Chronic Kidney Disease Guideline Team

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Initial Release:
November, 2013
Interim/Minor Revision:
March, 2014
June, 2016

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Literature search service
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These guidelines should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific clinical procedure or treatment must be made by the physician in light of the circumstances presented by the patient.

Management of Chronic Kidney Disease

Patient population: Adults with chronic kidney disease (CKD).

Objectives:

1. Identify populations that may benefit from more systematic screening for CKD and provide an overview of methods for screening and diagnosis.
2. Outline treatment options for patients with CKD to decrease progression of renal deterioration and potentially decrease morbidity and mortality.
3. Highlight common co-morbid conditions such as cardiovascular disease and diabetes, emphasizing the importance of aggressive management of these conditions to potentially decrease morbidity and mortality among patients with CKD.

Key points

Background

- Despite increasing prevalence of CKD, it is often under-recognized and under-treated. *[A]**
- Evidence for screening and management of early stage CKD is limited due to absence of large randomized controlled trials.

Definition and Staging (Tables 1 and 2)

- Kidney damage for $\geq$ 3 months, defined by structural or functional abnormalities of the kidney, with or without decreased GFR

Diagnosis

- Screen patients with diabetes annually for microalbuminuria if not on an ACE inhibitor or ARB and for creatinine and estimated glomerular filtration rate *[IA]*. Consider screening for CKD among patients at increased risk, especially those with hypertension *[IA]* and patients aged > 55 years. *[IID]*
- Laboratory studies needed to diagnose and stage CKD include an assessment of glomerular filtration rate (GFR) (usually estimated by the MDRD equation) and urine studies for the presence or absence of albuminuria. *[IC]*
- Ultrasound imaging for structural kidney disease may also be helpful in certain populations. *[IID]*

Treatment

- Blockade of the renin angiotensin aldosterone system with either an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) is the cornerstone of treatment to prevent or decrease the rate of progression to end stage renal disease. *[IA]*
- Blood pressure control (< 140/90) reduces renal disease progression and cardiovascular morbidity and mortality. Current evidence does not support stricter blood pressure control targets for the majority of patients with CKD *[IA]*. CKD patients with albuminuria may benefit from tighter control with a target of < 130/80 *[IIA]*.
- Optimally manage comorbid diabetes and address cardiovascular risk factors to decrease risk for cardiovascular disease – the leading cause of mortality for patients with CKD. *[IA]* Statin or statin/ezetimibe therapy is recommended in all CKD patients age $\geq$ 50 years to decrease the risk of cardiovascular or atherosclerotic events. *[IA]*
- Monitor for other common complications of CKD including: anemia, electrolyte abnormalities, abnormal fluid balance, mineral bone disease, and malnutrition. *[ID]*
- Avoid nephrotoxic medications to prevent worsening renal function. *[ID]*

Monitoring and Follow Up

- The timing and frequency of CKD monitoring and follow up depends on disease severity and risk for progression; GFR and albuminuria should be assessed a minimum of once per year. [ID] (table 16)
- Refer CKD stage G4 or G5 (see Table 2) to nephrology for co-management and preparation for renal replacement therapy. Consider referral at earlier stage to assist with diagnosis of underlying cause and/or treatment of common complications of CKD. *[IC]*

*** Strength of recommendation:**
I= generally should be performed; II = may be reasonable to perform; III = generally should not be performed.

Levels of evidence for the most significant recommendations
A = randomized controlled trials; B=controlled trials, no randomization; C=observational studies; D=opinion of expert panel

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Table 1. Definition of CKD

Abnormalities of kidney structure or function (defined by markers of kidney injury or decreased GFR) present for > 3 months with implications for health. *(Either criterion is sufficient for diagnosis.)*

1. Markers of kidney damage (one or more):
   - Albuminuria (AER ≥ 30mg/24hrs; ACR ≥ 30mg/g)
   - Urine sediment abnormalities
   - Electrolyte and other abnormalities due to tubular disorders
   - Abnormalities detected by histology
   - Structural abnormalities detected by imaging
   - History of prior kidney transplantation
2. GFR < 60 mL/min/1.73m^2

* GFR = glomerular filtration rate; AER = albumin excretion rate; ACR = albumin-to-creatinine ratio

Modified from KDOQI Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease: (2013)

Table 2. Staging of CKD

CKD is classified by the CGA system:
Cause, GFR category, Albuminuria category

GFR Categories	GFR (ml/min/ 1.73 m^2)	Terms
G1	> 90	Normal or high
G2	60-89	Mildly decreased
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	< 15	Kidney failure

Albuminuria Categories	AER (mg/24hrs)	ACR (mg/g)	Terms
A1	< 30	< 30	Normal to mildly increased
A2	30-300	30-300	Moderately increased
A3	> 300	> 300	Severely increased

AER = albumin excretion rate
ACR = albumin-to-creatinine ratio

Table 3. Common Risk Factors for the Development of CKD

Diabetes
Hypertension
Age > 55 years
Family history of kidney disease
Obesity or metabolic syndrome

Table 4. Common Causes of Acute or Acute on Chronic Kidney Injury

Volume depletion
Acute urinary obstruction
Use of diuretics, ACE or ARB
Use of NSAID, iodinated contrast agents, or other nephrotoxic agents
Heart failure
Acute glomerulonephritis or acute intestinal nephritis
Liver failure
Malignancy (e.g., myeloma)

Table 5. Key Aspects of the Medical History in Evaluating Patients with CKD

Prior kidney disease or dialysis
Incidental albuminuria or hematuria (microscopic or gross) in the past
Urinary symptoms such as nocturia, frequency, polyuria, urgency, hesitancy; a history of foamy/frothy urine may indicate prior heavy proteinuria
History of nephrolithiasis
Family history of kidney disease
Diseases that share risk factors with CKD: DM, HTN, CAD, PAD, heart failure
Systemic diseases that might affect kidney (e.g., rheumatologic diseases, especially SLE, Sjogren's, Progressive Systemic Sclerosis)
History of use of medications that might affect renal function: OTC (especially NSAIDs and herbal medications) or prescription (e.g., lithium, calcineurin inhibitors)

Table 6. Commonly Used Equations to Estimate GFR (eGFR)

MDRD (Modification in Diet and Renal Disease Study) 4-variable equation

GFR (mL/min/1.73 m^2) = **186** x (SCr) $^{-1.154}$ x (Age) $^{-0.203}$ x (0.742 if female) x (1.210 if African-American)

CKD-EPI (Epidemiology Collaboration) equation

GFR = 141 X min(SCr/κ,1)$^{\alpha}$ X max(SCr/κ,1)$^{-1.209}$ X 0.993^{Age} X 1.018 [if female] X 1.159 [if black]

Patient weight is not required for eGFR using either equation. Results are normalized to 1.73m^2 body surface area - BSA (accepted average adult surface area). Equations tend to underestimate GFR if large body surface area (e.g., obese or large, muscular) patients and overestimate GFR in small body surface area patients. Both equations should be used with caution when assessing GFR in those with extremes of body habitus or muscle mass, during pregnancy, and in the elderly.

Online CKD EPI & MDRD GFR Calculator (with SI Units): http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm

Table 7. Common Agents for Renin Angiotensin Aldosterone Blockade

Generic (Brand) Name	Dosage Range for Normal Kidney Function	Dose Adjustments Based on GFR (mL/min) (Percentage of Usual Dosage)			Cost 30 days Generic Brand	Comments
		30-59	10-29	< 10		
Angiotensin Converting Enzyme Inhibitors (ACE-I)						
Benazepril (Lotensin)	10 - 40 mg/day (divided q12-24h)	75%	50%	25%	$3-6 $62	Can cause acute increase in SCr and/or potassium; continue medication if increase is < 30%; monitor renal function and potassium levels with initiation and with each dosage change, every 1-2 weeks until values return to baseline (usually within 4-6 weeks)
Enalapril (Vasotec)	5 - 40 mg/day (divided q12-24h)	50-100%	50%	25%	$4-6 $152-239	
Captopril (Capoten)	25 - 50 mg q8-12h	75%	50-75%	50%	$25-42 $41-106	
Ramipril (Altace)	2.5 - 20 mg/day (divided q12-24h)	50%	25-50%	25%	$8-17 $99-127	
Fosinopril (Monopril)	10 - 40 mg/day (divided q12-24h)	-	-	75-100%	$8 $33	
Lisinopril (Prinivil, Zestril)	10 - 40 mg q24h	50-75%	50%	25-50%	$5-7 $41-88	
Quinapril (Accupril)	10 - 80 mg/day (divided q12-24h)	50%	25-50%	25%	$9 all $80 all	
Trandolapril (Mavik)	1 - 4 mg/day (divided q12-24h)	-	50%	50%	$16 $57	
Moexipril (Univasc)	7.5 - 30 mg/day (divided q12-24h)	50%	50%	50%	$18-35 $84-89	
Perindopril (Aceon)	4 - 16 mg q24h	50%	Max dose of 2mg q48h	Max dose of 2mg q48h	$20-39 $80-192	
Angiotensin Receptor Blockers (ARBs)						
Losartan (Cozaar)	50 - 100 mg q24h	-	-	-	$6-8 $93-126	Can cause acute increase in SCr and/or potassium; continue medication if increase is < 30%; monitor renal function and potassium levels with initiation and with each dosage change, every 1-2 weeks until values return to baseline (usually within 4-6 weeks)
Irbesartan (Avapro)	150 - 300 mg q24h	-	-	-	$12-15 $92-111	
Candesartan (Atacand)	16 - 32 mg/day (divided q12-24h)	-	-	-	$84-104 $92-125	
Olmesartan (Benicar)	20 - 40 mg q24h	-	-	50%	n/a $115-160	
Valsartan (Diovan)	80 - 320 mg q24h	-	-	-	n/a $140-190	
Telmisartan (Micardis)	40 - 80 mg q24h	-	-	-	$119 all $159 all	
Aldosterone Antagonists						
Eplerenone (Inspira)	25 – 100 mg/day (divided 12-24h)	50%	Avoid	Avoid	$65 all $189 all	Contraindicated in patients with Scr ≥ 2 mg/dL (males) or ≥ 1.8 (females) due to increased risk of hyperkalemia; monitor potassium levels with initiation and with each dosage change; extend dosing interval or decrease dose by 50% if necessary
Spironolactone (Aldactone)	25 - 200 mg/day (divided q12-24h)	-	50%	Avoid	$6-35 $40-247	Monitor potassium levels with initiation and with each dosage change; extend dosing interval or decrease dose by 50% if necessary

Pricing information for brand drugs, Average Wholesale Price minus 10%. AWP from Red Book Online 02/2014. For generic drugs, Maximum Allowable Cost plus $3 from BCBS of Michigan MAC List, 02/2014.

