Chronic Kidney Disease
Update

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Objectives

- Define CKD
- Discuss patients at risk
- Identify the stages of CKD
- Understand the consequences of CKD
- Learn how to treat the sequelae of CKD
- Apply above knowledge to daily practice
Definition

- Kidney damage or decreased function for > 3 mos
- Damage could be based upon imaging, biopsy or urinary markers
- Decreased function is usually noted by the eGFR
- Doesn’t identify a cause
- Doesn’t imply symptoms
Introduction

- Disproportionate financial resources consumed by ESRD patients
- NIH and Surgeon General’s Office are attempting to educate the public
- Nephrology work force shrinking
- Burden of work up and management falls on PCP’s
KDOQI

- Kidney Disease Outcome Quality Initiative 1997, mgd by the NKF (www.kidney.org)
- Evidence based clinical practice guidelines
  - Mgmt of CKD
  - Mgmt of related consequences of CKD
- Updated periodically
- www.kdoqi.com
KDIGO

- Kidney Disease Improving Global Outcomes, 2004
- Global non-profit organization mgd by NKF
- promotes coordination & collaboration to develop & implement practice guidelines
- 2012 released comprehensive set of guidelines
- www.kdigo.com
Patients at Risk

- Advanced age
- DM
- HTN
- + Family History
- Hx of ARF
- Obesity
- Smokers
- HIV
- Most minorities
- NSAID users
- Low income/education
- Reduced kidney size
- Hepatitis C
- Metabolic syndrome
- CT diseases
Symptoms

- Usually asymptomatic
- Edema/fluid retention
- Urinary symptoms occasionally
- Arthralgias, rash
- Vascular symptoms (angina, claudication)
- Wt loss, paresthesias, back pain
- Uremic symptoms
Detection of CKD

- New onset HTN
- Urinalysis with blood or protein
- ‘routine’ labs with abnormal BUN and creatinine
- Imaging study showing abnormal renal anatomy
Serum Creatinine

- Wide range of normal
  - interpret in the clinical context
- 10% lab error in serum creatinine depending upon calibration of serum creatinine assays
- Used to calculate the GFR
Creatinine Clearance

- **Inulin is the gold standard**
  - Impractical

- **Radionuclide and radiocontrast markers**
  - $^{123}\text{I}$-orthoiodohippuran
  - radioiodinated hippuran
  - Iohexol
  - $^{99m}\text{Tc}$-DPTA or $^{99m}\text{Tc}$-MAG$_3$
24 Hour Urine Collections

• Cumbersome, fraught with patient error, noncompliance

• Utility in select patients (where formulae are inaccurate):
  – Extremes of age and body size
  – Severe malnutrition or obesity
  – Diseases of skeletal muscle
  – Para/quadriplegia
  – Vegetarian diet
GFR

- Glomerular filtration rate = GFR
- GFR doesn’t equal creatinine clearance
- Multiple formulae
  - MDRD
  - CKD-EPI
- Formulae have limitations
MDRD

- 1999, new version 2007
- Requires steady state
- Falsely elevated in states of malnutrition (nephrosis, liver disease, vegetarian diet), high meat diet
- Less accurate in extremes of disease (high GFR and low GFR), extremes of body size and age
CKD-EPI

• 2009, CKD Epidemiology Collaboration Eq
• Slightly more precise & accurate, esp GFR > 60
• Should reduce over reporting of CKD
  – reduces prevalence of CKD 45 y/o
  – increases prevalence of CKD > 65 y/o
• No African Americans included in studies (done in Europe)
Diagnostic Studies

- Serology
- Urine studies
- Renal US (doppler if indicated)
- Determine CrCl (know limitations)
Serology

- BMP, phos, albumin, total protein, chol
- CBC
- Serum immunofixation if > 50yrs
- Intact PTH if GFR < 60
- Further serology may be warranted
Urine Studies

- **Urinalysis**
  - Assume: quality sample, no infection
  - Evaluate: sp gr, pH, blood, protein

- **Urine sediment**: WBC, RBC, crystals, casts

- **Urine immunofixation** if > 50 years
Proteinuria

- Urine dipstick
  - Misses light chains, microalbumin
  - Concentration dependent
- Urine microalbumin
  - Qualitative or quantitative
- Spot urine for total protein to creatinine ratio **
  - First morning sample is preferred
Proteinuria

