

CORE CURRICULUM IN NEPHROLOGY

Chronic Kidney Disease

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DEFINITION

- Kidney damage for ≥ 3 months, as defined by structural or functional abnormalities of kidney, with or without decreased glomerular filtration rate (GFR), manifest by either:
 - Pathological abnormalities
 - Markers of kidney damage, including abnormalities in composition of blood or urine, or abnormalities in imaging tests
- GFR < 60 mL/min/1.73 m² (< 1.00 mL/s) for ≥ 3 months, with or without kidney damage
- See Table 1

EPIDEMIOLOGY

- 7.6 million people have stage 3 chronic kidney disease (CKD); 400,000 have stage 4 CKD (National Health and Nutrition Examination Survey 1988-1994)
- 55.2 million people have estimated GFR between 60 and 89 mL/min/1.73 m² (1.00 and 1.48 mL/s)
- 4.7% of the US population had GFR < 60 mL/min/1.73 m² (< 1.00 mL/s)
- Diagnosis of CKD with GFR ≥ 90 mL/min/1.73 m² (≥ 1.50 mL/s) relies on presence of markers of kidney damage
- Prevalence of CKD stages 3 and 4 for US people older than 65 years is 20.6%
- 325,000 US people were on renal replacement therapy in 2003
- Above estimates are likely underestimates, as early stages of CKD often are unrecog-

nized, especially in the elderly and chronically ill

- Incidence and prevalence of CKD are increasing rapidly, having doubled in past decade due to enhanced longevity of patients with chronic diseases (eg, vascular disease, diabetes) and increased incidence of diabetes mellitus largely related to obesity in United States and worldwide

ESTIMATION OF KIDNEY FUNCTION

- GFR can be measured directly using parenteral inulin, iothexol, or iothalamate; however, these methodologies are not widely applied clinically
- In clinical practice, GFR is estimated by creatinine clearance (Ccr), which is directly proportional to creatinine generation from muscle and inversely proportional to serum creatinine concentration; estimation of GFR will be dependent on age, body mass, nutritional status, and laboratory measurement of creatinine

Methods for Estimation of GFR

- 24-hour urine for Ccr:
 - Patient instructed about collection of urine for 24 hours
 - Creatinine measured in blood and urine
 - Ccr calculated by following equation, where Ucr is urine creatinine and Scr is serum creatinine:

Table 1. Classification of CKD

Stage	GFR (mL/min/1.73 m ²)	Description
1	≥ 90	Kidney damage with normal or increased GFR
2	60-89	Kidney damage with decreased GFR
3	30-59	Moderately decreased GFR
4	15-29	Severely decreased GFR
5	< 15	Kidney failure

Note: To convert GFR in mL/min to mL/s, multiply by 0.01667.

From the University of Louisville, Louisville, KY.
Received February 15, 2006; accepted in revised form September 29, 2006.

Originally published online as doi:10.1053/j.ajkd.2006.09.021 on December 4, 2006.

Support: None except VA Merit Review support for laboratory research (E.L.). Potential conflicts of interest: None.

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0272-6386/06/4901-0020\$32.00/0

doi:10.1053/j.ajkd.2006.09.021

$$C_{cr} = \frac{U_{cr} \times \text{urine volume (mL)}}{S_{cr} \times 1,440 \text{ (min)}}$$

- Assumption made that creatinine excretions approximately 25 mg/kg for young healthy people, 15 to 20 mg/kg for middle-aged healthy people, and 10 mg/kg for older and chronically ill individuals
- Subject to errors in collection of urine and difficulty in determining lean body mass
- Cockcroft-Gault equation estimates C_{cr} , where P_{cr} is plasma creatinine:

$$\left[\frac{(140 - \text{age}) \times \text{weight (kgs)}}{72 \times P_{cr}} \right]$$

(multiply by 0.85 for women)

- Original description by Cockcroft and Gault is not adjusted for body surface area; it included hospitalized patients, primarily white males; age ranged from 18 to 92 years; calculation was compared to collected C_{cr}
- Modification of Cockcroft-Gault to account for body surface area:

$$\text{Cockcroft-Gault} \times \frac{1.73}{.00718 \times (\text{cm}^{.725}) \times (\text{kg}^{.425})}$$