Table 8. Other Drugs Commonly Used to Treat Hypertension

Generic (Brand) Name	Dosage Range for Normal Kidney Function	Dose Adjustments Based on GFR (mL/min) (Percentage of Usual Dosage)			Cost 30 days Generic Brand	Comments
		30-59	10-29	< 10		
Thiazide Diuretics						
Hydrochlorothiazide	12.5 - 50 mg q24h	-	-	Avoid	$4 n/a	Consider avoiding thiazide diuretics if GFR < 30 mL/min; potassium-sparing diuretics and aldosterone blockers can increase risk of hyperkalemia in CKD patients
Metolazone (Mykrox, Zaroxolyn)	Mykrox: 0.5 - 1 mg q24h; Zaroxolyn: 2.5 - 20 mg q24h	-	-	-	$33-48 $90 (for 2.5 mg Zaroxolyn)	
Chlorothiazide (Diuril)	0.5 - 1 g (divided q12-24h)	-	-	Avoid	$11-22 n/a	
Chlorthalidone (Thalitone)	15 - 50 mg q24h	-	-	Avoid	$21 n/a	
Potassium-sparing Diuretics						
Amiloride (Midamor)	5 mg q24h	50-100%	50%	Avoid	$13 n/a	
Other Diuretics						
Furosemide (Lasix)	20 - 600 mg q24h	-	-	-	$4-27 $14-230	
Torsemide (Demadex)	5 - 200 mg q24h	-	-	-	$11-31 $60-274	
Calcium Channel Blockers						
Amlodipine (Norvasc)	5 – 10 mg q24h	-	-	-	$5 $102-140	
Verapamil (Calan, Covera-HS, Isoptin SR, Verelan)	80 – 120 mg q8h	-	-	-	$18 all $167-226	
Felodipine (Plendil)	5 – 10 mg q24h	-	-	-	$20-29 n/a	
Diltiazem (Cardizem)	IR: 30 – 90 mg q6h CD: 180 – 360 mg q24h LA: 180 – 540 mg q24h	-	-	-	IR: $20-34 $80-147 CD: $20-32 $303 LA:$72-122 $130-221	
Nifedipine (Procardia, Adalat)	IR: 10 mg q8h XL: 30-120 mg q6h CC: 30-60 mg q24h	-	-	-	IR: $76 $136 XL: $59-84 $102-177 CC: $18-29 $44-77	
Beta Blockers						
Atenolol (Tenormin)	50 - 100 mg q24h	50-100%	50%	Max dose 25mg q24h	$4-5 $51-76	Atenolol is generally not recommended for BP control in CKD patients Atenolol, and nadolol are eliminated renally; others are metabolized hepatically and do not need any dose adjustments due to CKD (e.g., metoprolol , propranolol, labetalol);
Carvedilol (Coreg)	3.125 - 25 mg q12h	-	-	-	$10 $160	
Metoprolol tartrate (Lopressor)	100 - 450 mg/day (divided q12-24h)	-	-	-	$5-23 $24-96	
Propranolol (Inderal LA)	80 - 160 mg q24h	-	-	-	$30-48 $398-583	
Labetalol (Trandate)	100 - 400 mg q12h	-	-	-	$13-28 $20-68	
Bisoprolol (Zebeta)	5 - 20 mg q24h	75%	50-75%	50%	$14-31 $146	
Metoprolol succinate (Toprol XL)	25 - 400 mg q24h	-	-	-	$17-87 $39-93	
Nadolol (Corgard)	40 - 80 mg q24h	Extended dosing interval to q36h	Extended dosing interval to q48h	Extended dosing interval to q48-60h	$93-152 $127-175	

Pricing information for brand drugs, Average Wholesale Price minus 10%. AWP from Red Book Online 02/2014. For generic drugs, Maximum Allowable Cost plus $3 from BCBS of Michigan MAC List, 02/2014.

Table 9. Drugs Commonly Used to Treat Diabetes

Generic (Brand) Name	Dosage Range for Normal Kidney Function	Dose Adjustments Based on GFR (mL/min) (Percentage of Usual Dosage)			Cost 30 days Generic Brand	Comments
		30-59	10-29	< 10		
Biguanide						
Metformin (Glucophage)	500-1000 mg bid	50%	Avoid	Avoid	$10 $60-124	Contraindicated in patients with eGFR < 30 mL/min/1.73 m2 due to increased risk of lactic acidosis. Starting metformin in patients with eGFR between 30-45 mL/min/1.73 m2 is not recommended. Assess risk vs. benefit of continuing metformin if eGFR drops below 45 mL/min/1.73 m^2
Sulfonylureas (Second Generation)						
Glipizide (Glucotrol)	2.5-15 mg q24h	50-100%	50%	50%	$3-5 $25-78	Active metabolite can accumulate and cause prolonged hypoglycemia in patients with CKD
Glimepiride (Amaryl)	1-2 mg q24h	-	-	-	$4-6 $27-43	
Glyburide (Micronase)	1.25-20 mg q24h	0-50%	Avoid	Avoid	$7-27 $20-150	
Thiazolidinediones						
Pioglitazone (Actos)	15-45 mg q24h	-	-	-		Can cause dose-related edema. Contraindicated in patients with NYHA Class III and IV heart failure.
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors						
Sitagliptin (Januvia)	100 mg q24h	50 mg q24h (CrCl ≥ 30 to <50)	25 mg q24h	25 mg q24h	n/a $305	
Saxagliptin (Onglyza)	2.5-5 mg q24h	2.5mg q24h (GFR ≤ 50)	2.5mg q24h	2.5mg q24h	n/a $301	May increase risk for heart failure. Use with caution in patients with known risk factors for heart failure, including renal impairment.
Linagliptin (Tradjenta)	5 mg q24h	-	-	-		
Alogliptin (Nesina)	25 mg q24h	12.5 mg q24h	6.25 mg q24h	6.25 mg q24h		May increase risk for heart failure. Use with caution in patients with known risk factors for heart failure, including renal impairment.

Generic (Brand) Name	Dosage Range for Normal Kidney Function	Dose Adjustments Based on GFR (mL/min) (Percentage of Usual Dosage)			Cost 30 days Generic Brand	Comments
		30-59	10-29	< 10		
Incretin mimetics, injectable						
Exenatide (Byetta)	5 - 10 mcg bid	-	Avoid	Avoid	n/a $355	Post-marketing reports of acute renal failure and worsening of chronic renal failure. Use caution when initiating or escalating doses in patients with renal impairment. Monitor renal function closely in patients reporting adverse GI effects.
Exenatide Extended Release (Bydureon)	2 mcg once weekly	-	Avoid	Avoid		
Liraglutide (Victoza)	0.6-1.8 mg Q24h	-	-	-		
Dulaglutide (Trulicity)	0.75-1.5 mg once weekly	-	-	-		
Albiglutide (Tanzeum)	30-50 mg once weekly	-	-	-		

Pricing information for brand drugs, Average Wholesale Price minus 10%. AWP from Red Book Online 02/2014. For generic drugs, Maximum Allowable Cost plus $3 from BCBS of Michigan MAC List, 02/2014.

Table 10. Statin/Lipid Treatment in Patients with CKD

CKD Patient Population	Treatment
Age ≥ 50 years with eGFR < 60 ml/min/1.73 m2 and no previous kidney transplant (G3a-G5)	Statin or statin + ezetimibe [1]
Age ≥ 50 years with eGFR ≥ 60 ml/min/1.73 m2 (G1-G2)	Statin
Age 18-49 with eGFR ≥ 60 ml/min/1.73 m2 (G1-G2) and either: known coronary disease (myocardial infarction or coronary revascularization), diabetes mellitus, prior ischemic stroke, or estimated 10-year incidence of coronary death or non-fatal myocardial infarction > 10% [2]	Statin
Transplant recipient (adult any age)	Statin
Hypertriglyceridemia	Therapeutic lifestyle changes

Note: Adapted from the KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease, 2013.

[1] Option to add ezetemibe is based on the SHARP (Study of Heart and Renal Protection) trial.

[2] Calculators to estimate 10-year incidence of coronary death or non-fatal myocardial infarction include: Framingham risk score, Reynold's, SCORE, PROCAM, ASSIGN, or QRISK2.

Table 11. Drugs Commonly Used to Treat Dyslipidemia

Generic (Brand) Name	Dosage Range for Normal Kidney Function	Dose Adjustments Based on GFR (mL/min) (Percentage of Usual Dosage)			Cost [a] 30 days Generic Brand	Comments
		30-59	10-29	< 10		
Statins [b]						
Atorvastatin (Lipitor)	10 - 80 mg q 24h	-	-	-	$7 $151-216	
Rosuvastatin (Crestor)	5 - 40 mg q24h	-	Start at 5mg q24h; Max dose of 10mg q24h		n/a $123-185	Use with caution in Asian patients as drug levels can be two fold higher than usual.
Simvastatin (Zocor)	5 - 80 mg q24h [c]	-	-	Start at 5mg q24h	$4-5 $82-191	Myopathy risk highest with simvastatin 80mg. If need more than simvastatin 40 mg daily, switch to atorvastatin or rosuvastatin.
Pitavastatin (Livalo)	2 mg q24h (1 – 4 mg q24h)	Start at 1mg q24h Max dose of 2mg q24h	Start at 1mg q24h Max dose of 2mg q24h	Start at 1mg q24h Max dose of 2mg q24h	n/a $162	Contraindicated with cyclosporine.
Lovastatin (Mevacor)	20 - 80 mg q24h	-	50%	50%	$6 $85-306	Use doses over 20mg with caution in CKD stages G4 and G5.
Pravastatin (Pravachol)	10 - 80 mg q 24h	-	Start at 10mg q24h		$25 $60-173	
Fluvastatin (Lescol)	20 - 80 mg q24h	-	50%	50%	$95 $137	Use doses over 40mg with caution in CKD stages G4 and G5.
Nicotinic Acid (Niaspan)	500 - 2000 mg daily	-	50%	25-50%	$8-19 $144-248	
Absorption Inhibitors						
Bile Acid Resins						
Ezetimibe (Zetia)	10 mg daily	-	-	-	-- $177	May be used with other anti-hyperlipidemic drugs
Fibrates						
Gemfibrozil (Lopid)	600 mg bid	-	75-100%	50-100%	$14 $208	May increase SCr; consider alternate therapy if SCr > 2 mg/dL; more likely to cause rhabdomyolysis when used in conjunction with statins
Fenofibrates						
Fenofibrate (Various)	40 - 160 q24h	25%	25%	Avoid	n/a $47-67	Avoid use with statins due to increased risk of myopathy

[a] Pricing information for brand drugs, Average Wholesale Price minus 10%. AWP from Red Book Online 02/2014. For generic drugs, Maximum Allowable Cost plus $3 from BCBS of Michigan MAC List, 02/2014.

[b] The risk of myopathy is increased when statins are coadministered with medications that inhibit their metabolism (e.g., cytochrome P450 enzyme inhibitors) or with other medications that have been associated with myopathy (e.g., cyclosporine, danazol, niacin, fibrates). Adjust doses as needed, use statins cautiously with fibrates, and avoid coadministration with gemfibrozil if possible.

[c] Only patients who have been on simvastatin 80mg for at least 12 months without evidence of myopathy should continue to be treated at this dosage.

Table 12. KDIGO Recommended Statin Dosing in Adults with CKD

Statin	eGFR G1-G2	eGFR G3a-G5, including patients receiving dialysis or had a kidney transplant
Lovastatin	Any dose approved for general population	not done
Fluvastatin	Any dose approved for general population	80 [a]
Atorvastatin	Any dose approved for general population	20 [b]
Rosuvastatin	Any dose approved for general population [c]	10 [d]
Simvastatin/ezetimibe	Any dose approved for general population	10/10 [e]
Pravastatin	Any dose approved for general population	40
Simvastatin	Any dose approved for general population	40
Pitavastatin	Any dose approved for general population	2

Adapted from the KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease (2013).

All doses are mg/d. All statins may not be available in all countries. Lower doses than those used in major trials of statins in chronic kidney disease populations may be appropriate in Asian countries. Cyclosporine inhibits the metabolism of certain statins, resulting in higher blood levels.

