may be assessed by 24 hour urinary urea nitrogen excretion (UN g/day).

$$\text{Estimated Protein Intake (g)} = [\text{UN} + (.031 \times \text{weight (Kg)})] \times 6.25$$

See the Annotation on Nutrition, below, for further information on the management of hypoalbuminemia.

Note: Rule out other coexisting disease e.g. liver disease, chronic infection, protein-losing enteropathy or occult malignancy.

REFERENCES

Levin et al., 1996; USRDS, 1999

EVIDENCE

QE=II-2

SR=A

Metabolic Acidosis (CO₂ < 20 mEq/L and serum pH < 7.40)

Metabolic acidosis is common in kidney insufficiency and results from the accumulation of organic acids in plasma as well as impairment of kidney acidification mechanisms. It is important to maintain serum HCO₃ (measured as plasma CO₂) above 20 mEq/L. Correction of metabolic acidosis lessens kidney osteodystrophy (Lefebvre et al., 1989) and improves protein metabolism (Graham, 1997; Bergstrom et al., 1990).

Oral HCO₃ replacement in the form of NaHCO₃ tablets is indicated when the serum CO₂ falls below 20 mEq/L. The recommended dose of HCO₃ is 0.5 mEq/Kg/day, in divided doses. We recommend using 650 mg tablets (containing 7.7 mEq Na/7.7 mEq HCO₃⁻). The target is to titrate serum CO₂ to 20 mEq/L. Na citrate is not recommended because it facilitates aluminum absorption through the gut, resulting in possible severe and acute aluminum toxicity.

REFERENCES

Lefebvre et al., 1989; Graham et al., 1997; Bergstrom, 1990

2. Anemia

Anemia is a common consequence of chronic kidney failure, usually caused by erythropoietin deficiency (Besarab et al., 1989). Treatment of anemia improves exercise tolerance, decreases cardiovascular mortality, and promotes a sense of well being. The evaluation of the cause of the anemia in patients with kidney failure should be similar to that in patients without kidney failure. Iron deficiency and GI blood loss may be more common in patients with kidney failure. Measurement of erythropoietin level is not indicated for suspected anemia of kidney disease.

The usual diagnostic indices for iron deficiency may not be applicable in chronic kidney failure. Chronic kidney failure may result in an increase in serum ferritin due to the release of inflammatory cytokines. Although the exact value of serum ferritin that would exclude a response to iron therapy is controversial, there is evidence that treatment with iron in patients with serum ferritin up to 200 mg/ml may result in an increase in Hb/Hct in up to 50% of patients (Fishbane et al., 1996; Fishbane & Maesaka, 1997; Kalantar-Zadeh & Luft, 1997).

Therefore, we recommend determining serum ferritin in all kidney failure patients with anemia, and treating with oral iron if the serum ferritin is < 200 mg/ml. Although some investigators suggest using transferrin saturation (transferrin saturation % = serum iron x 100% / total iron binding capacity), most studies indicate that serum ferritin has better sensitivity and specificity for diagnosis (Fishbane et al, 1996; Fishbane & Maesaka, 1997; Kalantar-Zadeh, 1997). Oral iron should be given in a daily dose equivalent to 200 mg elemental iron (typically ferrous sulfate 325 mg tid) for six months (Wingard et al., 1995; NKF-DOQI clinical practice guidelines for anemia of chronic kidney disease, 2001).

If the cause of the anemia is identified and treated and the Hb remains < 10 gm/dl (or Hct < 30%), the patients should be referred to Nephrology/Hematology for further evaluation and consideration for epoietin therapy. Evidence suggests that treatment of kidney failure patients to increase their Hb to >10 gm/dL may improve quality of life and reduce cardiovascular morbidity (Canadian Erythropoietin Study Group, 1990; NKF-DOQI clinical practice guidelines for anemia of chronic kidney disease, 2001). A patient who has a Hb of 10-12 gm/dL, and no symptoms, should be followed with a repeat Hb on a semi-annual basis or as clinical condition requires.

REFERENCES

Besarab et al., 1989; Fishbane, et al., 1996; Fishbane & Maesaka, 1997; Kalantar-Zadeh & Luft, 1997; Wingard et al., 1995; NKF-DOQI clinical practice guidelines for anemia of chronic kidney disease, 2001; Canadian Erythropoietin Study Group, 1990.

EVIDENCE

Treatment with iron

QE=III

SR=B

Treatment improves quality of life

QE=I

SR=A

3. Volume Overload

Volume overload should be suspected in patients complaining of dyspnea, chest discomfort, orthopnea, paroxysmal nocturnal dyspnea, or progressive decrease in exercise tolerance. It may also be asymptomatic. Physical findings could include jugular venous distention, hepatojugular reflux, pulmonary rales, wheezing (in “cardiac asthma”), and S3 or S4, ascites, and peripheral edema. Patients with chronic kidney failure may also have significant volume overload even in the absence of the above symptoms and signs. Chest films may show evidence of pulmonary edema or may be subtle, showing only prominent pulmonary vasculature. The same findings may occur with heart failure, liver failure and various other conditions, so the patient’s change in weight over time is critical. Over weeks to months, these patients may lose lean body mass due to malnutrition and can develop fluid overload with relatively little change in weight. Therefore, serial assessment of patients’ lean body mass is also critical.

Contributors include:

- Excess salt intake
- Progressive kidney damage (nephrosclerosis)
- Fluid retention from blood pressure medications
- Inadequate diuretic therapy.

Consider fluid overload for sudden unexplained gains in weight, refractory hypertension, peripheral edema or shortness of breath. These may be secondary to the above causes. Hyponatremia, developing as a result of water retention in excess of sodium retention, may also be a marker for volume overload in the above setting.

Management:

- Patients should be weighed at every visit
- Dietary sodium restriction to 2 gm/d
- Loop diuretics, and if refractory to twice a day dosing, consider adding thiazide-type diuretics
- If advanced kidney failure, consider initiation of dialysis.

REFERENCE

Brater, 1998

4. Nutrition

ANNOTATION

All patients with chronic kidney disease should have an assessment by a kidney dietitian soon after diagnosis. Attention should be given to overall nutrition, including lipids, potassium, phosphate, sodium, protein and energy. In patients with early or moderate kidney insufficiency, daily energy intake should be 35 kcal/kg body weight and daily protein intake should be 0.8 g/kg body weight. For patients with more severe kidney insufficiency or nephrotic syndrome, severe protein restriction in conjunction with a dietary supplement may be useful to prevent symptoms and reduce proteinuria.

DISCUSSION

Energy intake

The nitrogen balance of uremic patients improves as caloric intake increases, according to some workers (Hyne et al., 1972; Kopple et al., 1986), but not others (Bergstrom, 1978). Based on these conflicting data, it seems prudent to recommend an intake of 35 kcal/kg/day for a patient on a protein-restricted diet who is below ideal body weight. For overweight patients, calories should be restricted. For others, caloric intake may be ad libitum, unless progressive weight loss occurs. If weight is an issue, a consultation with a dietitian is advisable.

Assessment of nutrition

Serum albumin concentration has traditionally been used to measure protein nutrition. However recent evidence has established that hypoalbuminemia may also reflect an inflammatory response to unknown stimuli (Kaysen, 1999). Therefore, it is advisable to measure other indicators as well, including transthyretin (pre-albumin) (Tuten, et al., 1985; Avram & Mittman, 1994) and C-reactive protein (Kaysen, 1999). Anthropometry may also be employed, but its value is limited, especially if data are from a single measurement (Maroni, 1998).

Dietary protein in severe kidney insufficiency and nephrotic syndrome

Protein restriction is indicated in every symptomatic patient with kidney failure. Protein restriction is the mainstay of dietary treatment, because almost all of the signs and symptoms are caused by retention of the products of protein catabolism. Yet protein malnutrition is a common and ominous complication of kidney insufficiency. Although it is commonly assumed that protein malnutrition is best avoided by encouraging greater protein intake, this advice may be counterproductive. The associated increase in signs and symptoms (especially anorexia) may reduce caloric intake and aggravate malnutrition. If intake of essential amino acids (abundant in high quality protein and also available as tablets) as well as calories is adequate, protein malnutrition will not develop and, if present, may be corrected (Walser, 2000).

Protein catabolism is increased in the presence of acidosis, and reduced when acidosis is corrected (Reaich, 1993; Graham, 1997; Mitch & Walser, 2000). Therefore, it is important to treat acidosis by sodium bicarbonate supplements. Sodium citrate is an alternative for patients who are not receiving aluminum hydroxide. If edema results, it can be treated by increasing the dosage of diuretics.

REFERENCES

Hyne et al., 1972; Kopple et al., 1986; Bergstrom, 1978; Kaysen, 1999; Tuten et al., 1985; Avram & Mittman, 1994; Maroni, 1998; Walser, 2000; Reaich, 1993; Graham, 1997; Mitch & Walser, 2000.

N. Prevent and Treat Cardiovascular Disease

OBJECTIVE

To improve cardiovascular health in patients with kidney disease, enhance their quality of life and improve survival rates for patients that progress on to ESKD and dialysis and/or transplantation.

ANNOTATION

Patients with kidney disease and/or proteinuria are at high risk for cardiovascular disease. Modification of risk factors may attenuate these risks. Effective treatment of hypertension, hyperlipidemia and anemia, along with smoking cessation and exercise, are essential.

For the treatment of hypertension, please review the VA/DoD Guideline for the Management of Hypertension in Primary Care.

For control of dyslipidemia, please refer to the VA/DoD Guideline for the Management of Dyslipidemia in Primary Care.

For the treatment of anemia see Annotation M.

For the treatment of smoking cessation, please refer to VA/DoD guideline on Tobacco Use Cessation.

For additional information on prevention and treatment of cardiovascular disease, refer to the VA/DoD Guideline for the Management of Ischemic Heart Disease.

The VA/DoD guidelines can be found on the VA web site, www.va.gov.

DISCUSSION

Cardiovascular abnormalities start early in kidney failure. Twenty-seven percent of patients with GFR greater than or equal to 50 ml/min exhibit left ventricular hypertrophy (Levin et al., 1996). The incidence of coronary artery disease in patients with kidney failure is not well known but the high death rates in this population suggest that it is quite high.