- Modification of Diet in Renal Disease (MDRD) equation estimates GFR (where P_{cr} is plasma creatinine, SUN is serum urea nitrogen, and Alb is albumin):

$$170 \times (P_{cr})^{-0.999} \times (\text{Age})^{-0.176} \times (\text{SUN})^{-0.017} (\text{Alb})^{+0.318} \times (0.762 \text{ if patient is female}) \times (1.180 \text{ if patient is black})$$

- “Four-variable” abbreviated MDRD equation (where S_{cr} is serum creatinine):

$$186 \times (S_{cr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.20 \text{ if African-American})$$

- MDRD study population was 88% white and only 6% diabetic; calculation was compared to ^{125}I -iothalamate measure-

ment of GFR; MDRD equation may underestimate GFR in early CKD

- Urea clearance:
 - When comparing iothalamate to C_{cr} and urea clearance, C_{cr} exceeds the GFR because of tubular secretion whereas urea clearance is usually lower than GFR because of tubular absorption
- Cystatin C:
 - A low-molecular-weight protein produced by all human nucleated cells
 - A serum marker of kidney insufficiency and may improve detection of early CKD
 - Preliminary studies have demonstrated superior estimation of GFR by cystatin C in children, transplant patients, and cirrhotics; notably, cystatin C appears to be more sensitive for detection of early CKD than serum creatinine

RISK FACTORS FOR DEVELOPMENT OF CKD

- Underlying disease:
 - Hypertension
 - Diabetes
 - Dyslipidemia
- Lifestyle factors:
 - Tobacco
 - Inactivity
- Family history
- Aging
- Prenatal factors:
 - Maternal diabetes mellitus
 - Low birth weight
 - Small-for-gestational-age status

RECOMMENDATIONS FOR SCREENING

- People at high risk should have urinalysis, including microalbumin testing, and imaging studies
- Urinalysis should include dipstick, microscopic, and determination of microalbuminuria:
 - Patient should be instructed to give mid-stream “clean-catch” specimen, including instruction on retracting the foreskin or labia; a first-void morning specimen, which is most likely to be acidic and concentrated, should be used whenever possible; specimens from concentrated and acidic urine may be expected to have greater density of formed elements than

dilute and alkaline specimens from same patients

- Dipstick usually includes color, pH, leukocytes, nitrite, protein, glucose, ketones, urobilinogen, bilirubin, blood, and hemoglobin
- For the microscopic specimen, urine should be centrifuged at approximately 2,000 revolutions per minute for 5 to 10 minutes; supernatant should be carefully poured off, pellet resuspended by gentle agitation, and a drop placed on slide under coverslip; urine should be examined for cells, casts, and crystals
- Microalbuminuria has been defined as urine albumin excretion of 30 to 300 mg/d and can be assessed by albumin-specific dipsticks or spot urines for albumin-to-creatinine ratios; exclusion of urinary tract infection is necessary for proper interpretation of microalbuminuria
- Dipsticks 1+ or greater should have protein-to-creatinine ratio or albumin-to-creatinine ratio done
- Future may include serum cystatin C or other novel urinary markers
- Renal ultrasound is quick, noninvasive modality for rapidly and accurately evaluating most structural abnormalities:
 - Scanning technique provides accurate determination of kidney size, assessment of cortical thickness, and echogenicity
 - Diseases leading to CKD (eg, polycystic kidney disease) can be diagnosed by ultrasound

PROGRESSION OF RENAL DISEASE

- Factors contributing to progression of renal disease:
 - Activation of renin-angiotensin-aldosterone system produces glomerular hypertension and activates fibrotic pathways
 - Hypoxia stimulates several pathways through activation of hypoxia-inducible factor, leading to increased production of free radicals, and apoptosis of tubular epithelium
 - Aberrant mineral metabolism contributes to development of vascular calcification
 - Increased oxidative stress produced by above factors, advanced glycation end