[a] Data based on Assessment of Lescol in Renal Transplantation trial

[b] Data based on Die Deutsche Diabetes Dialyse Studie

[c] 40 mg of rosuvastatin daily is not recommended for use in patients with CKD G1-G2 who did not have transplants because it may increase the risk for adverse renal events.

[d] Data based on A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events

[e] Data based on the Study of Heart and Renal Protection trial.

Table 13. Select Drugs That Can Affect Serum Potassium Levels

Increase Potassium	Decrease Potassium
Aldosterone receptor antagonists	Acetazolamide
Angiotensin II receptor blockers	Antacids
Angiotensin-converting enzyme inhibitors	Corticosteroids
Beta-blockers	Fluconazole
Cyclosporine	Insulin
Heparin	Loop diuretics
Nonsteroidal anti-inflammatory drugs	Salicylates
Potassium-sparing diuretics	Stimulant laxatives (e.g. senna)
Sulfonamide antibiotics	Sodium polystyrene sulfonate
	Theophylline
	Thiazide diuretics

Table 14. Key Elements of Patient Education for CKD

Elements

- Ensure patient awareness of CKD diagnosis
- "Know your numbers"- make patients aware of their kidney function (eGFR and creatinine) and blood pressure goals
- Provide familiarity with the need for screening and treatment of comorbid conditions (e.g., diabetes, hypertension, CAD)
- Instruct patients to avoid potentially nephrotoxic OTC medications, especially NSAIDS, herbal medications, unsupervised use of vitamin and minerals or nutritional protein supplements
- Encourage patients to talk with their primary care physician, nephrologist or pharmacist before starting new medications to ensure safety and appropriate renal dosing
- Promote lifestyle modifications
    - Diet, with special attention to sodium, potassium and phosphorus intake
    - Regular exercise
    - Maintain a healthy body weight
    - Immunizations
    - Tobacco cessation

Resources

Patient education resources are available at the National Kidney Foundation Website (kidney.org/)
For links to recommended patient education materials, visit the University of Michigan Clinical Care Guidelines website

Table 15. Drug-Induced Nephrotoxicity: Prevention Strategies, Patient Risk Factors, and Associated Drugs

General Strategies to Prevent Drug-Induced Nephrotoxicity
Assess baseline renal function prior to initiating potentially nephrotoxic drugs
Adjust medication dosages based on renal function as needed
Avoid nephrotoxic drug combinations
Use non-nephrotoxic alternatives whenever possible
Correct risk factors for nephrotoxicity before initiating drug therapy whenever possible
Ensure adequate hydration before and during therapy with potential nephrotoxic drugs
Limit dose and duration of therapy when possible

Key Risk Factors Predisposing Patients to Drug-Induced Nephrotoxicity	
Age greater than 60 years	Multiple myeloma
Diabetes mellitus	Sepsis
Drug-drug interactions resulting in synergistic nephrotoxic effects	Underlying kidney dysfunction (e.g., eGFR < 60 mL/min, renal artery stenosis)
Exposure to multiple or high doses of nephrotoxins	Vascular disease
Heart failure	Volume depletion
History of kidney transplant	

Select Drugs Associated with Nephrotoxicity	
Allopurinol	Lithium
Aldosterone inhibitors	Loop diuretics
Angiotensin-converting enzyme inhibitors	Methamphetamines
Angiotensin II receptor blockers	Methotrexate
Calcium channel blockers	Nonsteroidal anti-inflammatory drugs
Cephalosporins	Oral sodium phosphate solution
Combined phenacetin, aspirin, and caffeine analgesics	Pamidronate
Cyclooxygenase-2 inhibitors	Penicillamine
Cyclosporine	Penicillins
Digoxin	Propylthiouracil
Direct renin inhibitors	Proton pump inhibitors
Fluoroquinolones	Iodinated contrast agents
Foscarnet	Rifampin
Gold	Sulfonamides
Hydralazine	Tacrolimus

Note: See Tables 18 and 19 for drugs, natural products, and herbs that may affect CKD patients.

Table 16. Frequency of Monitoring CKD Patients Based on GFR and Albuminuria

			Albuminuria		
			A1	**A2**	**A3**
			Normal to mildly increased	Moderately increased	Severely increased
			< 30 mg/g < 3 mg/mmol	30-300 mg/g 3-30 mg/mmol	> 300 mg/g > 30 mg/mml
GFR					
G1	Normal or high	≥ 90	1/yr if CKD	1/yr	q 6mo
G2	Mildly decreased	60-89	1/yr if CKD	1/yr	q 6mo
G3a	Mild to moderately decreased	45-69	1/yr	q 6mo	q 4mo
G3b	Moderately to severely decreased	30-44	q 6mo	q 4mo	q 4mo
G4	Severely decreased	15-29	q 3mo	q 4mo	q 3mo or less
G5	Kidney failure	< 15	q 3mo or less	q 3mo or less	q 3mo or less

Adapted from KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease, 2013.

Table 17. Risk factors for CKD Progression

Advanced level of GFR decline
Advanced degree of albuminuria
Advanced age
Male gender
Race and ethnicity (i.e., higher rates of progression in African Americans, Hispanics, Pacific Islanders and Native Americans versus non-Hispanic whites)
Poorly controlled hypertension
Hyperglycemia
Dyslipidemia
Smoking/tobacco use
History of cardiovascular disease
Ongoing exposure to nephrotoxic agents

Table 18. Indications for Referral of Patients with CKD to a Nephrologist

Patients with CKD of uncertain cause/etiology (e.g., need for renal biopsy)
Persistent or severe albuminuria (e.g., category A3)
Persistent hematuria (i.e. RBC > 20 per HPF or urinary red cell casts)
Rapid decline in GFR or new AKI
Refer all patients with stage G4 or G5 CKD to initiate discussion of potential renal replacement therapy
Consider referral at earlier stages to assist with management of CKD complications: - Refractory hypertension (e.g., 4 or more antihypertensive medications) - Persistent hyperkalemia - Anemia - Mineral bone disease - Fluid overload and/or malnutrition.

Table 19. Select Drugs and Natural Products That Can Increase or Decrease the Effect of Immunosuppression Medications (e.g., cyclosporine, tacrolimus, sirolimus) Prescribed for Kidney Transplant Patients*

Prescription Medications:		Natural Products:
Amiodarone ↑	Nifedipine ↑	Grapefruit juice ↑
Azole antifungals ↑	Orlistat ↓	St. John's wort ↓
Carbamazepine ↓	Probucol ↓	Red wine ↑
Carvedilol ↑	Protease inhibitors ↑	Berberine ↑
Colchicine ↑	Quinolones ↑	Chaparral ↑
Diltiazem ↑	Rifamycins ↓	European Barberry ↑
Hydantoins ↓	Serotonin reuptake inhibitors ↑	Tree Turmeric ↑
Lovastatin ↑	Sulfonamides ↓	Echinacea ↑↓
Macrolide antibiotics ↑	Terbinafine ↓	
Metoclopramide ↑	Verapamil ↑	
Nefazodone ↑		

* ↑ indicates that the agent generally increases the effect of immunosuppression medications; ↓ indicates a decreased effect

Table 20. Select Herbs That May Be Harmful to CKD Patients

Alfalfa	Coltsfoot	Noni juice
Aloe	Comfrey	Panax
Aristolochic acid	Dandelion	Pennyroyal
Artemisia absinthium (wormwood plant)	Ephedra (Ma Huang)	Periwinkle
Autumn crocus	Ginger	Pokeroot
Bayberry	Gingko	Rhubarb
Blue cohosh	Ginseng	Sassafras
Broom	Horse chestnut	Senna
Buckthorn	Horsetail	St. John's wort
Capsicum	Licorice	Tung shueh
Cascara	Lobelia	Vandelia cordifolia
Chaparral	Mandrake	Vervain
Chuifong tuokuwan (Black Pearl)	Mate	Yohimbe
	Nettle	

Clinical Problem and Management Issues

Chronic kidney disease (CKD) is an increasingly common clinical problem that raises a patient's risk for developing several life-threatening medical conditions, including end stage renal disease (ESRD) and cardiovascular disease (CVD). Appropriate treatment can delay or prevent these adverse outcomes. However, CKD is often not recognized by clinicians or patients and as a result is often not optimally treated.

Prevalence. The 1999-2004 National Health and Nutrition Examination Survey (NHANES) study estimated that 26 million people in the United States (13% of the adult population) have CKD. The number of people with CKD has significantly increased since 1994 when an estimated 20 million adults were affected.

Problems with care for CKD. Despite the increased prevalence of CKD, it remains under-recognized by both health care providers and patients, especially in its early stages when patients are largely asymptomatic.

A 2007 study assessing the prevalence of CKD found only 11.6% of men and 5.5% of women with moderate kidney disease were aware of their diagnosis. Even among patients with more severe kidney disease less than half (42%) of affected patients were aware of their disease. For comparison, similar studies have estimated that for other chronic illness, such as hypertension and diabetes, greater than 70% of affected patients are aware of their disease diagnosis.

This under-recognition of CKD likely results from several factors, including providers being uncertain of whom to screen and of how to screen. For many providers, both the "who and how" of screening for CKD is uncertain. Provider communication with patients regarding this diagnosis may be problematic and likely fails to convey implications for future health, morbidity and mortality.

The consequence of under-recognition of CKD by both clinicians and patients is that it is also under-treated. This is worrisome as the adverse outcomes of CKD, including kidney failure and cardiovascular diseases, can be prevented or delayed with treatment and risk factor modification in the earlier stages of disease.

Clinicians need to identify patients with CKD and manage them appropriately in order to alter disease progression.

Definition and Etiology

Definition. CKD is defined as abnormal kidney structure or function persisting greater than 3 months. This can be determined either by evidence of kidney damage (typically detected by presence of persistent albuminuria) or by decreased glomerular filtration rate (GFR). Other markers may include evidence of pathologic abnormality (e.g., detected by renal biopsy), structural abnormalities (e.g., abnormalities on imaging studies), or serum electrolyte abnormalities (e.g., renal tubular syndromes).

In 2002, the Kidney Disease Outcomes Quality Improvement Initiative (KDIGO) Work Group on CKD provided a comprehensive definition and staging system of CKD in an effort to provide a common language among providers, patients and researchers, and hopefully improve communication and care for this diagnosis. This staging system was recently revised and updated in 2013 and includes increased focus on the cause of kidney dysfunction and the presence of albuminuria (Table 2).

Etiology. CKD can result from a wide array of distinct pathophysiologic processes associated with abnormal kidney function and a progressive decline in GFR. The most common causes in the U.S. are diabetic and hypertensive nephropathy. Other causes include glomerulonephritis, polycystic kidney disease, malignancy, or obstruction as seen in nephrolithiasis or prostate disease.

While ethnicity or race was previously thought to be a risk factor for CKD, based on data from the most recent NHANES study, racial and ethnic minorities do not appear to have an increased prevalence of CKD in the United States compared with non-Hispanic whites. The risk of progression from CKD to ESRD, however, is higher in African Americans, Hispanics, Pacific Islanders and Native Americans. The reasons for this disparity are unclear.

Screening

Despite the increasing incidence and prevalence of CKD, no organization currently advocates screening the general population for CKD. While the National Kidney Foundation (NKF) does not advocate general screening, it recommends that all persons should be assessed for the presence of CKD risk factors (Table 3) to determine whether they are at increased risk for developing CKD as part of routine health maintenance.