Annual mortality rates from cardiovascular disease for patients starting dialysis are extremely high. The 5-year survival of men > 64 years old starting dialysis is worse than that of men with colon and prostate cancer. The 5-year survival rate for similarly aged women is worse than that of women with breast and colon cancer (U.S. Renal Data System, 1998). About half of these deaths are attributable to cardiovascular events.

REFERENCES

Levin et al., 1996; USRDS, 1998

EVIDENCE

QE=II

SR=A

O. Provide Patient Education

OBJECTIVE

To enhance patient adherence to treatment.

ANNOTATION

Patient education should begin soon after the diagnosis of kidney insufficiency. The importance of strategies to delay progression of kidney disease and avoid further kidney injury must be highlighted.

Few kidney disease education curricula have been published. The Canadian Pre-Dialysis Advisory Board developed one such program (Porter, 1998; Mendelssohn & Toffelmire, 1998). Oschner Clinic Renal Services developed a pre-ESKD education program in 1997 called "Healthy Start" that may serve as a resource (Linberg et al., 1999; Self et al., 1998). Both programs have received support from Baxter Healthcare Renal Division through their Pre-ESKD Education Program. This program provides a nurse educator, at no charge, to interested hospitals, clinics, or physicians.

Key areas that need to be included in the education program for patients and their families are discussed below. Items 1-7 should be covered early in the course of kidney insufficiency. The others may be covered later, as kidney insufficiency progresses and additional complications become likely.

1. General overview

Anatomy and normal function of the kidneys, altered kidney function and the patient's disease process need to be explored. Laboratory tests and results, diet and medications should be reviewed. This can be done in small groups. Groups may be inappropriate, however, for patients who have low literacy skills or learning problems.

2. Control of blood pressure

Adherence to medications and dietary and lifestyle changes may reduce the rate of progression of kidney disease as well as reduce the risk of cardiac disease. For further information on this topic, please see the VA/DoD Clinical Guideline for the Management of Hypertension, Annotation K.

3. Low protein diet

There are several clinical trials that have suggested delay in the progression to end stage with moderate protein restriction to 0.6 gm/kg/day, although conclusive evidence is lacking. See section on nutrition, Annotation M.

4. Blood glucose control

Among diabetics, large-scale trials suggest delay in progression as well as amelioration of other complications of diabetes (DCCT, 1995). See the VA Clinical Guideline for Management of Diabetes Mellitus, Module G.

5. Angiotensin converting enzyme inhibitors (ACE-I)

There is mounting evidence that use of ACE-I delays progression of diabetic and non-diabetic kidney disease, even in the absence of hypertension (Lewis et al., 1993; Giatras, et al., 1997). There are the potential risks of developing hyperkalemia and worsening kidney function (especially if there is kidney vascular stenosis). Thus, initiation of this treatment must be done with close follow-up to monitor potassium and creatinine, and continuation may require dietary potassium restriction. Patients on ACE-I must be advised of the increased risk of ARF in the setting of

volume depletion, such as may be seen with protracted vomiting, diarrhea or high fevers. In such instances, patients must be instructed to seek evaluation.

6. Avoidance of NSAIDs and other nephrotoxic drugs, including illicit drugs

Patients should be counseled about the possible adverse consequences of NSAIDs, which are in many over-the-counter cold and pain preparations (Bennett & Porter, 1998; De Broe & Elseviers, 1998). They need to understand that the kidney is a frequent target for toxic injury because it is a major route of excretion for a variety of drugs. It is also important to obtain a history of any alternative medical therapies the patient may be using. It has been reported that only 30% of patients who use alternative therapies ever mention it to their health care providers. Therefore it is important to attempt to establish rapport, so that the patient will share information (Geraghty, 2000). Occupational and environmental exposures as well as the use of cocaine, heroin, and amphetamines (Ecstasy) need to be explored as well (Bakir & Dunea, 1996).

7. Lifestyle changes

Patients may need to make lifestyle changes in such areas as: smoking cessation, weight control, other dietary changes, drug and alcohol treatment, increased physical activity, stress management, social issues, vocational rehabilitation, family issues and issues of sexuality.

These changes may take a concerted team effort and may require on-going support groups. Repetitive contact, monitoring, and encouragement are all methods to reinforce behavior change. See Clinical Guideline for the Management of Diabetes Mellitus, Module R, Kidney Disease. Also see Module H for suggestions on smoking cessation, exercise, and stress management.

8. Abnormal calcium and phosphate metabolism

These may lead to bone disease, resulting in pain and fractures, and the deposition of Ca and PO₄ in microvasculature, leading to tissue ischemia and loss. Patients should be advised about the importance of the control of calcium and phosphate for the prevention of bone and cardiovascular disease (Martinez et al., 1997; Sherrard, 1994; Llach & Massry, 1985).

9. Anemia secondary to relative erythropoietin deficiency

Anemia is associated with the development of left ventricular hypertrophy and CHF, both of which may increase cardiovascular mortality among patients with kidney failure, but which may be ameliorated by improvement in the anemia with iron or EPO (Greaves et al., 1994; Parfrey et al., 1996; NKF-DOQI, 2001). Treatment of anemia may also maintain normal cognitive function (Wolcott et al., 1989).

10. Hyperkalemia related to reduced clearance

Hyperkalemia usually does not develop until late in the course of kidney insufficiency, once the GFR falls below 20 ml/min or oliguria has developed. However, earlier development of hyperkalemia may occur among patients with diabetic nephropathy (or other conditions associated with hyporeninemic hypoaldosteronism, such as chronic interstitial nephritis), and patients on ACE-I/ARBs, NSAIDs or potassium-sparing diuretics. Formal dietary counseling is recommended for potassium restriction for hyperkalemia that does not resolve with discontinuation of possible culprit medications. Potassium-binding resins may be necessary, along with close monitoring as kidney failure progresses. Patients must be told that significant hyperkalemia predisposes to cardiac dysrhythmias and death.

11. Preparation for Kidney Replacement Therapy

Once there is evidence of progression of kidney insufficiency, or at the latest when the creatinine is ≥ 3 mg/dL or the creatinine clearance is ≤ 40 -50 ml/min, the patient must be instructed to 'save' the non-dominant arm for hemodialysis access (no venipuncture or IV), and physicians must avoid central lines (in particular subclavian, but also IJ given the risk of IJ or SVC stenosis).

The various modalities of KRT, including hemodialysis, peritoneal dialysis and preemptive transplantation, should be introduced once there is clear evidence of progression to KRT. There are currently no age restrictions on the initiation of dialysis, thus the decision to withhold dialysis must be made in conjunction with a well-informed patient. The patient should also be referred to nephrology for full discussion of these issues—at the latest when the creatinine is ≥ 4 mg/dl or the creatinine clearance is ≤ 30 ml/min—to enable realistic exploration of living donor transplant prior to the requirement for dialysis.

DISCUSSION

Patient education is a field in itself that includes such complex issues as compliance, resistance to change, motivation, and the communication skills of the health provider.

1. Teaching must start early and must include the most basic information regarding kidney function and its relation to the patient's condition. Early education, while the patient feels relatively well, can reduce anxiety through preparation. It allows choices, assures informed consent, encourages independence, and promotes a sense of control (Hayslip & Suttle, 1995).

2. Conveying the information to the patient is a major challenge. Although the health care provider may be convinced that instructions are understood, the message frequently is misunderstood or not understood at all. Often, a patient's learning style and readiness to learn are not considered.

3. Common barriers to learning include anger, denial, language differences, physical disabilities, pain, fear, anxiety, cognitive limitations, cultural variables, health beliefs and religious practices. Other factors are age, co-morbid conditions, financial resources, distance to treatment center and support systems. Readiness to learn needs to be determined at each step since it has a profound effect on the patient's comprehension. An environment conducive to learning—free of interruptions such as beepers, phone calls, and foot traffic—is the responsibility of the educator.

4. Do not assume the patient can read or comprehend your printed materials. One out of every five adults reads at the 5th grade level or below. For older Americans (65 and over) and for inner city minorities, almost 2 out of 5 read below the 5th grade level. The average reading level of adults in this country is 8th-9th grade. Half of the population read at the 9th grade level or lower (Doak et al., 1996).

5. Health care professionals tend to overestimate the literacy skills of their patients. It is common to assume that a patient reads at the level of the last grade completed in school. Generally, however, adult reading levels are approximately 3-5 grades lower than their last grade completed. A recent study of VA patients over the age of 50 in Shreveport found the reading level to be at the 5th grade level. However, general VA guidelines require written instructions to patients to be at the 8th grade level.

6. Videos, audios, and flip charts are useful for instructions. Tell the patient what the instruction is aimed at and get to the point quickly. Avoid a patronizing tone and fear provoking messages. Also, avoid the use of the word "you" as in "you need to start taking your blood pressure pills everyday or you are going to have a stroke."

7. When assessing patient comprehension ask open-ended questions rather than questions that can be answered with a yes or no. An example of an open-ended question is "Tell me what medications you are taking for your blood pressure?" rather than "Are you taking your blood pressures medications?" Speak slowly and use simple words (Szczepanik, 1995). Be aware that health care providers tend to give too much information at one time. Instructions must be simple, focused, consistent and repetitive.

8. Education materials are available through a number of resources. See Appendix 5 for a listing of organizations that provide information including videos, pamphlets, fact sheets and books.

REFERENCES

Porter, 1998; Mendelssohn & Toffelmire, 1998; Linberg, 1999; Self et al., 1999; VA/DoD Guideline for the Management of Hypertension, 1999; DCCT, 1995; VA Guideline for the Management of Diabetes Mellitus; Lewis,

et al., 1993; Giatras et al., 1997; Bennett & Porter, 1998; De Broe & Elvseviens, 1998; Geraghty, 2000; Bakir & Dunea, 1996; Martinez et al., 1997; Sherrard, 1994; Llach & Massry, 1985; Greaves et al., 1994; Parfrey et al., 1996; NKF Task Force, 1998; Wolcott et al., 1989; Hayslip & Suttle, 1995; Doak et al., 1996; Szczepanik, 1995.

P. Follow-up

OBJECTIVE

To detect early changes in kidney function, clinical status, and biochemical parameters in order to prevent or to attenuate uremic complications and, possibly, to slow the progression of kidney disease.