products, and nitric oxide deficiency augment effects of hypoxia

- Systemic hypertension contributes to glomerular hypertension
- Failure of replicative/repairative mechanisms such as the decreased number and function of circulating endothelial cells diminishes ability to regenerate damaged tissue
- Inflammation resulting from above factors and primary immune disease perpetuates the cycle of hypoxia, fibrogenesis, and oxidative stress
- Rate of GFR decline:
 - Can be determined by graphing $1/cr$ over time
 - Acceleration in rate of GFR decline as manifested by change in slope of curve should trigger workup for potentially reversible cause of worsening renal function; this tool can be used to assess efficacy of interventions designed to slow progression of CKD
- Interventions to block progression:
 - Blockade of renin-angiotensin system is beneficial in most CKD whether by use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, or combinations of these agents
 - Decreasing proteinuria decreases progression to end-stage kidney disease; recommended level of proteinuria, <0.3 g/24 h
 - Lifestyle changes:
 - Smoking cessation may reduce disease progression 30%
 - Exercise even without change in body mass index may decrease proteinuria
 - Treatment of underlying risk factors:
 - Decreasing low-density lipoprotein (LDL) cholesterol <100 mg/dL (<2.59 mmol/L)
 - Decreasing blood pressure $<130/80$ mm Hg
 - Decreasing glycohemoglobin (HbA1c) $<7.5\%$
 - Early nephrology consultation:
 - Timing of referral not definitively established; recent studies suggest early referral results in improved mortality
 - Advantages of early referral include:

- Ability to detect and treat potentially reversible renal disease
- Patient education regarding potential nephrotoxins
- Management of CKD-related complications (eg, anemia, metabolic acidosis, and hyperphosphatemia) that primary care physicians are unfamiliar with and therefore unlikely to identify and manage effectively
- Patient referral to CKD multidisciplinary clinics for CKD education
- Adequate preparation time for end-stage renal disease therapy, including arteriovenous fistula placement and preemptive transplant, both of which may take in excess of 12 months time; fistula preparation includes:
 - Identification of suitable extremity by physical examination and either ultrasound or magnetic resonance imaging of venous structures of upper extremity
 - Education of patient in “protection” of chosen extremity including avoidance of needle sticks, central venous access, peripherally inserted central catheters lines, and blood pressure monitoring
 - Referral to competent and experienced vascular surgeon 6 to 12 months (12 preferable) before anticipated need for hemodialysis
- Avoid episodes of acute kidney failure that may accelerate decline in kidney function in CKD

COMPLICATIONS OF CKD: BONE/MINERAL, HEART, ANEMIA, ACIDOSIS, MALNUTRITION

- Elevations of phosphorus occur with decreases in Ccr around 50 to 60 mL/min (0.83 to 1.00 mL/s); this primary event triggers the following:
 - Diminished vitamin D production
 - Hypocalcemia due to diminished vitamin D production
 - Secondary hyperparathyroidism due to hypocalcemia, hypovitaminosis D, and hyperphosphatemia
- Metabolic bone disease
- Vascular calcification, although link between above events and vascular calcification has not been definitively determined
- Treatment recommendations based on studies performed almost exclusively in patients on dialysis and therefore predominantly opinion-driven; these include:
 - Phosphate metabolism:
 - Dietary phosphate restriction 800 to 1,000 mg/d
 - Administration of phosphate binders with meals to minimize phosphate absorption and phosphate retention:
 - Aluminum-containing binders are avoided due to aluminum toxicity associated with long-term use: severe anemia, painful osteomalacia, dialysis dementia
 - Calcium-containing binders are widely used but may be associated with the development of vascular calcification
 - Polymeric binders (only formulation available is sevelamer) are becoming preferred alternative to calcium-containing binders due to their lack of absorption and ability to lower LDL cholesterol
 - Lanthanum-containing binders have been released recently; their advantage is potency but long-term effects are unknown
 - Vitamin D and PTH metabolism:
 - Determination of vitamin D (including measurement of 25- and 1,25-vitamin D levels) and parathyroid hormone (PTH) status:
 - If 25-hydroxyvitamin D low (<30 ng/mL [<75 nmol/L]), replace with oral ergocalciferol unless patient develops severe hypercalcemia (>10.2 mg/dL [>2.54 mmol/L]) or hyperphosphatemia
 - If intact PTH >70 for stage 3 or >110 pmol/L for stage 4, initiate PTH-lowering measures as listed below to achieve intact PTH level