A recent cost-effectiveness analysis concluded that annual urine dipstick testing for albuminuria in patients with diabetes or hypertension, as well as those aged 55 years and older without concurrent diabetes or hypertension, was cost-effective. In diabetics, screening for microalbuminuria has been shown to be more sensitive, and thus is recommended annually by many professional organizations and guidelines. (See the UMHS clinical guideline "Management of Type 2 Diabetes Mellitus".)

Initial Workup and Evaluation

Establishing CKD

Review of available medical records indicating presence of abnormal kidney structure or function for 3 or more months can establish the diagnosis of CKD (Table 1). Ruling out acute (or acute on chronic) kidney injury involves clinical

judgment in the clinical context of either estimated GFR (eGFR) < 60, a drop of > 20% in eGFR, or an increase in serum creatinine ≥ 0.3.

During the initial evaluation of CKD, common causes and predisposing conditions for acutely decreased eGFR, including pre-renal and post-renal causes, should be considered based on appropriate clinical history, physical exam and laboratory studies (Table 4).

History. A thorough history is a key component of the assessment of CKD and often provides clues to the underlying etiology of renal dysfunction (see Table 5).

Symptoms of kidney disease often develop only in advanced stages, and therefore are less relevant to primary screening and evaluation of CKD. Of particular interest, however, are symptoms related to obstructive urologic disease (nocturia, dribbling, unable to empty bladder, frequency without dysuria), a history of nephrolithiasis, recurrent urinary tract infections, or hematuria.

Physical exam. No classic or diagnostic physical exam findings are present in early to moderate stage CKD. However, certain elements of the exam require special mention and attention.

A key aspect of the exam is a general assessment of a patient's fluid status, assessing for both signs of dehydration and fluid overload. Also important is an accurate assessment of blood pressure (see UMHS Clinical Care Guideline on Hypertension).

A thorough abdominal exam is also required looking specifically for renal enlargement, CVA tenderness or the presence of renal bruits. The exam should also include a focused assessment to rule out signs of or risk for urinary obstruction, including assessment for bladder distention, a prostate exam in men and assessment for pelvic mass or uterine enlargement in women. If there is concern for bladder distention or obstruction, office evaluation could also include assessment of a post-void residual using either a catheter or a bladder ultrasound.

Finally, the physical exam should also include assessment for clues to common underlying causes of renal disease and for signs of common co-morbid conditions. Findings include those suggesting underlying connective tissue disorders or evidence of microvascular complications of diabetes (such as retinopathy), as well as a complete cardiovascular examination to assess for signs of peripheral arterial disease and/or heart failure.

Laboratory tests. Relevant laboratory tests for CKD include: GFR, urinalysis, and spot urine albumin-to-creatinine ratio.

GFR. As noted above, persistently reduced GFR is used in establishing a diagnosis of CKD. The two equations used to estimate GFR are shown in Table 6.

Currently, the abbreviated Modification of Diet in Renal Disease equation (MDRD) is used more frequently to calculate eGFR by laboratories in the United States. Typically values for both African Americans and non-African Americans are reported, as race is typically unknown to the laboratory. Some laboratories only report a value for eGFR if it less than 60.

In general, both the MDRD and CKD EPI (Epidemiology Collaborative) Equation tend to underestimate GFR in overweight or muscular patients and overestimate GFR in underweight patients. The CKD EPI Equation is somewhat more accurate than the MDRD equation at GFR >60. Below a GFR of 60 the two equations are generally equivalent for clinical practice. Both equations should be used with caution when assessing GFR in those with extremes of body habitus or muscle mass, during pregnancy, and in the elderly.

Urinalysis. Urinalysis is performed to screen for hematuria and/or albuminuria, both of which are markers of kidney damage. Urine dipstick is usually adequate for routine screening. If this reveals any abnormalities or if the index of suspicion for presence of microalbuminuria is high (e.g., screening for nephropathy in a diabetic patient), follow-up with more specific urine tests (e.g., urine albumin-to-creatinine ratio and urine microscopy) is recommended.

Spot urine albumin-to-creatinine ratio**.** The preferred urine specimen to assess for albumin-to-creatinine ratio (ACR) is the first voided urine in the morning. If a value of 30-300 mg/g is obtained, consider repeat testing once in 2 weeks to establish persistence. Potential transient or benign etiologies of albuminuria to consider are functional albuminuria of exercise, fever, or severe emotional stress.

Ultrasound. While no formal studies have assessed the risk versus benefit of ultrasound of the kidneys in CKD evaluation, the size and echogenicity of kidneys can have important prognostic value. Findings such as stones, masses, or hydronephrosis should prompt urologic evaluation. Significant renovascular abnormalities should be referred to nephrologist.

Renal ultrasound may be considered in all patients with eGFR < 60 both for evaluation and establishing a baseline. Ultrasound is *strongly recommended* in a patient with any of the following:

- Symptoms or signs consistent with obstruction
- Family history of cystic kidney disease, especially if age > 20
- Rapid progression of CKD or significant change in the rate of progression of CKD

Renal ultrasound *with Doppler* should be considered for patients with resistant hypertension, bruit on physical exam, or finding of asymmetric kidney sizes on initial ultrasound or other imaging study.

Staging. The 2013 KDIGO staging criteria for CKD are outlined in Table 2. The current GFR categories are similar to the prior CKD staging system proposed by KDIGO in 2002 (stage 1-5) with subdivision of stage 3 into G3a and G3b due to the difference in the prognostic significance of a GFR greater than or less than 45. The new system also has increased emphasis on the presence and degree of albuminuria. This change reflects the findings from several large meta-analyses (both from pooled general population and CKD cohorts) showing that albuminuria significantly impacts prognosis and the likelihood of progression in CKD.

Management of CKD

The direct management of CKD focuses on renin angiotensin aldosterone blockade (RAAS) and blood pressure control. Management also includes optimal management of common comorbid conditions such as diabetes and addressing cardiovascular risk factors to decrease risk for CVD. Also essential are patient education and a multidisciplinary approach to disease management that utilizes dieticians and social workers in addition to physicians

Renin Angiotensin Aldosterone Blockade

Single RAAS agent therapy. RAAS therapy with either an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) is recommended for patients with CKD to prevent or decrease the rate of progression to ESRD. An ACEI or ARB should be the first-line agent for antihypertensive therapy for CKD patients and is recommended for patients with albuminuria regardless of need for blood pressure control.

Angiotensin causes greater vasoconstriction of efferent arteriole than afferent arteriole, leading to glomerular hypertension. This leads to hyperfiltration and prolonged hyperfiltration leads to glomerular structural and functional deterioration. Both ACEI and ARB can reverse this process and delay renal disease progression.

While the reduction of intraglomerular pressure has long-term benefit, it may cause a small rise in serum creatinine in the short term, since GFR is directly correlated to intraglomerular pressure. **A rise of up to 20-30% above the baseline is acceptable and not a reason to withhold treatment unless hyperkalemia develops.**

In conditions such as bilateral renal artery stenosis, where angiotensin serves the critical role of preserving the intraglomerular pressure and GFR, its blockade could lead to acute renal failure. Thus, checking serum creatinine and potassium about 1-2 weeks after initiating or changing the dose of ACEI or ARB is recommended.

Selecting ACEI or ARB. ACEIs and ARBs do not differ significantly in terms of overall mortality, progression to ESRD, or their anti-proteinuric effects.

Initial selection of a specific drug should be based on cost, potential side effects, and patient preference (Table 7). Both classes of medications have been studied extensively. However, a higher volume of evidence and more landmark studies have been done with ACEIs than with ARBs. Therefore, experts generally recommend starting with an ACEI. However, ACEIs have a higher rate of cough and may cause a slightly greater increase of potassium and serum creatinine levels compared with ARBs.

With decreasing kidney function, starting doses for both ACEIs and ARBs are lower (see Table 7). Dose titration should occur slowly as needed for control of blood pressure or albuminuria.

Starting ACEI or ARB. As discussed above, when starting an ACEI or an ARB, monitoring blood pressure, potassium, and serum creatinine levels is important. Potassium and/or serum creatinine are expected to increase when starting or changing the dose of an ACEI or an ARB. Obtain potassium and serum creatinine levels before starting or changing the dose. (If already measured within the previous two weeks, that measurement can be used.) One to two weeks after initiation or dose change, check potassium and serum creatinine levels.

Many clinicians would tolerate a potassium level of up to 5.5 mEq/L and a serum creatinine increase of up to 30% from baseline within the first three months with close monitoring. The medication may need to be reduced or discontinued if the potassium level remains elevated at > 5.5mEq/L or if the serum creatinine continues to rise or does not improve. For further discussion of management of potassium, see the section on potassium, phosphorus, and sodium balance on page 18.

Dual RAAS therapy. In general, dual therapy with ACEI and ARB is not recommended. Studies to date have not shown any clinically significant benefits on overall mortality for dual therapy over monotherapy. Although some additive anti-proteinuric effect occurs when two RAAS agents are used, the ONTARGET study showed that dual therapy increased the risk of worsening of kidney function and hyperkalemia. Several large RCTs are currently ongoing to assess the role of dual therapy for CKD patients specifically.

Dual therapy with an ACEI and an ARB should be considered only for patients with severe albuminuria (> 1 g/day). A nephrology consult should be obtained at this point to help initiate and monitor dual RAAS therapy.

Spironolactone. Increasing evidence indicates that the aldosterone receptor antagonist spironolactone can decrease albuminuria and several small studies have evaluated its combination with an ACEI or an ARB. One theory for this combination regimen is the "aldosterone escape"

phenomenon, which refers to the fact that ACEIs and ARBs do not provide sustained decreases in aldosterone levels. The combination of ACEI and spironolactone is commonly seen in patients with concomitant heart failure, but may also be considered for those with severe albuminuria with nephrology input. Patients on combined spironolactone and ACEI or ARB therapy should be monitored carefully for hyperkalemia.

Blood Pressure Control

In general, optimum blood pressure control (< 140/90) reduces renal disease progression and cardiovascular morbidity and mortality. The 2013 KDIGO guidelines on CKD and blood pressure control state the following blood pressure goals for patients with CKD:

Urine Albumin Excretion	Blood Pressure Goal
< 30mg/24 hours	< 140/90 (recommended)
> 30mg/24 hours	< 130/80 (suggested)

Until recently, expert opinion had been that strict blood pressure (BP) control (BP < 130-135/80 mmHg; BP < 120-130/75-79 mmHg in overt albuminuria) reduced renal disease progression and cardiovascular morbidity and mortality. However, evidence from recent clinical trials have refuted that idea, demonstrating that there is no difference in overall mortality, progression to ESRD, myocardial infarction, stroke, or reported composite vascular or renal outcomes between strict BP control and usual BP control. In certain CKD populations, including the elderly and those with diabetes mellitus, aggressive BP control could lead to negative outcomes such as acute deterioration in kidney function, increased risk for cardiovascular events and orthostatic hypotension. In general, systolic blood pressure should remain > 110 and even higher if orthostatic symptoms occur. For diastolic blood pressure, caution is suggested when diastolic BP falls below 60 mmHg or less. Mortality increased when patients with diabetes had diastolic BP below 70.

Of the antihypertensive agents, ACEIs and ARBs are particularly effective in slowing disease progression in both diabetic and non-diabetic CKD. If ACEI or ARB is not effective on its own to control BP, then a thiazide or dihydropyridine calcium channel blocker (e.g., amlodipine) may be added. It should be noted that dihydropyridine calcium channel blockers should not be prescribed without the concomitant usage of ACEI or ARB, since their sole use may lead to greater hyperfiltration and albuminuria.