ANNOTATION

The frequency of follow-up visits depends on the severity of kidney disease. It is unlikely that patients with mild kidney insufficiency (Scr < 2.0 mg/dL) will develop electrolyte disturbances, anemia or uremic bone disease. Similarly, patients with normal kidney function and mild proteinuria (< 1.0 g/24 h), in the absence of diabetes mellitus, are less likely to develop more serious kidney problems. These patients, if they do not have other comorbidities and if their kidney function has been stable, can be seen about two to three times per year.

It is advisable that a nephrologist be consulted, at least initially, for the care of patients with more advanced kidney insufficiency (Scr > 2.0 mg/dL or GFR < 50 ml/min) and for patients with larger amount of proteinuria. Patients with nephrotic range proteinuria (> 3g/24h) need additional work-up that may include kidney biopsy. There is a high possibility that kidney insufficiency will progress to end-stage-kidney-disease in patients with serum creatinine greater than 2 mg/dL (or GFR less than 50 ml/min). Many biochemical abnormalities that will eventually lead to clinical symptoms associated with uremia are already detectable at this level of GFR. Education about ESKD and treatment options should be given to these patients. Dietary protein restriction may be helpful in preventing uremic symptoms and in delaying the progression of kidney disease in patients with chronic kidney failure. Low protein diet can also reduce proteinuria in patients with nephrotic syndrome. In addition to dietary protein restriction, attention should be given to overall nutritional status, hyperlipidemia and electrolyte balance. These patients should be seen by a kidney nutritionist at least twice yearly. They also need more frequent follow-up (usually every 2 to 3 months) in the clinic. The care of these patients could be transferred to a specialty clinic or could be coordinated between primary care physicians and the specialty clinic.

Patients with serum creatinine greater than 4 mg/dL (GFR < 25 ml/min) have severe kidney insufficiency and should be referred to a nephrologist without any delay. These patients are at high risk of developing uremic complications. They could also progress to ESKD in a relatively short time. By this time the patient should have a good knowledge about ESKD and its treatments. If hemodialysis is the treatment option, the patient should receive the instruction not to use the non-dominant arm for blood drawing. An exercise program to build up forearm muscle and to increase the size of forearm veins should be instituted. A permanent vascular access (preferably an AV fistula) should be placed when the GFR is ~ 15 ml/min (20 ml/min in diabetics). If preemptive kidney allograft transplantation is an option, work-up for the patient and potential donors must be initiated. These patients obviously need frequent follow-up, usually every one to two months. They also need to be evaluated more frequently by a nutritionist.

Frequent follow-up visits are also indicated in patients with rapid change in kidney function or in whom there are not enough data to determine the rate of progression of kidney failure. Other groups of kidney patients who need to be seen frequently are patients with poorly controlled BP and diabetic patients with poorly controlled BP or blood sugar, or both. Poorly controlled BP (BP > 130/80 mmHg) can adversely affect the progression of kidney disease in diabetics as well as in patients with kidney insufficiency from other causes. Poor glycemic control may also adversely affect the progression of diabetic kidney disease. It may be necessary to see these patients and to adjust their medications at least monthly until their BP readings and/or their blood sugar are in the acceptable ranges. If hypertension or diabetes mellitus is difficult to manage, a consultation with a specialist may be appropriate. See the VA/DoD guidelines for hypertension and diabetes mellitus for more details.

Serum electrolytes, BUN/creatinine, Ca/P, serum albumin and urinalysis should be done routinely at each visit. An asymptomatic patient with a stable level of Hgb at 10 g/dL or more should have his/her Hgb checked at least twice yearly. In diabetic patients who do not have macroalbuminuria, determination of microalbuminuria should be done at least yearly.

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PRE-ESKD IN THE PRIMARY CARE SETTING

APPENDIX 1

ETIOLOGIC EVALUATION

	CLUES	SEDIMENT	RANGE of PROTEINURIA	SPECIAL TESTS
Essential Hypertension	Look for other signs of end organ damage	No formed elements	Trace → Moderate	N/A
Diabetes mellitus	Frequently associated with retinopathy	<25% have microscopic hematuria	Microalbuminuria → Nephrotic	N/A
Glomerulo-nephritis	Use H&P to focus serological evaluation	Dysmorphic Rbcs or Rbc casts	Trace → Nephrotic	C3, C4, ASO, ANCA, HIV, HEP B & C, ANA, RPR, Blood cultures, Cryoglobulin, anti-GBM; SPEP, UPEP
Interstitial nephritis	Medication history, fever, rash, eosinophilia. Classic triad of fever, rash, & eosinophilia is present in a minority only.	Pyuria, Wbc casts, eosinophiluria.	Trace → Moderate	
Pre-kidney	Clinical diagnosis; Volume depletion, hypotension R & L CHF, sepsis, liver disease.	Hyaline casts may be present	None → Trace	FE _{Na} <1%
Urinary tract obstruction	Suggested by history and physical exam.. May or may not be oliguric.	Benign or may have hematuria	None	Kidney ultrasound, bladder scan, other imaging studies may be necessary
Paraprotein-emia	Globulin > albumin; constitutional symptoms, anemia out of proportion to kidney failure.	May have hematuria, Rbc casts, granular casts	May have false negative dipstick, trace to Nephrotic range by spot protein/creatinine.	SPEP/UPEP, IEP or immunofixation to confirm, hypercalcemia may be present, ESR
Polycystic kidney disease	Palpable kidneys, +/- family history, flank pain	May have hematuria	Trace → Moderate	Kidney ultrasound or CT
Renovascular Disease	Late onset or refractory hypertension, smoking history, clinical evidence of atherosclerotic disease	Benign	None → Trace	Asymmetric kidney size on ultrasound; abnormal doppler of kidney arteries. Additional investigation (e.g. captopril radionuclide scan, MRA) may be indicated.
Vasculitis	Constitutional symptoms, fever, peripheral neuropathy, rash, may have respiratory involvement	Hematuria; granular casts	Trace → Nephrotic	C3, C4, ANA, ANCA; HepBsAg; HepC Ab; cryoglobulins; ESR, CRP; RF; HIV
Acute Tubular Necrosis	Medication history; history of hypotension; crush injury; iv. contrast	Granular casts; crystalluria;	Trace	FE _{Na} >2%; Uosm < 500 mOsm/l CPK, urine myoglobin;
Atheroembolic Disease	“Stuttering” GFR loss, stigmata of emboli, history of endovascular procedure	Hematuria &/or eosinophiluria may be present.	Trace → Moderate	Eosinophilia

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APPENDIX 2

SPECIALIZED LABORATORY STUDIES FOR THE DIAGNOSIS OF KIDNEY DISEASE	
Laboratory Test	Significance
Serum Complement Levels (C3,C4)	May be decreased in: Post-streptococcal glomerulonephritis Endocarditis-associated glomerulonephritis Immune-complex glomerulonephritis Membranoproliferative glomerulonephritis Lupus nephritis Cryoglobulinemia Atheroembolic disease
ANA	Positive in: Lupus nephritis
Anti-neutrophil cytoplasmic antibody (ANCA)	Positive in: Wegener's granulomatosis (C-ANCA) Microscopic polyangiitis (P-ANCA) Pauci-immune RPGN (P-ANCA)
Anti-glomerular basement membrane antibodies (anti-GBM)	Positive in: Goodpasture's syndrome Anti-GBM associated RPGN
Serum protein electrophoresis (SPEP) Urine protein electrophoresis (UPEP)	Positive for monoclonal antibody in: Multiple myeloma Amyloid Light-chain deposition disease
Cryoglobulins	Positive in: Cryoglobulinemia
Hepatitis B surface antigen	Associated with: Membranous nephropathy Polyarteritis nodosa Membranoproliferative nephritis
Hepatitis C antibody	Associated with: Mixed cryoglobulinemia Membranoproliferative glomerulonephritis Membranous nephropathy
HIV serologies	Associated with: Focal and segmental glomerulosclerosis(FSGS)
Eosinophiluria	Associated with: Acute allergic interstitial nephritis Atheroembolic disease May be positive in any condition with eosinophilia or pyuria

KIDNEY IMAGING STUDIES	
Imaging study	Significance
Kidney ultrasound	Diagnosis of: Obstructive kidney disease Polycystic kidney disease Assessment of kidney size: Enlarged in diabetic nephropathy, amyloid Small in chronic kidney disease Asymmetric in renovascular disease
Kidney doppler	Diagnosis of: Renovascular disease Kidney vein thrombosis
Radioisotope kidney scan	Diagnosis of: Renovascular disease Obstructive uropathy Assessment of split kidney function
CT scan	Assessment of: Kidney masses Atypical kidney cysts
Magnetic resonance angiography	Diagnosis of: Renovascular disease
Kidney angiography	Diagnosis of: Renovascular disease (gold standard) Kidney artery thrombosis/thromboembolism Polyarteritis nodosa
Retrograde ureterogram	Diagnosis of: Upper-tract obstruction
Intravenous pyelogram	Not indicated in kidney insufficiency

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APPENDIX 3

Parameter	Level	Issues	Treatment
Albumin	< 3.5 g/dL	Associated with increased mortality. General causes of hypoalbuminemia include abnormal metabolism, chronic inflammation, liver disease. Specific causes that could be addressed are: Reduced intake Nephrotic syndrome Acidosis Poorly controlled diabetes	Nutritional assessment and supplementation Assess urinary protein Assess and treat acidosis Maximize diabetic control
Hct	Hct < 33% Hgb <11g/dL (Premenopausal female) Hct < 37% Hgb <12g/dL (Male & post-menopausal female)	Usual causes of anemia must be excluded before attributing to kidney disease Common causes in chronic kidney insufficiency: Inadequate erythropoiesis Reduced RBC half-life Coagulopathy	Erythropoietin levels are not helpful for diagnosis of suspected anemia of kidney disease Initiate oral Fe treatment if the transferrin saturation is < 20% and/or the ferritin is < 200 ng/ml If the patient is symptomatic, or the HCT < 30% and/or Hgb is < 10g/dL despite iron therapy, refer to nephrology for consideration of erythropoietin therapy
Bicarbonate	< 20 mEq/L	Other causes of acidosis must be considered prior to ascribing to kidney disease, especially if the HCO ₃ is < 15 mEq/L Common in CKI. Kidney causes include: Impaired kidney acidification Accumulation of organic acids	NaHCO ₃ tablets when the serum bicarbonate falls below 20 mEq/L Usual starting dose: 0.5 mEq/Kg/day in divided doses. One 650mg NaHCO ₃ tablet contains 7.7 mEq Na/7.7 mEq HCO ₃