- of 35 to 70 pmol/L for stage 3 or 70 to 110 pmol/L for stage 4 CKD
 - Administration of vitamin D and vitamin D analogues:
 - Calcitriol has efficacy in reducing serum PTH levels but is associated with significant hypercalcemia
 - 1α -hydroxyergocalciferol (doxercalciferol) and 19-nor-paricalcitol have less hypercalcemia with similar PTH-suppressing efficacy
 - One recent study suggests that paricalcitol may confer mortality benefit over calcitriol in patients on dialysis
 - Applicability to stage 3 and 4 CKD patients is unknown
 - Administration of calcium-sensing receptor agonists:
 - Advantage is lack of calcemic effect and potential for ameliorating vascular calcification
 - Major side effects are hypocalcemia and nausea
 - Long-term studies in stages 2 to 4 CKD are lacking
 - Parathyroidectomy:
 - Generally not required for stages 2 to 4 CKD, as degree of secondary hyperparathyroidism usually manageable
- CKD is associated with increased risk for cardiovascular disease, even at very early CKD stages; many nontraditional risk factors, including vascular calcification, hyperhomocysteinemia, anemia, oxidant stress, dyslipidemia, elevated levels of asymmetric dimethylarginine, and inflammation, as well as traditional risk factors, such as hypertension and glucose intolerance, appear to contribute to risk
 - Pathophysiology:
 - Hypertension occurs in 50% to 75% of patients with CKD; mechanisms include chronic volume overload, chronic stimulation of the renin-angiotensin-aldosterone and sympathetic nervous systems, endothelial dysfunction due to oxidative stress and inflammation, and vascular calcification
 - Vascular calcification is associated with accelerated risk of stroke, amputation, and myocardial infarction through loss of vessel compliance and contributes to left ventricular hypertrophy, poor coronary artery perfusion, increased pulse wave velocity, and increased pulse pressure; factors contributing to development of vascular calcification include deranged bone and mineral metabolism, decreased levels of inhibitors of calcification such as fetuin A, stimulation of osteogenic pathways in endothelial cells by uremic “toxins,” and impaired endothelial repair mechanisms
 - Anemia is associated with development of left ventricular hypertrophy and failure; frequency of cardiac hypertrophy is inversely related to degree of anemia in CKD patients; of note, treatment of anemia in heart failure not associated with CKD ameliorates degree of heart failure
 - Lipid profile in CKD associated with nephrotic syndrome shows hypercholesterolemia with severe elevations in serum LDL levels; in contrast, lipid profile in nonproteinuric CKD, especially advanced CKD, is frequently characterized by normal to low total cholesterol levels, low high-density lipoprotein levels, relatively elevated serum LDL levels, and elevated triglycerides; CKD also associated with elevated levels of lipoprotein a
 - Elevated levels of homocysteine, advanced glycation end products, and C-reactive protein are associated with higher mortality
 - Endothelial dysfunction contributes to enhanced cardiovascular mortality in patients with CKD
 - Recommendations to address all risk factors are made (although controlled studies demonstrating efficacy are lacking):
 - General:
 - Institute lifestyle changes including maintenance of normal body mass index, restriction of salt and satu-

- rated fat in diet, increased level of exercise, cessation of smoking, intense glycemic control to achieve HbA_{1c} level 7.0%, and moderation of alcohol intake
- Hypertension:
 - Control blood pressure to level of <130/80 mm Hg
 - Preferentially use maximal doses of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers in proteinuric and diabetic patients with CKD; monitor serum potassium and renal function; decrease or discontinue agents if potassium consistently exceeds 5.5 mg/dL or if renal function deteriorates greater than 30% from baseline within 4 months
 - Anemia:
 - Monitor hemoglobin and hematocrit every 3 to 6 months during CKD stages 2 to 4
 - Treat anemia to maintain hematocrit at 12 mg/dL through the use of iron and erythropoietic-stimulating agents; beneficial effects of these agents have been attributed to their anemia-ameliorating effects, however a potential role for erythropoietin (EPO) and darbepoietin in directly modulating endothelial and cardiac function is under investigation
 - Vascular calcification:
 - Strict control of serum phosphorus and serum calcium to maintain phosphorus <4.6 mg/dL (<1.49 mmol/L), calcium <9.5 mg/dL (<2.37 mmol/L), and calcium-phosphate product <55
 - Restrict dietary phosphorus ingestion to 800 to 1,000 mg/d
 - Restrict dietary calcium ingestion to <2,000 mg/d but not <1,500 mg/d
 - Role of vitamin D in development of vascular calcification is controversial; evidence for direct deleterious effect of vitamin D on process is lacking, furthermore there is evidence that vitamin D antagonizes activation of renin angiotensin system and plays role in immune function; therefore, avoidance of vitamin D deficiency is warranted as outlined above
 - Role of PTH in development of vascular calcification also controversial; recommendation is to maintain serum PTH at levels recommended for maintenance of bone health
 - Early studies suggested thiosulfate may prove useful in prevention or even treatment of established vascular calcification
 - Anemia of renal disease is multifactorial:
 - Mechanisms of anemia:
 - EPO deficiency
 - Blood loss through frequent blood draw and increased tendency toward gastrointestinal bleeding due to diminished platelet function
 - Decreased red blood cell lifespan
 - Complications of anemia include:
 - Left ventricular hypertrophy and failure
 - Poor quality of life
 - Impaired intellectual functioning
 - Recommendations are to treat anemia aggressively:
 - Assess nutritional factors including iron stores, vitamin B12, and folate
 - Replete nutritional deficiencies promptly; target ferritin 200 to 500 ng/mL ($\mu\text{g/L}$); may need to use intravenous iron formulations if unable to achieve target stores
 - Administer erythropoietic agents to maintain hematocrit 33% to 36%
 - Failure of anemia to respond to exogenous EPO should prompt search for other factors (eg, nutritional deficiencies, bone marrow infiltrative disorders, chronic inflammatory conditions, or bleeding, especially gastrointestinal)
 - Adherence to regimen enhanced by use of biweekly or monthly injections