Once GFR declines to stage G4 or worse, thiazides are generally ineffective, and loop diuretics (e.g., furosemide) are usually needed to control volume-dependent hypertension. It should also be noted that patients with more advanced CKD often have resistant hypertension requiring multiple medications. These patients can be prone to orthostatic hypotension and aggressive blood pressure control (< 120/80) should be avoided.

Combined use of ACEI and ARB for blood pressure control is controversial, with no clear evidence of its benefit and possibly an increase in adverse events, including hyperkalemia and worsening of renal function. (See earlier discussion of dual RAAS therapies.)

See Table 8 for an overview of medications commonly used to address hypertension and necessary renal dose adjustments.

For more information on blood pressure control, see the UMHS clinical guideline "Essential Hypertension."

Management of Comorbid Conditions

Common comorbid conditions among patients with CKD include diabetes, cardiovascular disease, and hyperlipidemia. Managing these comorbid conditions aggressively is important. Suboptimal control of these secondary conditions increases the risk for progression of CKD. Additionally, the presence of CKD increase risk of morbidity and mortality associated with the comorbid conditions themselves.

Diabetes mellitus. Relatively strict control of blood glucose (hemoglobin A1C ≤7%) in both type 1 and type 2 diabetes reduces the development of diabetic nephropathy and its progression. Diligent BP control reduces renal disease progression and cardiovascular morbidity and mortality among patients with diabetes.

Drugs commonly used for glucose control in patients with diabetes are listed in Table 9. Dose adjustments based on renal function are noted. Renal deterioration leads to decreased renal metabolism of hypoglycemic drugs and/or insulin. As a result, dose adjustment of these medications may be required as CKD progresses to prevent hypoglycemia.

Preferred antihypertensive therapy among diabetics with hypertension would be an ACEI or an ARB. While no evidence supports use of RAAS therapy among normotensive normoalbuminuric patients with diabetes, ACEI or ARB therapy is recommended among normotensive diabetics with microalbuminuria.

Due to the high incidence of CKD among patients with diabetes, annual surveillance for CKD using serum creatinine and urine microalbumin to creatinine ratio is recommended for this patient population.

For more detailed information regarding diabetes care, see the UMHS clinical guideline "Management of Type 2 Diabetes Mellitus".

Cardiovascular disease (CVD). Cardiovascular disease is the leading cause of morbidity and mortality among patients with CKD.

Recent studies have demonstrated that even early stage CKD constitutes a significant risk factor for cardiovascular events and death. Similarly, CVD is a risk factor for progression of CKD. The frequency of cardiovascular complications in patients with CKD can be reduced with appropriate treatment of other CVD risk factors.

Statins to reduce cardiovascular risk. Statins reduce the relative risk of cardiovascular events to a similar extent among patients with and without CKD. However, the benefit is greater in patients with CKD because of the greater baseline risk for patients with CKD. In addition to reducing cardiovascular risk, statins may also have a role in preventing progression of kidney disease and reducing albuminuria, though evidence for these outcomes is less robust.

Based on the most recent KDIGO guideline, statin use is:

- Recommended for all non-dialysis CKD patients ≥ 50 years of age regardless of stage of disease or the presence or absence of albuminuria
- Suggested for non-dialysis or non-kidney transplant CKD patients who are 18-49 years of age and have an estimated risk of > 10% for 10-year incidence of coronary death or non-fatal myocardial infarction (includes any with coronary disease, diabetes mellitus, or ischemic stroke)
- Suggested for all kidney transplant patients, regardless of age.
- Suggested to continue in patients already receiving statins at the time of dialysis initiation
- Suggested not to be *initiated* in patients with dialysis-dependent CKD.

Table 10 summarizes the groups for which statin therapy is indicated.

The recent KDIGO clinical practice guideline on lipid management in patients with CKD recommends against using LDL cholesterol as a main target or determinant for initiation of statin therapy. This recommendation is based on a possible misleading association between LDL cholesterol level and coronary artery disease risk, especially among patients with more advanced CKD. In advanced CKD, confounders such as inflammation and malnutrition may be associated with lower LDL cholesterol levels, but in fact have the highest CVD risk.

The recent KDIGO clinical practice guideline is similar to the recent AHA/ACC guideline for lipid management in the general population in recommending statin therapy in all CKD patients with > 10% 10-year predicted risk of coronary disease. Given that all patients ≥ 50 years of age who have CKD meet this criterion, statin use is recommended for all non-dialysis patients aged ≥ 50 years.

For patients with CKD who are < 50 years of age who are not treated with chronic dialysis or kidney transplantation, the most recent guideline recommends suggests statin treatment for:

- Known coronary disease (myocardial infarction or coronary revascularization)
- Diabetes mellitus
- Prior ischemic stroke
- Estimated 10-year incidence of coronary death or non-fatal myocardial infarction.

To estimate risk of 10-year incidence of coronary death or non-fatal myocardial infarction, any of the validated risk prediction models may be used, e.g., Framingham risk score, SCORE, PROCAM, ASSIGN, Reynolds or QRISK2. For example, the Framingham risk score is calculated using the individual's age, gender, total cholesterol, HDL cholesterol, smoking status, and systolic blood pressure.

The risk of coronary disease for all kidney transplant patients is also elevated, therefore statins are recommended for this population as well.

Recent studies have provided conflicting evidence regarding the benefit of statins among patients with ESRD receiving renal replacement therapy. Some of the studies have demonstrated an increased risk of cerebrovascular events among dialysis patients taking statins. As a result, current guidelines do not recommend the *initiation* of statin therapy in patients on dialysis. CKD patients already taking statins at the time of dialysis initiation may continue on it.

Statin drugs and dosing. The use of standard doses of statins appears safe among most patients with CKD and does not require special monitoring beyond that for non-CKD patients. More intensive statin regimens have not been well studied in patients with CKD and there is concern that this population is at higher risk for adverse events related to the medication. This increased risk is thought to be due in part to decreased renal excretion, likely polypharmacy, and the high rate of comorbid illness. As a result, cardiovascular benefit of high dose statins needs to be weighed against this increased risk in this population.

CKD patients with good renal function may be treated with any statin regimen that is approved for use in the general population. "Good renal function" is defined as eGFR ≥ 60/ml/min/173 m2 (G1 and G2) and no history of kidney transplantation, so drug toxicity of less concern. Recommendations for statin drugs and dosing in the general population are presented in the UM Lipid Management guideline. For patients with CKD G1-G2, the only exception to drugs used in the general population is that 40 mg of rosuvastatin daily is not recommended because of potential increased risk for adverse renal event.

CKD patients with limited renal function require reductions from usual statin dosing due to decreased renal excretion. Limited renal functioning is eGFR < 60 ml/min/1.73 m2 (G3a-G5), including patients on dialysis or with kidney transplant. Tables 11 and 12 outline recommended dose adjustments and limitations for specific statins based on renal function.

A recent large randomized controlled trial (SHARP) compared combination therapy with statin plus ezetimibe versus placebo in patients with CKD. A significantly lower incidence of cardiovascular events occurred in the treatment arm. As a result, the most recent KDIGO guideline suggests statin + ezetimibe as an alternative to statin monotherapy, especially in patients with a eGFR ≤ 60 ml/min/1.73 m2 (e.g., g3a-5). In clinical practice, this approach may be limited by the higher cost of ezetimibe compared with statin monotherapy.

Antiplatelet agents. Evidence is limited regarding the use of aspirin or other antiplatelet agents for both primary and secondary prevention of CHD among patients with CKD.

Due to strong evidence of its benefit among non-CKD patients and insufficient evidence to recommend a different approach among CKD patients, aspirin has been recommended for CKD patients with known CHD for secondary prevention of future cardiovascular events. Aspirin is also often recommended among patients with diabetes.

Previously, a post-hoc subgroup analysis of a large primary prevention trial among patients with hypertension demonstrated a greater absolute risk reduction in major cardiovascular events and mortality from the use of aspirin (75mg) among patients with CKD compared to patients with normal renal function. While there was a trend toward increased bleeding risk among patients with lower GFR, increased risk in this group seemed outweighed by substantial benefits of aspirin use with regard to cardiovascular disease.

More recently, a meta-analysis was completed to address the use of antiplatelet agents among persons with CKD both with known stable or unstable CHD and those "at risk" for CHD. For CKD patients with known stable CHD or "at risk" for CHD, antiplatelet regimens (aspirin, aspirin plus dipyridamole [Aggrenox®] or a thienopyridine [Plavix®]) appeared to reduce fatal or nonfatal myocardial infarction by approximately 33% but their impact on stroke or all-cause and cardiovascular mortality was uncertain. Among these stable patients, antiplatelet agents appeared to increase risk for minor bleeding but their use did not clearly increase risk for major bleeding events.

Given the limited quality of evidence currently available to address the role of these agents among patients with CKD, further research is necessary to clarify their role in the prevention and treatment of CHD in this population.

For more information on prevention of vascular disease, see the UMHS clinical guideline "Secondary Prevention of Coronary Artery Disease."

Smoking. Smoking cessation should be strongly recommended among patients with CKD as a means to reducing cardiovascular risk.

Some studies have also suggested that smoking leads to a more rapid progression of CKD especially among patients with diabetes and hypertension. Data are limited on the impact of tobacco cessation on progression of CKD.

For more information on smoking cessation, see the UMHS clinical guideline "Tobacco Treatment".

Dyslipidemia. Dyslipidemia is common among patients with CKD. As previously discussed, statin use is now recommended for many CKD patients independent of lipid levels, based instead on overall cardiovascular risk. However, baseline assessment of lipid levels is still recommended in patients with CKD.

Baseline lipid profile and follow up. All adults with CKD should have a baseline assessment of their lipid profile at the time of their diagnosis of CKD. Ideally, the baseline lipid profile should be obtained when the patient is fasting for a more accurate evaluation of potential dyslipidemias, including hypertriglyceridemia, which are common in the setting of CKD. However, if patient convenience or compliance is an issue, non-fasting lipid profiles (when the LDL is calculated directly if TG > 400 mg/dL) may be adequate if the primary goal is to assess cardiovascular risk, especially in patients age < 50 years of age. Only total cholesterol and HDL-C are needed for most cardiovascular risk calculators.

The need, indications for and timing of repeat lipid assessment in patients with CKD (with or without statin use) is unclear. It is likely not required for the majority of patients, especially those started on statins. The most recent KDIGO lipid guidelines advocate a "fire and forget" approach to statin therapy in patients deemed appropriate for statin use.

Repeat assessment of lipids may be necessary or considered to assess medication compliance (e.g., 6-12 weeks after initiation) or if secondary causes of dyslipidemia are suspected. Additionally, in CKD patients not on statin therapy, repeat lipids may be needed to reassess cardiac risk at different intervals. As stated above, a non-fasting lipid profile is adequate to assess cardiovascular risk and to monitor statin compliance

Clinicians should be aware that many "pay-for-performance" programs (e.g., based on current HEDIS measures) still recommend annual monitoring though the indication for this is not clear.

Hypertriglyceridemia. Combined dyslipidemias are common in patients with CKD.