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APPENDIX 4

MEDICATIONS IN PATIENTS WITH KIDNEY DISEASE

DRUG	COMMENTS
Antihypertensives	
Diuretics	Loop diuretics preferred because of superior efficacy in low GFR states. Higher doses or combination (e.g. furosemide + metolazone) may be required to obtain clinical response. Spironolactone and other K ⁺ sparing diuretics should be used with caution to avoid hyperkalemia.
ACEI/ARB	Beneficial effects in patients with diabetic nephropathy, heart failure, and some kidney diseases. May decrease GFR in some patients with kidney insufficiency or kidney artery stenosis. Serum K ⁺ should be monitored. Contraindicated in pregnancy.
Beta Blocker	Metoprolol is the preferred β -blocker due to hepatic excretion.
Calcium Antagonists	Generally safe to use in patients with kidney disease.
Alpha Blockers	Beneficial in patients with prostatic hypertrophy.
Clonidine	Generally safe to use in patients with kidney disease.
Vasodilators	Generally safe to use in patients with kidney disease, although may cause sodium retention. Not usual first line therapy, although hydralazine is useful substitute for patients that do not tolerate ACEI/ARB
Antibiotics	Dosage adjustments frequently required in kidney failure. Acyclovir, other antivirals, and sulfa drugs may cause crystaluria. Acyclovir/gancyclovir dose must be decreased to avoid encephalopathy. Trimethoprim can cause hyperkalemia. Aminoglycosides are nephrotoxic and dose adjustment required based on eGFR.
NSAIDs	Use with caution in patients with kidney disease. Frequent cause of acute kidney failure. COX 2 agents are not kidney protective. Other side effects include worsening of hypertension, hyperkalemia, and sodium retention.
Lipid lowering agents	Avoid fibrates. May need to lower statin doses due to increased risk of myopathy. See VA/DoD Guideline for the Management of Dyslipidemia in Primary Care.
Hypoglycemic Agents	
Insulin	Half life prolonged in patients with kidney disease and dosage of insulin must be decreased accordingly.
Oral agents	Biguanides (e.g. metformin) use with caution in patients with decreased GFR. Kidney insufficiency prolongs half life of many agents, requiring dosage adjustment to avoid hypoglycemia.
Cardiac glycosides	Half life prolonged with kidney insufficiency, and dosage must be decreased. For example, typical dosage of digoxin in end stage kidney disease is 0.125 mg 2 or 3 times per week.
Gout therapy	Allopurinol dosage should be decreased in patients with kidney insufficiency. Allopurinol may cause interstitial nephritis and should be stopped if kidney function deteriorates acutely. Colchicine should be used with caution in patients with kidney disease to avoid neutropenia and GI side effects.
Anti-epileptics	Dosage adjustments often required with decreased GFR.
Over Counter Meds	
Antacids	Avoid magnesium or aluminum containing antacids. In general, calcium carbonate or acetate is safe in kidney failure.
Salt substitutes	Often contain potassium and may cause hyperkalemia.
Decongestants/antihistamines	May be associated with worsening hypertension, and urinary retention.

DRUG	COMMENTS
Herbal remedies	Effects on kidney function and other organs unknown. Ephedrine containing products worsen hypertension, and some weight loss therapies can cause volume depletion.
Vitamins	Multivitamins and folate generally beneficial in patients with kidney disease. Vitamin A and D usage should be monitored to avoid toxicity and hypercalcemia.
Alkalinizing agents	Sodium bicarbonate is used to treat chronic acidosis of kidney disease and is preferred to Shohl's solution. Both agents contain sodium and volume status should be monitored. Avoid aluminum containing antacids when using Shohl's solution.
Phosphate binding agents	Calcium carbonate/acetate preferred. New non-calcium containing agents are becoming available but are expensive and generally not more efficacious than calcium carbonate, but may be useful in special situations.
Anemia therapy	Anemia management module of this guideline should be referenced

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APPENDIX 5

RESOURCES FOR PATIENT EDUCATION

American Association of Kidney Patients 800-749-AAKP

National Kidney Foundation 800-622-9010

<http://www.kidney.org>

American Kidney Fund 800-638-8299

<http://www.akfinc.org>

U. S. Department of Health and Human Services Health Care Financing Administration

Amgen

Baxter Healthcare Renal Division

<http://kidneydirections.com>

Fresenius Medical Care North America

<http://www.frecna.com>

National Kidney and Urologic Disease Information Clearinghouse

<http://www.niddk.nih.gov/health/kidney>

“Kidney Disease Dictionary”

“ESKD & Choosing A Treatment That is Right For You”

“Your Kidneys and How They Work “

“Vascular Access for Hemodialysis”

“Eat Right to Feel Right on Hemodialysis”

The Nephron Information Center

<http://www.nephron.com>

“How the Kidney Works”

“Early Renal Insufficiency” by Stephen Z. Fadem, M.D., FACP

“ESKD Diet Books and Brochures”

NKF of Southeast Texas

<http://www.nkfset.org>

Kidney Transplant/Dialysis Association, Inc.

<http://www.ultra.com/~ktda/handbook.html>

Forum of ESKD Networks

<http://esrdnetworks.org>

Renalnet

<http://www.renalnet.org>

R &D Laboratories

<http://www.ikidney.com>

The above list of sites is not all-inclusive. Some of the sites have links to other sites as well.

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APPENDIX 6

VHA/DoD DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH HYPERTENSION IN THE PRIMARY CARE SETTING

Patient with HTN
(SBP \geq 140 or DBP \geq 90)
(Annotation E)

Is SBP > 210 or DBP > 120? Treat or refer immediately

Perform history, physical exam, laboratory and other diagnostic procedures
(Annotations F, G, H)

Is a secondary cause suspected? Continue evaluation and treatment as indicated
(Annotation I) Manage secondary cause and/or consider referral to specialist

<p>IF</p> <p><input type="checkbox"/> SBP \geq 180 or DBP \geq 110</p> <p><input type="checkbox"/> SBP 160-179 or DBP 100-109</p> <p><input type="checkbox"/> SBP 140-159 or DBP 90-99</p> <p><input type="checkbox"/> control adequate</p>	<p>Initiate/Continue drug therapy. Prescribe diet and lifestyle modification. (Annotation K, L)</p> <p>Drug therapy is preferred. Consider aggressive lifestyle modification alone in selected patients. (Annotation K, L, M)</p> <p>Initiate diet and lifestyle modification and patient education. Drug therapy if end organ damage or diabetes or if inadequate control. (Annotation K, L)</p> <p>Continue current treatment. Reinforce lifestyle modification. Follow-up at next regular visit. (Annotation O)</p>
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Recommendations for Follow-up Based on Initial Blood Pressure Measurements for Adults^a

Systolic	Diastolic	Recommended Follow-up
< 130	< 85	Recheck in 2 years
130-139	85-89	Recheck in 1 year ^b
140-159	90-99	Confirm within 2 months ^c
160-179	100-109	Evaluate or refer to source of care within 1 month
> 180	> 110	Evaluate or refer to source of care immediately or within 1 week, depending on clinical situation

^aIf systolic and diastolic categories are different, follow recommendations for shorter follow-up (e.g. 160/86 mm Hg should be evaluated or referred to source of care within 1 month).

^bModify the scheduling of follow-up according to reliable information about past blood pressure measurements, other cardiovascular risk factors, or target organ disease.

^cProvide advice about lifestyle modifications

General Principles for Pharmacologic Management:

- Emphasize adherence to the medication regimen.
- If control not achieved, continue a once a day regimen by increasing drug dose as tolerated OR substituting another drug OR adding an agent from a different class.
- Multi-drug regimens should include a thiazide diuretic for synergy, unless contraindicated.

If BP control is not achieved with three drugs in compliant patients, further evaluation or referral should be considered.

Recommended Dosage for Selected Hypertension Drug Therapy (Adapted from PBM-MAP The Pharmacologic Management of HTN, Supplement to the VHA/DoD Clinical Practice Guideline on HTN)

Drug^a	Dosage Range^{d,e}	Comments
THIAZIDE DIURETICS		
Hydrochlorothiazide ^b HCTZ/Triamterene ^b	12.5-25 mg/day (max=50mg/day) 25/37.5-50 mg/75 mg/day	Use HCTZ/Triamterene with caution with ACEI and other K ⁺ retaining drugs or supplements
β-BLOCKERS		
<i>Noncardioselective</i>		
Propranolol ^b	IR: 40-480 mg/day in divided doses SR: 80-160 mg/day	β-blockers are contraindicated in asthma patients Discontinue with slow taper over 1 week
<i>Cardioselective</i>		
Atenolol ^b Metoprolol	25-100 mg/day (adjust dose in CKI) IR: 50-300 mg/day (once daily or divided doses)	As doses increase, cardioselectivity decreases
CCBs		
Verapamil IR ^b Verapamil SR ^c Diltiazem IR ^b Diltiazem SR (Tiazac ^{®b})	120-360 mg/day (in 2-3 divided doses) 120-480 mg/day (once daily or 2 divided doses) 90-360 mg/day (in 3-4 divided doses) 120-540 mg/day	Verapamil is contraindicated in AV node dysfunction (2 nd or 3 rd degree heart block), systolic CHF and decreased LV function Diltiazem may decrease sinus rate and cause heart block
<i>Dihydropyridines</i>		
Felodipine Nifedipine SR (Adalat ^{®CCb})	2.5-10 mg/day 30-120mg/day (manufacturer max=90 mg/d)	Monitor adverse effects (DHPs may cause ankle edema, dizziness, flushing, headache) Use CCBs with caution in patients with liver or kidney dysfunction
ACEIs		
Captopril ^b Fosinopril Lisinopril ^b	25-150 ^f mg/day (in 2-3 divided doses) 10-40 mg/day 5-40 mg/day	Avoid in 2 nd and 3 rd trimesters of pregnancy due to possible fetal and neonatal morbidity and death Monitor K ⁺ and kidney function
α-BLOCKERS		
Prazosin ^b Terazosin ^b	1-15 mg/day (in 2-3 divided doses) (max=20mg/d) 1-5 mg/day (max=20 mg/d)	Initiate at low doses (1mg) with 1 st dose given at bedtime to avoid syncope
ANGIOTENSIN II ANTAGONIST		
Candesartan Irbesartan Losartan Telmisartan Valsartan	8-32 mg/day (once daily or 2 divided doses) 150-300 mg/day 25-100 mg/day (once daily or 2 divided doses) 20-80 mg/day 80-320 mg/day	Contraindicated in 2 nd and 3 rd trimesters pregnancy due to potential for fetal and neonatal morbidity and death
CENTRALLY ACTING		
Clonidine Tablet ^b Clonidine Patch Methyldopa	0.1-0.8 mg/day (in 2-3 divided doses) (max can be up to 2.4 mg/d) 0.1-0.6 mg patch weekly 500 mg-3g/day (in 2-4 divided doses)	Taper dose to discontinue Clonidine patches are costly but may be useful in selected patients
PERIPHERALLY ACTING		
Reserpine	0.05-0.25 mg/day	Monitor for sedation, nightmares, tremors, nasal congestion, activation of peptic ulcer
VASODILATING AGENTS		
Minoxidil Hydralazine ^b	5-40 mg/day (once daily or 2 divided doses) (max=100 mg/day) 30-200 mg/day (in 2-3 divided doses)	Should be used with a diuretic and β-blockers to reduce edema and reflex tachycardia Monitor for hypertrichosis, pericardial effusions with minoxidil Monitor for headache and SLE (dose-related) with hydralazine