- as opposed to twice- or thrice-weekly injections
- Metabolic acidosis:
 - Characteristics:
 - Normal or high anion gap
 - Plasma bicarbonate 12 to 22 mEq/L (mmol/L)
 - Inability to enhance bicarbonate generation with acid load
 - Mechanisms include:
 - Impaired renal acidification processes, including renal tubular acidosis
 - Impaired ammoniogenesis due to declining renal mass as well as hyperkalemia
 - Impaired excretion of titratable acid, especially in patients with poor dietary phosphate intake
 - Loss of nephron mass
 - Complications include:
 - Chronic bone loss due to suppression of 1 α hydroxylase and chronic bone buffering of acid load
 - Muscle wasting due to accelerated muscle breakdown
 - Anorexia and weight loss
 - Hypoalbuminemia
 - Acceleration of deterioration of renal function
 - Impaired cardiac function
 - Insulin resistance
 - Abnormal growth hormone and thyroid hormone function
 - Treatments include:
 - Supplemental sodium bicarbonate to maintain serum bicarbonate level at 22 mEq/L (mmol/L)
- Malnutrition:
 - Potential mechanisms include:
 - Anorexia
 - Imposed dietary restrictions
 - Accelerated protein catabolism
 - Chronic inflammation
 - Complications include:
 - Hypoalbuminemia, hypocholesterolemia
 - EPO hyporesponsiveness
 - Growth retardation (children)
 - Progressive muscle weakness, poor exercise tolerance, and debilitation
- Increased mortality
- Treatment:
 - Nutritional assessment to include dietary history, serum albumin, prealbumin, vitamin B12, transferrin, 25-hydroxyvitamin D, and 24-hour urine for urea nitrogen excretion
 - Protein intake 0.6 g/kg/d for CKD stages 4 to 5, 0.75 g/kg/d for earlier stage CKD
 - Energy intake of 30 kcal/kg/d for CKD stages 4 to 5, higher for earlier stage CKD
- Increased infection risk:
 - Potential mechanisms include:
 - Nutrient deficiency including vitamin D
 - Decreased B-cell, T-cell, and macrophage function due to uremic toxins
 - Diminished mucocutaneous barrier due to dry skin, gastrointestinal ulcerations, poor mucus clearance from airways
 - Complications include:
 - Increased infection risk
 - Decreased response to vaccination
 - High mortality rates
 - Second most common cause of death in CKD patients
 - Treatment:
 - Attention to personal and personnel hygiene
 - Enhance nutritional status
 - Aggressive vaccination including routine Hepatitis B, pneumococcus, and influenza vaccination and booster, which results in lower rates of hospitalization and death
 - Vaccination for hepatitis A, tetanus, varicella, *Haemophilus influenzae* also considered
- General measures for CKD:
 - Dose adjust medications
 - Avoid nephrotoxic agents
 - Early referral to nephrology
 - Patient education

ADDITIONAL READING

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