For treatment of high triglycerides, current guidelines for patients with CKD recommend therapeutic lifestyle change (TLC). While evidence for use of TLC for treatment of hypertriglyceridemia is weak, given the low potential for negative side effects, this is currently the recommended management strategy for CKD patients with serum TG > 500mg/dl. TLC includes dietary modification, increased

exercise, reduced alcohol intake and treatment of hyperglycemia (especially in patients with concurrent diabetes mellitus). Specific dietary changes include following a low fat diet (< 15% of total calories), reducing intake of mono- and disaccharides, reducing total carbohydrate intake and adding fish oils in place of long-chain triglycerides. Given the risk of malnutrition in patients with advanced stages of CKD, a referral to a nutritionist to guide patients in this type of diet modification is recommended. Therapeutic lifestyle interventions are discussed in more detail in the UM Lipid Management guideline.

Previous guidelines have suggested the use of fibric acid derivatives (e.g, gemfibrozil, fenofibrate) in patients with elevated triglycerides (TG) both to reduce risk of pancreatitis and decrease cardiovascular risk. Based on their most recent analysis, however, the KDIGO lipid work group felt that evidence is insufficient to support the use of fibric acid derivatives for either of these indications. While these agents may still be reasonable to consider in CKD patients with severe dyslipidemias (i.e. fasting serum TG > 1000 mg/dl), the work group considered the risk for potential side effects to outweigh the potential benefits in the majority of patients. As a result, fibric acid derivatives are no longer recommended to reduce either risk for pancreatitis or reduce cardiovascular events in this patient population. If gemfibrozil or fenofibrate are prescribed to CKD patients, renal dose adjustment is required (see table 11).

For CKD patients with severe dyslipidemias, a referral to a lipid specialist for further guidance on management could also be considered.

Other lipid medications. The recent SHRAP trial demonstrated both safety and efficacy of ezetimibe in CKD patients when used in combination with statins. Combination statin/ezetimibe therapy is currently recommended as an alternative to statin therapy alone in CKD patients > 50 years of age with eGFR < 60 ml/min/1.73 m2 (i.e. G3a-G5).

Nicotinic acid has not been well studied in patients with advanced CKD. It also has a high risk of side effects (i.e. flushing, hyperglycemia). As a result, it is not recommended for treatment of dyslipidemia in the CKD population.

Complications of CKD

CKD can result in several important complications including: anemia, mineral bone disease, metabolic acidosis, potassium and sodium imbalance, fluid imbalance, and malnutrition. Patients with CKD need to be monitored for these conditions and treated once a complication is identified.

Anemia. Anemia is a complication of CKD that is proportional to eGFR and is independently associated with morbidity and mortality. Significant drop in hemoglobin (Hgb) is typically seen among patients with CKD G3b or worse.

Based on 2013 KDIGO guidelines, anemia in CKD is defined as Hgb < 13 in men and Hgb < 12 in women. Evaluation should include CBC, reticulocyte count, serum ferritin, and serum iron saturation (TSAT) to assess for iron deficiency.

If iron deficiency is diagnosed, an age-appropriate evaluation and treatment independent of CKD should be followed. The target Hgb for all stages of CKD is 10-12 although this is a controversial area. Primary care physicians should consider referral to a nephrologist if Hgb < 10 and no obvious non-renal cause is identifiable with initial work up.

Consideration of use of an erythropoesis stimulating agent (ESA) and/or parenteral iron should be done in consultation with a nephrologist. In general, clinicians should avoid transfusion in patients with CKD if possible due to potential sensitization which might delay or preclude kidney transplant in the future. No specific Hgb threshold for transfusion exists. Clinical judgment is key; transfusion may be indicated for symptomatic anemia, especially among patients with cardiac failure.

For additional details of anemia management in CKD, please refer to the 2013 KDIGO guidelines on anemia in CKD (see annotated references).

CKD mineral bone disease (CKD-MBD). Abnormalities of calcium and phosphate metabolism typically become apparent in late stages of CKD (G3b or worse). Observational studies suggest that addressing CKD-MBD in earlier stages of CKD may potentially slow or prevent progression of CKD and may prevent vascular calcification.

Clinicians should consider checking Ca, Phos, iPTH, Alk Phos, and 25-OH vitamin D at least once in patients with CKD stages G1-G3a. For G3b or worse, a similar lab assessment would be recommended every 6 months. In general, CKD-MBD should be managed in conjunction with the nephrologist

Vitamin D supplementation is recommended for those with evidence of vitamin D deficiency. Renal hydroxylation is generally adequate in CKD stage 1-3, and any form of vitamin D would be useful in treating a deficiency. The threshold for vitamin D supplementation should be especially low in geographic areas where patients are at high risk for deficiency due to low sun exposure (e.g., New England, Midwest).

We recommend referral to nephrologist for the use of active forms of vitamin D or management of vitamin D deficiency or CKD-MBD in CKD stage G4 or G5.

Diagnosis and treatment of osteoporosis (including use of bisphosphonates) should be approached as in the general

population in CKD stages G1-G3a. We recommend co-management of osteoporosis with nephrologist at later stages of CKD as dose adjustments will be necessary.

Metabolic acidosis. A small number of trials have demonstrated the potential benefit of sodium bicarbonate in patents at all stages of CKD to prevent kidney disease. However, given the limited data available and the potential adverse effect on blood pressure, we recommend that the use of sodium bicarbonate be deferred to a nephrologist.

Potassium, phosphorous and sodium balance. Hyperkalemia is a frequent problem in CKD, especially in patients who might benefit from ACEI/ARB. High (> 5.5 mEq/L), as well as low (< 4 mEq/L) potassium has been associated with a shorter time to ESRD and higher mortality in patients with CKD stages G3-G5.

A low-potassium diet is recommended for patients with CKD for patients with K > 5.5 mEq/L. If the patient's potassium is normal and stable, fruits and vegetables should not be curtailed. However, a close review of medications and diet is necessary when hyperkalemia of any degree is encountered (see Table 13).

Target phosphorous levels are 3-5mg/dl. Phosphate restriction or phosphate binders should be prescribed in consultation with the nephrologist.

Modest sodium restriction of approximately 2g of sodium per day is recommended in most CKD patients as an adjunct to pharmacotherapy for better control of blood pressure.

The National Kidney Foundation provides helpful web-based links for clinicians and patients on the topics on potassium and phosphorus management (Table 14).

Fluid balance. Monitoring fluid balance includes addressing hypervolemia and diuretic use and also salt and water intake. Patients with CKD are susceptible to both hyper- and hypovolemia. At advanced stages of CKD, the ability to compensate for electrolyte and volume changes is progressively compromised.

Hypervolemia and diuretics. Subclinical volume expansion may be present even at GFR category G3a CKD. Overt hypervolemia may be seen when a patient becomes oliguric or has nephrotic syndrome, liver disease or accompanying heart failure. Regardless of the etiology of hypervolemia, some practical issues occur for diuretic management in patients with CKD:

- Dietary sodium restriction should, in general, be emphasized, unless one suspects salt-wasting nephropathy, which is relatively rare.
- Loop diuretics are preferred when GFR is < 40 ml/min.
- Addition of spironolactone or eplerenone might be beneficial, especially in proteinuric patients already on maximized RAAS-blocker therapy.
- Larger dose loop diuretics (2 to 3 times the usual dose) are often needed in nephrotic syndrome, due to binding of drugs to albumin.
- Addition of metolazone to be taken 15-20 minutes before a loop diuretic may increase the response. This can be done for 3-5 days until approaching euvolemia, then reassessed.
- Adjusting diuretic dose and frequency based on patient's accurate weight is preferred.
- High dose or combination diuretic therapy should preferably be initiated in consultation with a nephrologist.

Fluid intake. High fluid intake is recommended for three conditions commonly seen in patients with CKD:

- Nephrolithiasis: recommended fluid intake of at least 2-3L daily.
- Salt-wasting nephropathies (e.g., chronic interstitial kidney diseases, medullary cystic disease), are rare conditions in which the renal concentrating ability is diminished: these require a daily intake of > 4L of fluid and a high salt diet.
- Central and nephrogenic diabetes insipidus: fluid intake of > 5 L daily may be needed.

Secondary Preventive Care

The risk of complications in patients with CKD can be reduced by preventive care that includes maintaining a healthy lifestyle, avoiding nephrotoxic medications, administering appropriate immunizations, and monitoring for common secondary diagnoses. Emerging evidence identifies obesity as a potential modifiable risk factor for both development and prevention of CKD, so overweight and obesity should be aggressively addressed.

Dietary recommendations. Assessment of dietary intake of patients with CKD is important. Inadequate caloric intake and malnutrition are common problem among patients with advanced CKD (especially eGFR < 25).

Protein. In general, an adequate protein intake of 0.8 g/kg per day is recommended for patients with CKD.

High protein intake (> 1.3 g/kg/day) has been linked with CKD progression and should be avoided.

The potential risks versus benefits of moderate dietary protein restriction (0.6 to 0.8 g/kg per day) on the progression of CKD are unclear. However, any benefit of moderate-to- intense protein restriction is likely to be small compared with the benefits of RAAS blockade. Any consideration of protein restriction below 0.8 g/kg per day should be accompanied by regular and close dietary supervision to avoid the real risk of malnutrition in CKD patients.

Potassium, phosphorous, and sodium. Patients with CKD should be educated to be aware the intake of foods high in

potassium (most important in the patients with hyperkalemia), phosphorous and sodium. While the DASH diet has been proven efficacious for treatment of hypertension, hypertensive patients with CKD should follow caution when using the DASH diet due to its high intake of potassium and phosphate. At all stages, CKD patients with hyperkalemia (> 5.5) should be advised to follow a low-potassium diet. Several web-based resources exist for patients regarding foods high in potassium and phosphorus (Table 14).

The effect of sodium intake on the progression of CKD is controversial, and multiple inconclusive studies exist. No specific recommendation is advisable at this time beyond general recommendations to limit sodium in patients with hypertension and/or fluid overload, both of which are common among those with CKD stages G3-G5.

Nutritional counseling. Periodic visits with trained renal nutritionists are encouraged to assist patients with moderate to severe CKD in making appropriate dietary choices. Most insurers cover dietary consultation for patients with a diagnosis of CKD. Visits can begin as early as eGFR < 60. The American Dietetic Association recommends that advanced stage CKD patients be referred to a dietician at least 12 months before expected initiation of renal replacement therapy. Evidence showing impact of this intervention on progression of renal disease and mortality is limited, so these recommendations are based on expert opinion.

Obesity. While no data are available from large scale randomized controlled trials, smaller case-control, cohort studies and epidemiologic data suggest that obesity may be an independent and potentially modifiable risk factor for CKD.

One systematic review suggested that weight loss may be associated with improvement in albuminuria though evidence regarding durability of this change was limited and no impact on GFR occurred.

Obesity is a known risk factor for progression of comorbidities such as type 2 diabetes, hypertension, dyslipidemia and CVD. Therefore, counseling overweight and obese patients with CKD regarding strategies for weight loss is appropriate and recommended.

For further information on treatment of obesity, see the UMHS clinical guideline "Obesity Prevention and Management".

Physical activity. The NKF/KDOQI Guidelines recommend engaging in exercise for 30 minutes most days of the week. Data from the National Health and Nutrition Examination Survey III (NHANES III) have shown that physical activity was associated with lower mortality in patients with CKD of stage G3 or worse. Additionally, increased physical activity may lead to better control of hypertension, diabetes, and depression. Both aerobic and resistance exercises are beneficial.

For further information on physical activity recommendations and targets, see the UMHS clinical guideline "Obesity Prevention and Management" (Table 3).