^a Partial list^b DoD BCF item; all BCF items are available through the DoD NMOP^c Calan[®] SR, Isoptin[®] SR, and generic equivalents are on the DoD BCF^d Once daily dosing unless specified otherwise^e IR=immediate release; SR=sustained release^f Patients should take 1 hour prior to food ingestion (empty stomach)

Special Populations, Comorbidities, and Preferred Agents^{a,b}

	PREFERRED AGENTS	ALTERNATE AGENTS	OTHER SELECTED AGENTS	COMMENTS
Uncomplicated	thiazide diuretic, β -blocker	ACEI, CCB	α -blocker, clonidine, reserpine	Short-acting nifedipine should not be used for long-term management of HTN
African-American Race	thiazide diuretic	CCB, β -blocker, ACEI	α - β -blocker, clonidine, α -blocker	Differences in efficacy among patient populations are not as apparent when diuretics are added to ACEIs and β -blockers
Asthma/COPD	thiazide diuretic	ACEI, CCB	clonidine, α -blocker	β -blockers generally contraindicated in patients with bronchospastic disease
BPH – Symptomatic	α -blocker ^c	β -blocker, ACEI, thiazide diuretic (low dose), CCB	clonidine	Diuretics may influence symptoms of polyuria and frequency
Coronary artery disease	β-blocker (non-ISA post-MI)	<i>verapamil, diltiazem</i>	DHP SR, ACEI, thiazide diuretic	Non-ISA β -blockers are the drugs of choice post-MI; ACEIs are also indicated post-MI in patients with systolic dysfunction
LVD – Diastolic	β -blocker, diuretic	verapamil, diltiazem	ACEI, α -blocker	Diuretics are first-line agents if symptoms of volume overload exist
LVD – Systolic	ACEI^d, diuretic^d	angiotensin II antagonist, hydralazine/nitrates	amlodipine, felodipine	ACEIs are preferred for their potential improvement in morbidity and mortality in this patient population; diuretics should be used if symptoms of volume overload exist; angiotensin II antagonists may be used where an ACEI is not tolerated; other selected agents may be used in conjunction with an ACEI in stable CHF patients; β -blockers ^d and CCBs should be used with caution
CKI (eGFR < 25ml/min or S_{cr} >2.5 mg/dL)	furosemide, ACEI	β -blocker, CCB, α -blocker, indapamide, metolazone	clonidine, minoxidil, hydralazine	Potassium (K ⁺)-sparing diuretics, K ⁺ supplements, and/or ACEI may cause \uparrow K ⁺ ; use ACEI with caution in patients S _{cr} >3.0 mg/dL; metoprolol is the preferred β -blocker due to hepatic excretion
Depression	thiazide diuretic	ACEI, CCB, α -blocker		Clonidine, reserpine, methyl dopa, β -blockers may exacerbate depression
DM	ACEI^e (types 1 & 2 DM with proteinuria)	<i>thiazide diuretic (low dose), CCB, β-blocker, α-blocker</i>	angiotensin II antagonist	High-dose thiazide diuretics and β -blockers may worsen glucose control; β -blockers may mask hypoglycemia; use of DHP SR in patients with HTN and type 2 DM remains controversial
Elderly (age >65 yrs)	thiazide diuretic	β -blocker, CCB, ACEI	α -blocker	Use caution with α -blockers in elderly due to first-dose syncope or dizziness
Gout	β -blocker	ACEI, CCB, thiazide diuretic (low dose)	α -blocker	Diuretic-induced hyperuricemia does not require treatment in the absence of gout or kidney stones
Dyslipidemia	thiazide diuretic (low dose), β -blocker	ACEI, CCB, α -blocker		Thiazide diuretics may \uparrow TC and \uparrow TG and non-ISA β -blockers may \downarrow HDL and \uparrow TG, although these effects may be transient
Isolated systolic hypertension	thiazide diuretic	DHP SR, β -blocker, ACEI	α -blocker	The use of DHP SR as first-line therapy remains controversial, although studies are available to indicate benefit
Left ventricular hypertrophy	ACEI, thiazide diuretic, β -blocker	CCB	α -blocker, clonidine	Direct-acting vasodilators do not reduce left ventricular hypertrophy
Peripheral vascular disease	thiazide diuretic, ACEI	CCB, β -blocker	α -blocker	Nonselective β -blockers without α -blockade may worsen resting ischemia or severe claudication symptoms
Pilots	thiazide diuretic, lisinopril			
Pregnancy (chronic HTN)	methyl dopa	labetalol	hydralazine (generally used for preeclampsia)	Except for ACEI and angiotensin II antagonists that are contraindicated during pregnancy, any antihypertensive drug may be continued if taken prior to pregnancy; β -blockers may cause growth retardation in 1st trimester

^aAdapted from JNC VI; **Bold**=compelling indication per outcome data (unless contraindicated); *Italics*=may have favorable effect on comorbid conditions

^bACEI=angiotensin-converting enzyme inhibitor; BUN=blood urea nitrogen; CCB=calcium channel blocker; DHP SR=long-acting dihydropyridine; COPD=chronic obstructive pulmonary disease; BPH=benign prostatic hyperplasia; ISA=intrinsic sympathomimetic activity; MI=myocardial infarction; LVD=left ventricular dysfunction; CHF=chronic heart failure; CKI=chronic kidney insufficiency; DM=diabetes mellitus; TC=total cholesterol; TG=triglyceride; HDL=high-density-lipoprotein cholesterol

^cGenerally recommended for use as adjunct therapy to other antihypertensive agents

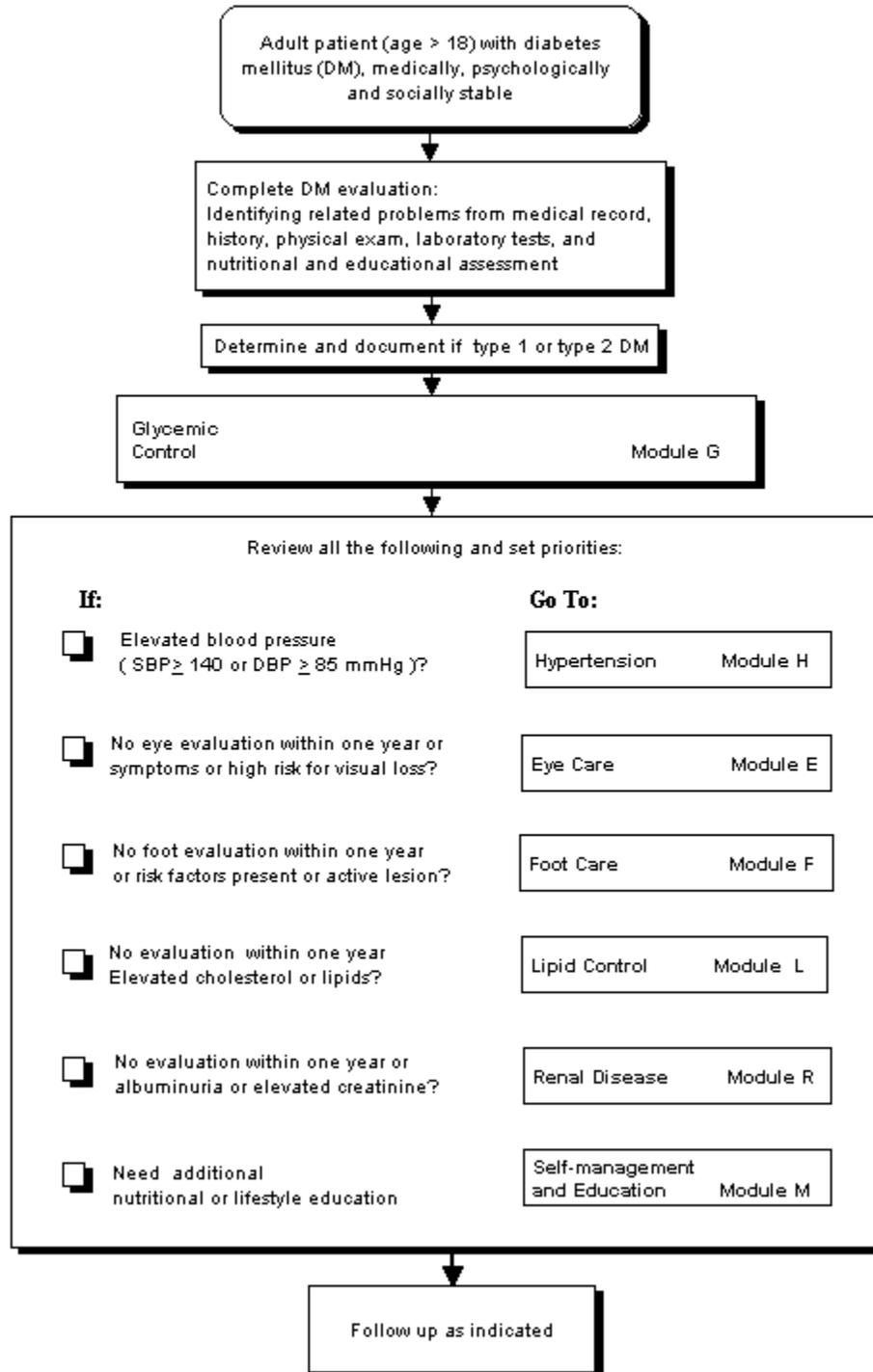
^dThere is compelling evidence to use β -blockers as adjunct therapy in patients with NYHA II to III CHF who are stable on an ACEI with or without a diuretic; refer to PBM-MAP The Pharmacologic Management of Chronic Heart Failure at www.vapbm.org or <http://vaww.pbm.med.va.gov>

^eCompelling indication in type 1 DM with proteinuria; preferred agent in types 1 and 2 DM with proteinuria

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APPENDIX 7

MANAGEMENT OF DIABETES MELLITUS
Primary Care Core Algorithm



CLASSIFICATION OF BLOOD PRESSURE IN DM (a)

	Systolic	and	Diastolic
Optimal	< 120 mm Hg		<80 mm Hg
Normal	< 130 mm Hg		< 85 mm Hg
High-normal	130-139 mm Hg	or	85-89 mm Hg
Hypertension	> 140 mm Hg	or	> 90 mm Hg

Blood pressure goal should be less than <140/85, with lower target levels individualized .

TARGET VALUE FOR HEMOGLOBIN A1c (HbA_{1c})

Major Co-Morbidity or Advanced Physiologic Age	Risk factor		
	Microvascular Disease		
	Absent or Mild ¹	Moderate ²	Advanced ³
Absence ⁴	< 7% (<1% above upper normal range)	< 8% (<2% above upper normal range)	< 9% (<3% above upper normal range)
Present ⁵	< 8% (<2% above upper normal range)	< 8% (<2% above upper normal range)	< 9% (<3% above upper normal range)
Marked ⁶	< 9% (<3% above upper normal range)	< 9% (<3% above upper normal range)	< 9% (<3% above upper normal range)

Major co-morbidity includes, but is not limited to, any or several of the following conditions: cardiovascular disease, chronic obstructive pulmonary disease, chronic liver disease, stroke, malignancy, etc.

¹ Mild microvascular disease is defined by early background retinopathy, and/or microalbuminuria and/or mild neuropathy

² Moderate microvascular disease is defined by pre-proliferative retinopathy, macroalbuminuria and/or demonstrable peripheral neuropathy (sensory loss)

³ Advanced microvascular disease is defined by severe non-proliferative retinopathy and/or kidney insufficiency (serum creatinine > 2.0 mg/dl) and/or insensate extremities or severe autonomic neuropathy (gastroparesis, impaired sweating, orthostatic hypotension, etc.)

⁴ Surrogate for > 15 years of life expectancy

⁵ Moderate degree of major co-morbid condition (surrogate for 5-15 years of life expectancy)

⁶ Severe degree or end-stage major co-morbid condition (surrogate for <5 years of life expectancy)

Every person with diabetes must have an annual documented foot risk assessment

Visual inspection at routine primary care visit for high-risk patient

RECOMMENDED TREATMENT OPTIONS FOR TYPE 2 DM

Therapy	Drugs	Expected reduction in HbA _{1c} <i>Over a 2 to 3 month period of follow-up</i>
Lifestyle modification, diet and exercise	None	
Lifestyle modification, diet and exercise Monotherapy with oral agent	Sulfonylurea or biguanide	1-2 percent
Lifestyle modification diet and exercise Combination (add a second oral agent)	Sulfonylurea + biguanide	1-2 percent
	Sulfonylurea or biguanide + alpha-glucosidase inhibitor	0.5 to 1 percent
	Sulfonylurea or biguanide + thiazolidenedione	0.7 to 1.75 percent
	Biguanide + repaglinide	0.1 to .3 percent
Insulin with oral agent	Biguanide + insulin Thiazolidenedione + insulin Sulfonylurea + insulin	
Insulin	Insulin alone	

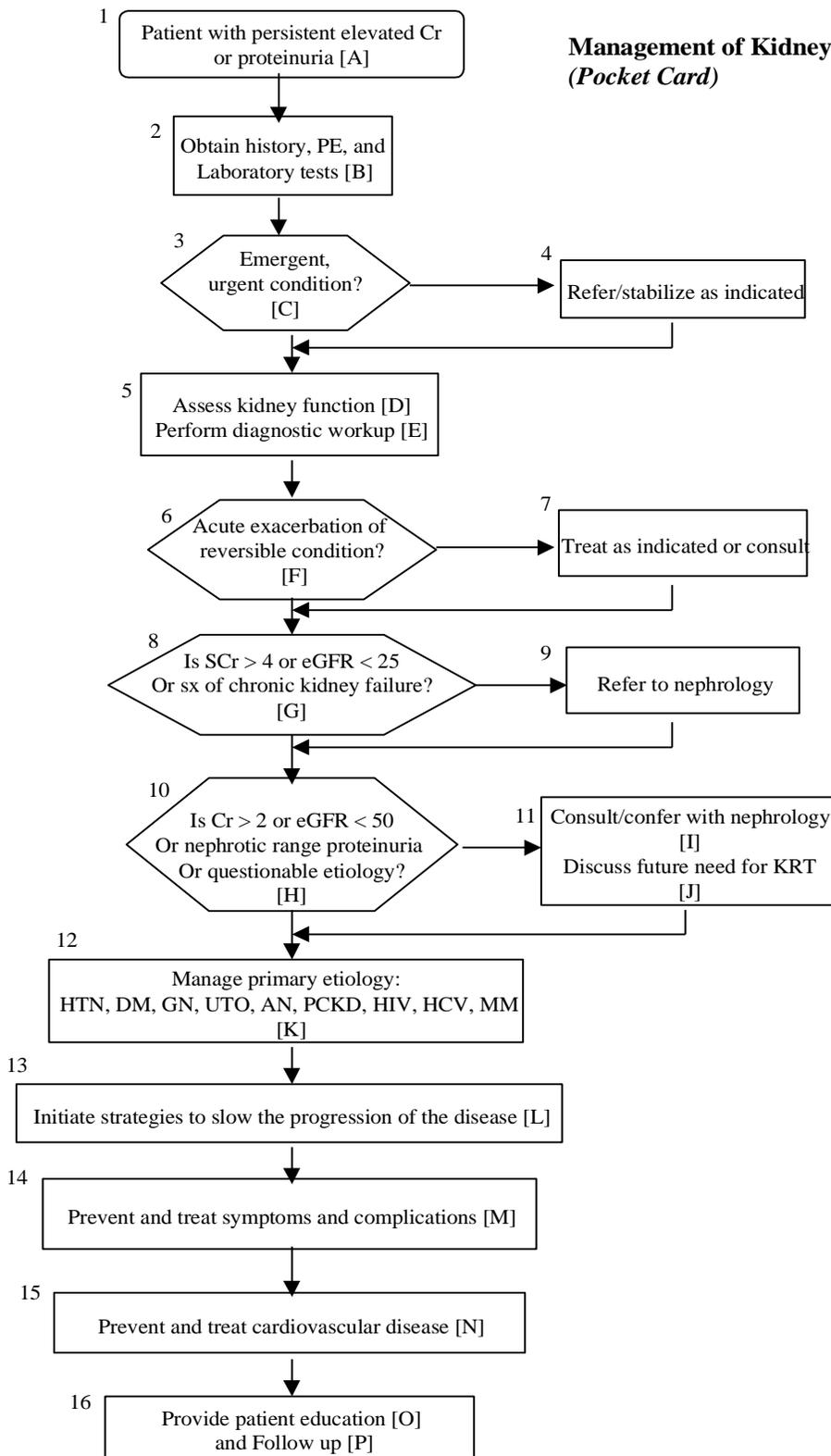
- Carefully selected individuals may benefit from three-drug oral hypoglycemic therapy. In general, such patients may benefit from referral to a diabetes care team.

A. <u>ORAL</u>		B. <u>DOSING</u>	C. <u>COMMENTS</u>
<u>HYPOGLYCEMIC</u>			
D. <u>Sulfonylureas</u>			
1 st generation			
tolazamide	Initial Maintenance Maximum	100-250mg once daily 250-500mg once daily 1000mg/d in 2 divided doses	
tolbutamide	Initial Maintenance Maximum	1000-2000mg in 1 or 2 divided doses 250-3000mg in 1 or 2 divided doses 3000mg in 1 or 2 divided doses	
2 nd generation			
glyburide	Initial Maintenance Maximum	1.25-5mg once daily 1.25-20mg in 1 or 2 divided doses 20mg in 1 or 2 divided doses	Administer once daily doses with breakfast or first main meal
glyburide micronized	Initial Maintenance Maximum	0.75-3mg once daily 0.75-12mg in 1 or 2 divided doses 12mg in 1 or 2 divided doses	Administer once daily doses with breakfast or first main meal
glipizide	<i>Initial</i> Maintenance Maximum	<i>2.5-5mg once daily</i> 5-20mg once daily 40mg in 2 divided doses	Administer once daily doses with breakfast or first main meal Doses greater than 15mg/day should be divided and given twice daily
glipizide extended release	<i>Initial</i> <i>Maintenance</i> Maximum	<i>5mg once daily</i> <i>5-10mg once daily</i> 20mg once daily	Administer with breakfast
glimiperide	Initial Maintenance Maximum	1-2 mg once daily 1-4 mg once daily 8mg once daily	Administer with breakfast or first main meal
Biguanides			
metformin	Initial Maintenance Maximum	500mg bid or 850mg q am 850mg bid 2550mg in 3 divided doses	Administer with meals
E. <u>Alpha-glucosidase inhibitors</u>			
F. <u>acarbose</u>	Initial Maintenance Maximum	25mg tid 50mg tid 100 mg tid; 50mg tid (≤ 60 kg)	Administer with first bite of each main meal
G. <u>miglitol</u>	Initial Maintenance Maximum	25mg tid 50mg tid 100 mg tid	Administer with first bite of each main meal
H. <u>Thiazolidinediones</u>			
I. <u>troglitazone</u>	Initial Maintenance Maximum	200mg qd 400mg qd 600mg qd	Administer with meals
J. <u>rosiglitazone</u>	Initial Maintenance Maximum	4mg qd or 2mg bid 8mg qd or 4mg bid	May be given without regard to meals
K. <u>pioglitazone</u>	Initial Maintenance Maximum	15 or 30mg qd 30mg qd 45mg qd	May be given without regard to meals 45mg dose studied only as monotherapy
L. <u>Meglitinides</u>			
M. <u>repaglinide</u>	Initial Maintenance Maximum	0.5mg tid (for patients who are hypoglycemic agent naïve or have HbA1c <8%). 1-2 tid mg (for patients previously treated with hypoglycemics or have HbA1c >8%) 0.5-4mg tid 16mg/day	Administer within 15-30 minutes of each meal