Avoidance of nephrotoxic medications. Medications can cause or worsen kidney dysfunction and these effects are exacerbated in patients with underlying CKD. Many commonly used drugs, including over-the-counter medications, can cause nephrotoxicity. Several of these drugs are listed in Table 15.

Drug-induced kidney damage can be acute or chronic, is variable in severity, and can affect any part of the kidneys. However, most drug-induced damage is reversible if detected and treated early. Signs of early kidney damage may include acid-base abnormalities, electrolyte imbalances, and mild urinary sediment abnormalities.

Factors predisposing patients to drug-induced nephrotoxicity are listed in Table 15. Drugs that have been associated with nephrotoxicity should be used cautiously in these patient populations and concurrent use of multiple nephrotoxic agents should be avoided. Table 15 outlines some general strategies to prevent drug-induced nephrotoxicity. These strategies should be employed in all patients with CKD.

Three commonly used agents deserve additional comment:

NSAIDs. Ibuprofen, indomethacin, naproxen and other NSAIDs are associated with a 3-fold increase in risk for acute kidney failure, which can occur within days and can be reversed if the medication is promptly discontinued. Allergic interstitial nephritis may occur around 6 months of therapy and may need a steroid course to resolve. Of the NSAIDs, indomethacin is most likely to cause acute kidney failure and aspirin is least likely to result in damage. NSAID treatment also increases the risk of GI bleeding. NSAID use in patients with heart disease or its risk factors increases overall risk of heart attack or stroke.

Oral sodium phosphate products. Oral sodium phosphate (NaP) products (such as Visicol, OsmoPrep) products have been associated with acute phosphate nephropathy when used for bowel cleansing prior to colonoscopy or other procedures. This form of kidney injury is associated with deposits of calcium-phosphate crystals in the renal tubules and may result in permanent kidney damage. Symptoms can occur within hours or weeks (up to 21 days reported), and can include malaise, lethargy, decreased urine output, and edema. CKD patients, especially those on an ACEI/ARB, are at increased risk of developing acute phosphate nephropathy. Consider using a polyethylene glycol solution for these patients instead (such as GoLytely). NaP (Fleet) enemas can be used for bowel cleansing before sigmoidoscopy, but should be avoided in elderly patients or in those with severely decreased GFR

(stage G5) due to the risk of hyperphosphatemia and subsequent hypocalcemia.

Contrast media. Both iodinated and gadolinium-based contrast media are associated with potential for complications among those with CKD.

Recent studies have cast doubt on the nephrotoxicity of intravascular administration of iodinated contrast. However, it remains prudent to be concerned about possible nephrotoxic effects of intravascular iodinated contrast media in patients with low eGFR (various risk thresholds at eGFR of 30 to 45 mL/min/1.73m2 have been suggested by various specialty societies). The nephrotoxicity of iodinated contrast agents, when it occurs, likely occurs promptly after administration, although detection typically requires 12-24 hours because time is required for creatinine to be produced and serum creatinine to rise. Should renal functional damage occur, management consists of adequately hydrating the patient and recovery usually occurs within 4-10 days after exposure. To minimize the nephrotoxicity risk from these agents, clinicians should ensure adequate hydration and may want to consider intravenous administration of normal saline or sodium bicarbonate infusion. Prophylaxis with drugs such as antioxidants (including N-acetylcysteine or ascorbic acid) has no proven reliability. There is some (albeit poorly understood) relationship between the dose of the iodinated agent and nephrotoxicity risk, so that reducing dose (if that will not interfere with the quality of the study) may be helpful.

Consider holding nephrotoxic drugs, such as NSAIDs, for 24 hours prior to and after exposure to contrast media in patients with CKD. The FDA states that metformin should be stopped at or before the administration of intravascular iodinated contrast media, and held for at least 48 hours after contrast media is administered, due to the risk of lactic acid accumulation and toxicity if acute kidney injury from the iodinated contrast agent should occur. (Metformin is not itself nephrotoxic nor does it increase the nephrotoxicity of iodinated contrast agents.) The decision to resume metformin should be based on the follow-up serum creatinine level. Some specialty societies suggest that this warning about metformin is unnecessary in patients with normal or near-normal renal function given the lack of demonstrable clinical nephrotoxicity from iodinated contrast agents in this patient subset.

The FDA has updated labeling recommendations on how and when kidney function is measured in patients receiving metformin, including the following information:

- Before starting metformin, obtain the patient's eGFR.
- Metformin is contraindicated in patients with an eGFR below 30 mL/minute/1.73 m2.
- Starting metformin in patients with an eGFR between 30-45 mL/minute/1.73 m2 is not recommended.
- Obtain an eGFR at least annually in all patients taking metformin. In patients at increased risk for the development of renal impairment such as the elderly, renal function should be assessed more frequently.
- In patients taking metformin whose eGFR later falls below 45 mL/minute/1.73 m2, assess the benefits and risks of continuing treatment. Discontinue metformin if the patient's eGFR later falls below 30 mL/minute/1.73 m2.
- Discontinue metformin at the time of or before an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/minute/1.73 m2; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart metformin if renal function is stable.

Administration of gadolinium-based contrast media used for magnetic resonance imaging (MRI) is associated with the development of nephrogenic systemic fibrosis (NSF) in a small percentage of at-risk patients; all reported cases occurred in patients with stages G4-G5 CKD. Therefore, these agents are not recommended for use as contrast agents for radiography, computed tomography, or angiography, and should be used with caution for MRI in patients who have an eGFR less than 30 mL/min/1.73m2. If necessary, use of the smallest dose possible and not more than 0.3 mmol/kg of any formulation is recommended. The FDA contraindicates Magnevist, Omniscan, and Optimark in patients with AKI or with chronic, severe kidney disease. Agents considered to be at the lowest risk of NSF are Dotarem, Gadavist, MultiHance and ProHance.

Immunizations. The Centers for Disease Control and Prevention recommend the following for patients with CKD:

- Influenza vaccine annually for all CKD patients
- Pneumococcal vaccines for patients with end stage renal disease or CKD likely to progress to end stage renal disease:
  - Vaccination with both conjugate vaccine (PCV13/Prevnar) and polysaccharide vaccine (PPSV25/Pneumovax). If giving the initial vaccination, give PCV13 followed by PPSV23 $\geq$ 8 weeks later. If the patient was previously vaccinated with PPSV23, give PCV13 $\geq$ 1 year after last PPSV23 dose. If the patient was previously vaccinated with PCV13, give PPSV 23 $\geq$ 8 weeks after PCV13.
  - Give a PPSV23 booster in 5 years
  - Give another PPSV23 booster if the patient is age $\geq$ 65 years and if most recent PPSV23 vaccination was done at age < 65 years and $\geq$ 5 years ago.
- Hepatitis B vaccine for CKD patients nearing ESRD and preparing to go on renal replacement therapy, especially hemodialysis.

Renal transplant recipients on chronic immunosuppressive therapy should **NOT** be given live vaccines such as MMR, varicella and herpes zoster vaccines.

Monitor for secondary diagnoses. Compared to the general population, CKD patients have a higher prevalence of several common diagnoses:

- Depression (found in 20-30% of patients with CKD vs 10% of the general population)
- Sexual dysfunction
  - In men with CKD, 70% had self-reported erectile dysfunction
  - In women with CKD, 40%–80% report sexual dysfunction
  - For comparison, in the general population, only 13%–33% of men and women report sexual dysfunction.
- Obstructive sleep apnea (found in 30% of patients with CKD vs 2-4% of the general population)

Clinicians should remain alert for the possible presence of these conditions in CKD patients.

Patient Education

Among patients with mild-moderate stage CKD (G1-G4), patient awareness of their diagnosis is poor. This is problematic for many reasons. CKD progression and complications are clearly impacted by use of common over the counter medications (including NSAIDs, vitamins and herbal preparations), dietary and lifestyle choices, and management of co-morbid conditions like hypertension, diabetes and dyslipidemia. Improving patient awareness and providing patient education and associated informational materials may help patients manage their chronic disease and may lead to improved outcomes (see Table 14).

Successful chronic disease management involves physician partnering with nurses, nutritionists and pharmacists to assist with and improve patient education and behaviors including lifestyle, diet and medication compliance.

Many on-line resources are also available to help patients better manage their disease.

Monitoring and Follow Up

Monitoring for progression. The diverse population of patients with CKD makes the appropriate interval for patient follow up and laboratory assessment highly variable and patient specific.

General guidelines for follow up were provided in the most recent KDIGO CKD Guidelines. They suggest the following:

- All patients with CKD should have an assessment of their GFR and be checked for the presence or absence of albuminuria at least annually.
- Patients at higher risk for progression, such as those in a more advanced GFR category or with more advanced albuminuria, should be screened more frequently (see Table 16 and 17).

While small fluctuations in GFR are common in CKD patients, a significant decline (20% or more) is concerning for CKD progression. Rapid progression is defined as a persistent decline in GFR by greater than 4-5ml/min/1.73 m^2/year. A mild to moderate decline in GFR should prompt primary care providers to review current CKD management and assess for potential reversible causes of acute kidney injury (AKI) or progression of CKD. A rapid decline in function is an indication for referral to a nephrologist.

The progression of CKD, including the time course of and whether progression leads to ESRD or nephritic syndrome, is highly dependent on the underlying cause of kidney dysfunction. It can be influenced by adequacy of blood pressure control and the presence or absence of proteinuria. Depending on the primary care provider's comfort level with the disease responsible for the patient's CKD, earlier referral to a nephrologist may be considered.

CKD patients are at increased risk for AKI. Physicians involved in their care should actively try to avoid situations that increase risk for AKI. If high-risk situations are unavoidable (Table 4), monitor closely for acute decline.

When to refer to a specialist. Indications for referral to a nephrologist are presented in Table 18. Many patients reach end stage renal disease (ESRD) without adequate preparation for transition to renal replacement therapy (RRT). Nearly 50% of all patients reaching ESRD in the United States either do not see a nephrologist at all or see one only within 6 months prior to requiring RRT. Delayed referral is associated with higher mortality among patients on dialysis.

Timely referral in Stage 4 (or earlier if CKD progressing rapidly) allows for adequate physical and psychological preparation, including optimization of vascular access and work-up for potential kidney transplantation. Comprehensive multi-disciplinary care by a nephrology team that includes nurses, social workers and dieticians is recommended. Such care can help slow renal disease progression, optimize management of CKD complications prior to initiation of dialysis and provide a higher likelihood of permanent vascular access placement (preferably AV fistula) prior to beginning dialysis. Early referral to nephrology and involvement of a multidisciplinary team also increases the likelihood of CKD patients choosing peritoneal dialysis or other home-based dialysis therapies.

Other potential indications for nephrology referral outlined in Table 18 include rapid decline in GFR and the potential need for renal biopsy to identify the cause of kidney dysfunction.

Special Populations

Pregnancy

Patients with G3 CKD or worse may have an accelerated decline in their renal function during pregnancy. A multidisciplinary approach is necessary, with involvement of nephrologists and high-risk obstetricians skilled in pregnancy management for patients with CKD.

Ideally, a patient's renal function and albuminuria should be stable and blood pressure well controlled prior to attempting pregnancy. Patients who have had a transplant should be encouraged to wait 1 year after a living relative–donor transplant and 2 years after a cadaveric renal transplant before attempting pregnancy.

Clinicians should also be aware that ACEIs and ARBs are *contraindicated* in pregnancy (category X, known to cause birth defects). Common agents used for blood pressure control in pregnancy include methyldopa or labetolol, but other common medications such as hydrochlorothiazide, amlodipine, some beta blockers, and hydralazine are also felt to be safe for use in most pregnant patients.