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APPENDIX 8

**Management of Kidney Failure in Primary Care
(Pocket Card)**



SPECIALIZED LABORATORY STUDIES FOR THE DIAGNOSIS OF KIDNEY DISEASE	
Laboratory Test	Significance
Serum Complement Levels (C3,C4)	May be decreased in: Post-streptococcal glomerulonephritis Endocarditis-associated glomerulonephritis Immune-complex glomerulonephritis Membranoproliferative glomerulonephritis Lupus nephritis Cryoglobulinemia Atheroembolic disease
ANA	Positive in: Lupus nephritis
Anti-neutrophil cytoplasmic antibody (ANCA)	Positive in: Wegener's granulomatosis (C-ANCA) Microscopic polyangiitis (P-ANCA) Pauci-immune RPGN (P-ANCA)
Anti-glomerular basement membrane antibodies(anti-GBM)	Positive in: Goodpasture's syndrome Anti-GBM associated RPGN
Serum protein electrophoresis (SPEP) Urine protein electrophoresis (UPEP)	Positive for monoclonal antibody in: Multiple myeloma Amyloid Light-chain deposition disease
Cryoglobulins	Positive in: Cryoglobulinemia
Hepatitis B surface antigen	Associated with: Membranous nephropathy Polyarteritis nodosa Membranoproliferative nephritis
Hepatitis C serologies	Associated with: Mixed cryoglobulinemia Membranoproliferative glomerulonephritis Membranous nephropathy
HIV serologies	Associated with: Focal and segmental glomerulosclerosis(FSGS)
Eosinophiluria	Associated with: Acute interstitial nephritis Atheroembolic disease May be positive in any condition with eosinophilia or pyuria

KIDNEY IMAGING STUDIES	
Imaging study	Significance
Kidney ultrasound	Diagnosis of: Obstructive kidney disease Polycystic kidney disease Assessment of kidney size: Enlarged in diabetic nephropathy, amyloid Small in chronic kidney disease Asymmetric in renovascular disease
Kidney doppler	Diagnosis of: Renovascular disease Renal vein thrombosis
Radioisotope kidney scan	Diagnosis of: Renovascular disease Obstructive uropathy Assessment of split kidney function
CT scan	Assessment of: Kidney masses Atypical kidney cysts
Magnetic resonance angiography	Diagnosis of: Renovascular disease
Kidney angiography	Diagnosis of: Renovascular disease (gold standard) Renal artery thrombosis/thromboembolism Polyarteritis nodosa
Retrograde ureterogram	Diagnosis of: Upper-tract obstruction
Intravenous pyelogram	Not indicated in kidney insufficiency

Parameter	Abnormality	Issues	Treatment
Albumin	< 3.5 g/dL	Associated with increased mortality. General causes of hypoalbuminemia include abnormal metabolism, chronic inflammation, liver disease. Specific causes that could be addressed are: Reduced intake Nephrotic syndrome Acidosis Poorly controlled diabetes	Nutritional assessment and supplementation Assess urinary protein, refer if worse Assess and treat acidosis Maximize diabetic control
Hct	Hct < 33% Hgb <11g/dL (Premenopausal female) Hct < 37% Hgb <12g/dL (Male & post-menopausal female)	Usual causes of anemia must be excluded before attributing to kidney disease Common causes in chronic kidney insufficiency: Inadequate erythropoiesis Reduced RBC half-life Coagulopathy	Erythropoietin levels are not helpful for diagnosis of suspected anemia of kidney disease Initiate oral Fe treatment if the transferrin saturation is < 20% and/or the ferritin is < 100 ng/ml If the patient is symptomatic, or the HCT < 30% and /or Hgb is < 10 despite iron therapy, refer to nephrology for consideration of erythropoietin therapy
HCO ₃	< 20 mEq/L	Other causes of acidosis must be considered prior to ascribing to kidney disease, especially if the HCO ₃ is < 15 mEq/L Common in CKI. Kidney causes include: Impaired kidney acidification Accumulation of organic acids	NaHCO ₃ tablets when the serum bicarbonate falls below 20 mEq/L Usual starting dose: 0.5 mEq/Kg/day in divided doses. One 650mg NaHCO ₃ tablet contains 7.7 mEq Na/7.7 mEq HCO ₃

MEDICATIONS IN PATIENTS WITH KIDNEY DISEASE

DRUG	COMMENTS
Antihypertensives	
Diuretics	Loop diuretics preferred because of superior efficacy in low GFR states. Higher doses or combination (e.g. furosemide + metolazone) may be required to obtain clinical response. Spironolactone and other K ⁺ sparing diuretics should be used with caution to avoid hyperkalemia.
ACEI/ARB	Beneficial effects in patients with diabetic nephropathy, heart failure, and some kidney diseases. May decrease GFR in some patients with kidney insufficiency or kidney artery stenosis. Serum k ⁺ should be monitored.
Beta Blocker	Metoprolol is the preferred β-blocker due to hepatic excretion.
Calcium Antagonists	Generally safe to use in patients with kidney disease.
Alpha Blockers	Beneficial in patients with prostatic hypertrophy.
Clonidine	Generally safe to use in patients with kidney disease.
Vasodilators	Generally safe to use in patients with kidney disease, although may cause sodium retention. Not usual first line therapy, although hydralazine is useful substitute for patients that do not tolerate ACEI/ARB
Antibiotics	Dosage adjustments frequently required in kidney failure. Acyclovir, other antivirals, and sulfa drugs may cause crystaluria. Acyclovir/gancyclovir dose must be decreased to avoid encephalopathy. Trimethoprim can cause hyperkalemia.
NSAIDS	Use with caution in patients with kidney disease. Frequent cause of acute kidney failure. COX 2 agents are not kidney protective. Other side effects include worsening of hypertension, hyperkalemia, and sodium retention.
Lipid lowering agents	No dosage changes generally required in patients with kidney disease. Maintain usual monitoring of CPK and liver function tests.
Hypoglycemic Agents	
Insulin	Half life prolonged in patients with kidney disease and dosage of insulin must be decreased accordingly.
Oral agents	Biguanides (e.g. metformin) contraindicated in patients with decreased GFR. Kidney insufficiency prolongs ½ life of many agents, requiring dosage adjustment to avoid hypoglycemia.

DRUG	COMMENTS
Cardiac glycosides	Half life prolonged with kidney insufficiency, and dosage must be decreased. For example, typical dosage of digoxin in end stage kidney disease is 0.125 mg 2 or 3 times per week.
Gout therapy	Allopurinol dosage should be decreased in patients with kidney insufficiency. Allopurinol may cause interstitial nephritis and should be stopped if kidney function deteriorates acutely. Colchicine should be used with caution in patients with kidney disease to avoid neutropenia and GI side effects.
Anti-epileptics	Dosage adjustments often required with decreased GFR.
Over Counter Meds	
Antacids	Avoid magnesium or aluminum containing antacids. In general, calcium carbonate or acetate is safe in kidney failure.
Salt substitutes	Often contain potassium and may cause hyperkalemia.
Decongestants/antihistamines	May be associated with worsening hypertension, and urinary retention.
Herbal remedies	Effects on kidney function and other organs unknown. Ephedrine containing products worsen hypertension, and some weight loss therapies can cause volume depletion.
Vitamins	Multivitamins and folate generally beneficial in patients with kidney disease. Vitamin A and D usage should be monitored to avoid toxicity and hypercalcemia.
Alkalinizing agents	Sodium bicarbonate is used to treat chronic acidosis of kidney disease, and is preferred to Shohl's solution. Both agents contain sodium and volume status should be monitored. Avoid aluminum containing antacids when using Shohl's solution.
Phosphate binding agents	Calcium carbonate/acetate preferred. New non-calcium containing agents are becoming available but are expensive and generally not more efficacious than calcium carbonate, but may be useful in special situations.
Anemia therapy	Anemia management module of this guideline should be referenced.