Older Patients

Age is one of the most important underlying risk factors for CKD, often compounded by the presence of other comorbidities such as diabetes, hypertension and vascular disease. With increasing life expectancy, the prevalence of both CKD and ESRD is rising. The prevalence of CKD among those over 65 years of age may range between 25%-35%. Among healthy individuals, creatinine clearance peaks at approximately 120-130 mL/min/1.73m^2 around age 30 years and then declines by roughly 8 mL/min/1.73m^2 per decade.

The equations used to estimate renal function have not been validated in large numbers of elderly patients and tend to underestimate GFR.

Currently, no age-specific definitions exist for CKD. In general, older individuals with reduced kidney function are at higher risk for acute kidney injury from pre-renal, renal and post-renal causes. **Nephrotoxic drugs have greater impact on the elderly and should be used with particular caution.** Blood pressure control may need to be customized for elderly patients with CKD including more gradual escalation of treatment and careful monitoring for adverse effects.

Minorities

Although African Americans, Native Americans, Hispanics, Asians and Pacific Islanders were previously felt to have higher risk of developing CKD compared to non-Hispanic whites, more recent data have raised doubts about this racial and ethnic variance in prevalence of the condition. Current data continues to indicate that Hispanics, Native Americans, Pacific Islanders and, in particular, African Americans suffer from a disproportionately higher incidence of ESRD. For African Americans, kidney failure also occurs at an earlier age compared to non-Hispanic whites.

Transplant Patients

All kidney transplant recipients are considered to have CKD. While transplant patients will almost always be co-managed by a nephrologist, the role for primary care physicians in the management of transplant patients includes:

- Early detection of decreased renal function as a possible warning sign of allograft dysfunction
- Prevention, assessment and management of common co-morbid conditions after transplant (including new onset diabetes related to immunosuppressant medications, cardiovascular disease, infection, cancer)
- Patient education and medication monitoring to reduce risk for acute kidney injury

Common signs of acute rejection or allograft dysfunction can include hypertension, increased creatinine, decreased GFR, or increased albuminuria. Many of these same signs can also be associated with immunosuppressant drug toxicity. In general, the threshold for ultrasound imaging among patients with kidney transplants is much lower as this is relatively inexpensive and reasonably accurate to diagnose treatable causes of allograft dysfunction.

Primary care providers should be aware that medications commonly used for immunosuppression following kidney transplant (such as cyclosporine, tacrolimus, and sirolimus) can interact with many medications and with some juices and herbs. Table 19 provides an abbreviated list of these drugs and natural products that can interact with immunosuppressants. Since this is not a comprehensive list, an assessment for drug interactions should be performed prior to starting any new drug or natural product in patients on immunosuppressant medications.

Complementary and Alternative Medicines

Few studies have been performed regarding complementary and alternative medicines in CKD. While small studies have shown potential benefits of low dose vitamin C and omega-3 polyunsaturated fatty acids on kidney function, more rigorous clinical trials are needed to confirm this, especially since high doses of vitamin C (> 500mg daily) may be associated with nephrotoxicity due to calcium oxalate crystal deposition.

Patients should be advised to avoid herbs if possible, especially if they are on immunosuppressive therapy. Many herbs can potentially interact with prescription medications or cause additional kidney damage in patients with underlying CKD. Table 20 lists herbs that may be especially harmful to CKD patients, such as St. John's wort

and ginkgo. Some products (including alfalfa, dandelion, and noni juice) contain potassium, which can cause or exacerbate hyperkalemia. Others may contain heavy metals that are nephrotoxic or ephedra-like compounds that are vasoconstrictive and can cause or worsen hypertension. Chinese herbal medicines that contain aristolochic acid can cause severe and permanent kidney damage.

Strategy for Literature Search

The team began the search of literature by accepting the results of the literature searches performed for fairly recent systematic reviews (see "annotated references" for full citation):

Black C, Sharma P, Scotland G, McCullough K, McGurn D, Robertson L, *et al*. Early referral strategies for management of people with markers of renal disease: a systematic review of the evidence of clinical effectiveness, cost-effectiveness and economic analysis. *[Medline search through Jan 2009.]*

Kidney Disease: Improving Global Outcomes (KDIGO) CKD–MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD–MBD). *[full search through Dec 2007, RTCs through Nov 2008]*

VA/DoD Clinical Practice Guideline for Management of Chronic Kidney Disease in Primary Care *[search through Dec. 2006]*

K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. *[search through June 2000]*

To update those searches with more recent literature and to examine literature on other topics, a systematic search of literature on Medline was performed.

The major search terms were: "chronic kidney disease excluding end stage renal disease"; time frame started with 1/1/07 unless a more recent review (above) addressed the topic; type of publication was guidelines, controlled trials (including meta-analyses), and cohort studies; population was human/adult; and language was English.

Within these parameters individual searches were performed for the following topics: screening; assessment of renal function/staging; history and symptoms; physical exam; laboratory tests; imaging; renin-angiotensin system blockade (ACEI, ARB, optimizing blood pressure, reducing albuminuria, inhibition of renal fibrosis); treatment of diabetes mellitus and of hypertension; management of dyslipidemia, smoking, and aspirin therapy; management of anemia, mineral bone disease, metabolic acidosis, potassium and sodium balance, fluid balance/volume management, and malnutrition; dietary recommendations (sodium, protein, malnutrition), medication dose adjustment/medications to avoid/nephrotoxic medications; psychiatric disorders (depression); sleep quality and sleep disorders; sexual dysfunction, monitoring and follow-up; pregnancy, geriatrics, minorities, and other results for the major search terms not included in the above specific searches. The specific search strategy is available upon request.

The search was conducted in components each keyed to a specific causal link in a formal problem structure, which is available upon request. The search was supplemented with very recent clinical trials known to expert members of the panel. Negative trials were specifically sought. The search was a single cycle. Conclusions were based on prospective randomized clinical trials if available, to the exclusion of other data; if randomized controlled trials were not available, observational studies were admitted to consideration. If no such data were available for a given link in the problem formulation, expert opinion was used to estimate effect size. The "strength of recommendation" for key aspects of care was determined by expert opinion.

Related National Guidelines

The UMHS Clinical Guideline on Chronic Kidney Disease is consistent with:

ACP. Screening, Monitoring, and Treatment of Stage 1 to 3 Chronic Kidney Disease: A clinical Practice Guideline from the Clinical Guidelines Committee of the American College of Physicians

ACIP/CDC. Guidelines for Vaccinating Kidney Dialysis Patients and Patients with Chronic Kidney Disease (2012)

ACC/AHA. Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (2013)

Kidney Disease: Improving Global Outcomes (KDIGO) clinical guidelines for:

- Anemia in Chronic Kidney Disease (2012)
- CKD Classification and Management. (2013)
- Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (2013)
- Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease (2013)
- Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD–MBD) (2009)
- Management of Blood Pressure in Chronic Kidney Disease (2012)

National Kidney Foundation. Update of the KDOQI Clinical Practice Guideline for Diabetes and Chronic Kidney Disease (2012)

USPSTF. Screening for Chronic Kidney Disease (2012)

VA/DoD Clinical Practice Guideline for Management of Chronic Kidney Disease in Primary Care (2007)

Measures of Clinical Performance

At this time no major national programs have clinical performance measures specifically for CKD diagnosis and treatment. However, all national programs have performance measures for medical conditions often seen in patients with CKD, including hypertension, diabetes, cardiovascular disease, dyslipidemia, immunizations, tobacco use, dehydration, depression, patient education, and shared decision making. These programs include: Centers for Medicare & Medicaid Services (Physician Quality Reporting Measures for Group Practice Reporting option, Clinical Quality Measures for financial incentive for Meaningful Use of certified Electronic Health Record technology, Quality measures for Accountable Care Organizations), National Committee for Quality assurance: Healthcare Effectiveness Data and Information Set, and programs in our region (Blue Cross Blue Shield of Michigan: Physician Group Incentive Program clinical performance measures, Blue Care Network: clinical performance measures).

Disclosures

The University of Michigan Health System endorses the Guidelines of the Association of American Medical Colleges and the Standards of the Accreditation Council for Continuing Medical Education that the individuals who present educational activities disclose significant relationships with commercial companies whose products or services are discussed. Disclosure of a relationship is not intended to suggest bias in the information presented, but is made to provide readers with information that might be of potential importance to their evaluation of the information.

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Review and Endorsement

Drafts of this guideline were reviewed in clinical conferences and by distribution for comment within departments and divisions of the University of Michigan Medical School to which the content is most relevant: Family Medicine, General Medicine, and Nephrology. The final version was endorsed by the Clinical Practice Committee of the University of Michigan Faculty Group Practice and the Executive Committee for Clinical Affairs of the University of Michigan Hospitals and Health Centers.

Annotated References

Baigent C, Landray MJ, Reith C, et al; SHARP Investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet. 2011 Jun 25;377(9784):2181-92. Epub 2011 Jun 12.

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Beddhu S, Baird BC, Zitterkoph J, Neilson J, Greene T. Physical activity and mortality in chronic kidney disease (NHANES III). Clin J Am Soc Nephrol 2009;4(12):1901-1906

This survey provides incidence and other descriptive information regarding CKD patients.

Black C, Sharma P, Scotland G, McCullough K, McGurn D, Robertson L, *et al*. Early referral strategies for management of people with markers of renal disease: a systematic review of the evidence of clinical effectiveness, cost-effectiveness and economic analysis. *Health Technol Assess* 2010;14(21).

This summary assembles ACIP recommendations for all vaccines relevant to patients with CKD.

Chi c, Patel P, Pilishvili T, et al. Guidelines for Vaccinating Kidney Dialysis Patients and Patients with Chronic Kidney Disease – summarized from recommendations of the Advisory Committee on Immunization Practices. Atlanta, GA: Centers for Disease Control, 2012. Available at http://www.cdc.gov/vaccines/pubs/downloads/dialysis-guide-2012.pdf (accessed 3/15/13).

This review summarizes available evidence, with limited evidence concerning the role of CKD screening or monitoring in improving clinical outcomes, but evidence for CKD treatment benefit.

Fink HA, Ishani A, Taylor BC, et al. Screening for, monitoring, and treatment of chronic kidney disease stages 1 to 3: A systematic review for the U.S. Preventive Services Task Force and for an American College of Physicians clinical practice guideline. Annals of Internal Medicine 2012, 156 (8): 570-581.

This review summarizes available evidence, with limited evidence concerning the role of CKD screening or monitoring in improving clinical outcomes, but evidence for CKD treatment benefit.

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patients.

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KDIGO developed the above evidence-based and evidence-graded clinical guidelines based on systematic reviews of relevant literature. Accompanying them are details concerning the evidence and references to it. All KDIGO guidelines are available at http://www.kdigo.org (accessed 11/17/12).

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UMHS publishes these guidelines in Ann Arbor, MI. Current versions of all UMHS clinical guidelines are available through the National Guideline Clearinghouse (www.guideline.gov) and through the University of Michigan Health System (either www.med.umich.edu/1info/fhp/practiceguides/ccg.html or cme.med.umich.edu/iCME/).

VA/DoD Clinical Practice Guideline for Management of Chronic Kidney Disease in Primary Care: 2007. www.healthquality.va.gov/ckd/ckd_v478.pdf

This review provides detailed information regarding CKD management in primary care practice.