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VHA/DoD CLINICAL PRACTICE GUIDELINE FOR THE
MANAGEMENT OF **CHRONIC KIDNEY DISEASE AND**
PRE-ESKD IN THE PRIMARY CARE SETTING

ACRONYM LIST

MANAGEMENT OF CHRONIC KIDNEY DISEASE AND PRE-ESKD IN THE PRIMARY CARE SETTING

Acronym List

ACEI	Angiotensin Converting Enzyme Inhibitor
AN	Analgesic Nephropathy
ANA	Antinuclear Antibody
ANCA	Anti-neutrophil Cytoplasmic Antibody
ARB	Angiotensin Receptor Blocker
ASO	Antistreptolysin O Titer
ATN	Acute Tubular Necrosis
BUN	Blood Urea Nitrogen
C3, C4	Serum Complement Levels
Ca	Calcium
CKF	Chronic Kidney Failure
CKI	Chronic Kidney Insufficiency
Cl	Chloride
CO ₂	Carbon Dioxide
Cr	Creatinine
CRP	C-reactive Protein
DM	Diabetes Mellitus
eGFR	Estimated Glomerular Filtration Rate
EPO	erythropoietin
ESKD	End Stage Kidney Disease
ESR	Sedimentation Rate
FGS	Focal and Segmental Glomerulonephritis
GBM	Glomerular Basement Membrane
GFR	Glomerular Filtration Rate
GN	Glomerulonephritis
HAN	Hepatitis-associated neuropathy
HCV	Hepatitis C Virus
HD	Hemodialysis
HIV-AN	HIV-Associated Nephropathy
HTN	Hypertension
HUS	Hemolytic Uremic Syndrome
IEP	Immuno-Electrophoresis
K	Potassium
KCl	Potassium chloride
KRT	Kidney Replacement Therapy
MM	Multiple Myeloma
MPGN	Membrane Proliferative Glomerulonephritis
Na	Sodium
NLM	National Library of Medicine
nPNA	Normalized Protein Nitrogen Appearance Rate
NSAIDs	Non-steroidal Antiinflammatory
PCKD	Polycystic Kidney Disease
PD	Peritoneal Dialysis
PTFE	Polytetrafluoroethylene
PTH	Parathyroid hormone
QE	Quality of evidence
RF	Rheumatoid Factor
RPGN	Rapidly Progressive Glomerulonephritis
RPR	Rapid Plasma Reagin Test

**MANAGEMENT OF CHRONIC KIDNEY DISEASE AND PRE-ESKD
IN THE PRIMARY CARE SETTING**

**Acronym List
(continued)**

RVD	Renovascular Disease
SCr	Serum Creatinine
SPEP	Serum Protein Electrophoresis
SR	Strength of Recommendation
TTP	Thrombotic Thrombocytopenic Purpura
UPEP	Urine Protein Electrophoresis
USPSTF	U.S. Preventive Services Task Force
UTI	Urinary Tract Infection
UTO	Urinary Tract Obstruction
VHA	Veterans Health Administration

VHA/DoD CLINICAL PRACTICE GUIDELINE FOR THE
MANAGEMENT OF **CHRONIC KIDNEY DISEASE AND**
PRE-ESKD IN THE PRIMARY CARE SETTING

INTRODUCTION

MANAGEMENT OF CHRONIC KIDNEY DISEASE AND PRE-ESKD IN THE PRIMARY CARE SETTING

Introduction

Kidney failure is a significant concern in the Veterans Health Administration (VHA) population. In the past decade, patients starting dialysis in this country have become older (to an average age of 61 years) and more likely to have comorbidities. Dialysis incidence rates have doubled and transplants have become less available as a percent of total patients. Pre-end stage kidney disease (ESKD) care can have an impact on the management of the disease and its rate of progression. It can also influence the choice of kidney replacement therapy (KRT) and the decision about vascular access for patients starting hemodialysis. Between 1996-1998, 29% of kidney-related hospitalizations were for vascular-access related procedures (Pereira, 1998). This suggests that optimal management of pre-ESKD care can benefit both the patient and the health care delivery system.

There are accepted strategies for slowing the progression of chronic kidney disease, for managing the primary etiology, for preventing and treating symptoms, and for assisting patients to become effective participants in their care. The goal of this guideline is to present these strategies in an evidence-based format that will foster the delivery of optimal care.

Guideline Development Process

The current guideline for the management of kidney failure represents hundreds of hours of diligent effort on the part of participants from the VHA, DoD, academia, and a team of private guideline facilitators. An experienced moderator facilitated the panel that included internists, family practitioners, nephrologists, nurses, pharmacists, and policy-makers. The process is evidence-based whenever possible. Where evidence is ambiguous or conflicting, or where scientific data are lacking, the clinical experience of the expert panel was used to guide the development of consensus-based recommendations.

The goal in developing this guideline was to incorporate information from several existing, national recommendations into a format that would maximally facilitate clinical decision-making (Woolf, 1992). This effort drew heavily from the following sources:

- Eknoyan, G. & Levin, N. (2001) NKF-DOQI clinical practice guidelines: Update 2000. The National Kidney Foundation-Dialysis Outcomes Quality Initiative. *Am J Kidney Dis*, 37(1 Suppl 1), S5-S6.
- The U.S. Preventive Services Task Force Guide to Clinical Preventive Services. Second Edition 1996:15-38.
- Pharmacy Benefits Management—Medical Advisory Panel. The pharmacologic management of hyperlipidemia. VHA PBM-SHG Publication. Hines, IL: Pharmacy Benefits Management Strategic Health Group, Veterans Health Administration, Department of Veterans Affairs, 1999.

We are confident that the current guideline represents a significant step forward for primary health care in the VHA/DoD. However, it is only the first step in the mission to improve the care of those with kidney failure. In the future, the challenge will be in:

- Guideline implementation
- Guideline promotion
- Development of teaching tools for graduate and continuing medical education
- Development of automation tools that include:
 - Provider specific report cards
 - Performance monitors that assist the practitioner/facility in outcome tracking based on guideline use.

The guideline is designed to be adapted to an individual facility's needs and resources. It will also be updated periodically or when relevant research results become available. The guideline should be used as a starting point for

innovative plans that improve collaborative effort and focus on key aspects of care. The system-wide goal is to improve local management of patients with kidney failure and thereby improve patient outcomes.

The clinical practice guideline is presented in an algorithmic format. There are indications that this format improves data collection and clinical decision-making and helps to change patterns of resource use. A clinical algorithm is a set of rules for solving a clinical problem in a finite number of steps. It allows the practitioner to follow a linear approach to the recognition and treatment of kidney failure. It is recognized, however, that clinical practice often requires a nonlinear approach, and must always reflect the unique clinical issues in an individual patient-provider situation. The use of guidelines must always be considered as a recommendation within the context of a provider's clinical judgment in the care for an individual patient.

A clinical algorithm diagrams a guideline into a step-by-step decision tree. The steps in this tree are represented as a sequence of actions (rectangle "do boxes") and questions (hexagonal "decision boxes"). A letter within a box of an algorithm refers the reader to the corresponding annotation. The annotations elaborate on the recommendations and statements that are found within each box of the algorithm. These annotations include a reference, when required, and evidence grading for each recommendation. The strength of the recommendation (SR) and the quality of the evidence (QE) are both noted. The reference list at the end of each annotation includes all the sources used—directly or indirectly—in the development of the annotation text. A complete bibliography is provided at the end of the document.

Literature

The literature supporting the decision points and directives in this guideline is referenced throughout the document. The working group leaders were solicited for input on focal issues prior to a review of the literature.

A search was carried out using the National Library of Medicine's (NLM) MEDLINE database. The term "kidney failure" was searched along with the following terms:

- Epidemiology
- Screening
- Diagnosis
- Primary Care
- Protocols
- Therapy
- Patient Education
- Economics

Forty articles were identified for inclusion in a table of information that was provided to each expert participant. The table of information contained:

- Title
- Author(s)
- Author(s) affiliation
- Publication type
- Abstract
- Source
- Relevance

Copies of these tables were made available to all participants. Copies of specific articles were provided on an as needed basis.

The working group reviewed articles for relevance and graded the evidence using the following rating scheme, published by the U.S. Preventive Services Task Force (U.S. PSTF, 1996).

The U.S. Preventive Services rating scheme:

Strength of Recommendation (SR)

A	There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination.
B	There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination.
C	There is insufficient evidence to recommend for or against the inclusion of the condition in a periodic health exam, but recommendations may be made on other grounds.
D	There is fair evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.
E	There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.

Quality of Evidence (QE)

I	Evidence obtained from at least one properly randomized controlled trial.
II-1	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence obtained from well-designed cohort or case-control analytical studies, preferably from more than one center or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

The QE rating is based on the quality, consistency, reproducibility, and relevance of the studies. Information about harmful effects must also be presented. The SR rating is influenced primarily by the science. Other factors that are taken into consideration when making an SR determination are:

- The burden of suffering
- Cost issues
- Policy concerns.

For many recommendations, there is insufficient evidence to determine whether or not routine intervention will improve clinical outcomes. Lack of evidence of effectiveness does not mean there is evidence of ineffectiveness. Rather, lack of evidence (SR = C) means:

- Insufficient statistical power or
- Unrepresentative populations or
- Lack of clinically important endpoints or
- Design flaws (USPSTF, 1996).

The experts themselves, after an orientation and tutorial on the evidence grading process, formulated QE and SR ratings. Each reference was appraised for scientific merit, clinical relevance, and applicability to the populations served by the Federal health care system. Recommendations were based on consensus of expert opinions and clinical experience only when scientific evidence was unavailable.

The assembled experts were an invaluable source of additional information and suggested numerous references. These were distributed to participants on an as needed basis. It must be noted that this document does not, however, include reference to any publications dated after December 1999. More recent information will be included in future guideline updates.

Performance Measurement

The inability of consumers and health care purchasers to determine if medical care is appropriate and effective has given rise to the concept that the health care system should be held accountable for what is done and the outcomes achieved. This principle of accountability has resulted in the development of so-called “performance and outcome measures,” administered through “report card” systems. Measures must be seen as fair and reasonable, and able to be carried out in various practice settings.

Performance measures are indicators or tools to assess the level of care provided to populations of patients. The measures are constructed to make the best use of the evidence available for assessing care or outcomes in systems where patient characteristics (e.g. co-morbidity) and compliance cannot be easily determined and taken into consideration (i.e. the measures are not case-mix adjusted).

The VHA instituted performance measures for implementation of clinical practice guidelines in FY 1998. These measures included screening for kidney abnormalities in diabetic patients. Along with the work on the current guideline itself, additional performance measures are being developed.

Overview of the Chronic Kidney Failure and Pre-ESKD Guideline

The Management of Chronic Kidney Failure and Pre-ESKD guideline is a single module that addresses all aspects of care for the patient with incipient kidney disease. The one-page algorithm is followed by detailed “Annotations” and “Discussion.”

This guideline also contains appendices that provide more information on the spectrum of treatment options, and give details on pharmacologic and other interventions.

- Appendix 1. Etiologic Evaluation
- Appendix 2. Specialized Studies for the Diagnosis of Kidney Disease
- Appendix 3. Metabolic and Hematologic Complications of Kidney Disease
- Appendix 4. Medications in Patients with Kidney Disease
- Appendix 5. Resources for Patient Education

The bibliography for the body of text is provided at the end of the document.

**MANAGEMENT OF CHRONIC KIDNEY DISEASE AND PRE-ESKD
IN THE PRIMARY CARE SETTING**

Bibliography for Introduction

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VHA/DoD CLINICAL PRACTICE GUIDELINE FOR THE
MANAGEMENT OF **CHRONIC KIDNEY DISEASE AND**
PRE-ESKD IN THE PRIMARY CARE SETTING

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