- 24 hour collection
  - Assure specimen adequacy by creatinine secretion (varies with gender and age)
  - Largely being replaced by spot tests
- > 3 gms/day suggests glomerular in origin
  - Specifically epithelial cell
- < 1 gm/day suggests tubular origin
Renal Ultrasound

- R/O obstruction
- Assess kidney size
- Cortical thickness
- Cortical echogenicity
- Evaluate for PCKD
Renal Artery Dopplers

- Asymmetric kidneys
- Cortical thinning
- Hypertension
- PVD, bruits or high suspicion
CT Scan

- Imaging of choice in the setting of nephrolithiasis
- May be beneficial in setting of other diseases to identify more anatomy
- Obvious limitation of contrast
<table>
<thead>
<tr>
<th>Imaging Modality/Feature</th>
<th>Associated Kidney Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ultrasonography</strong></td>
<td></td>
</tr>
<tr>
<td>General appearance</td>
<td>May show nephrocalcinosis or discrete stones, hydrenephrosis, cysts or masses.</td>
</tr>
<tr>
<td>Increased echogenicity</td>
<td>May indicate cystic disease or “medical renal disease.”</td>
</tr>
<tr>
<td>Small, “hyperechoic” kidneys</td>
<td>Generally indicate chronic kidney disease.</td>
</tr>
<tr>
<td>Large kidneys</td>
<td>Generally indicate tumors, infiltrating diseases or diseases causing nephrotic syndrome.</td>
</tr>
<tr>
<td>Size disparities and scarring</td>
<td>Suggest vascular, urologic or tubulointerstitial diseases due to stones or infection.</td>
</tr>
<tr>
<td>Doppler interrogation</td>
<td>May be useful in investigation of venous thrombosis, less so in arterial stenosis.</td>
</tr>
<tr>
<td><strong>Intravenous pyelography (IVP)</strong></td>
<td>May reveal asymmetry of kidney size or function, presence of obstructing stones, tumors, scars, or dilated collecting ducts in medullary sponge kidney.</td>
</tr>
<tr>
<td><strong>Computed tomography (CT)</strong></td>
<td>May show obstruction, tumors (e.g. angiomyolipoma), cysts or ureteral calculi. Helical CT with contrast may show sites of anatomic renal artery stenosis.</td>
</tr>
<tr>
<td><strong>Magnetic resonance imaging</strong></td>
<td>May show mass lesions, renal vein thrombosis, cysts, etc. MR angiography using gadolinium may be useful in patients with decreased kidney function.</td>
</tr>
<tr>
<td><strong>Nuclear scans</strong></td>
<td>May reveal asymmetry of kidney size or function, functional evidence of renal artery stenosis, acute pyelonephritis, or scars.</td>
</tr>
</tbody>
</table>

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\[a\] This modality has been largely supplanted by computed tomography, although it remains useful to describe fine detail in the collecting system.

\[b\] With or without contrast

\[c\] Captopril renography, mercaptoacetyltriglycine (MAG3), dimercaptosuccinic acid (DMSA)
### Stages of Chronic Kidney Disease

**National Kidney Foundation–Kidney Disease Outcome Quality Initiative**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage w/ normal GFR</td>
<td>&gt;90</td>
</tr>
<tr>
<td>2</td>
<td>Mild decrease in GFR</td>
<td>60-89</td>
</tr>
<tr>
<td>3a</td>
<td>“early” moderate kidney dysfunction</td>
<td>45-59</td>
</tr>
<tr>
<td>3b</td>
<td>“late” moderate kidney dysfunction</td>
<td>30-44</td>
</tr>
<tr>
<td>4</td>
<td>Severe kidney dysfunction</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt; 15</td>
</tr>
</tbody>
</table>
Stages of CKD

- Cut-offs are arbitrary, based upon informed opinion
- Progression of kidney disease varies depending upon disease entity and patient
Consider the Causes

- Diabetic kidney disease
- Nondiabetic kidney disease
  - Tubulointerstitial diseases
  - Vascular diseases
  - Glomerular diseases
  - Cystic diseases
Initiation factors

- Diabetes mellitus
  - Classic presentation
- Hypertension
  - Other end organ damage
- CHF, global ischemia
- ASVD, hyperlipidemia
- Autoimmune diseases
- OSA

- Urinary tract infections
  - recurrent
- Nephrolithiasis
- Obstruction (BPH)
- Drug toxicity (NSAIDS)
- Systemic infections (HIV, hepatitis)
Exposures

• Occupation
  – Lead (soldering), mercury or cadmium

• Cigarette use

• Alcohol, particularly moonshine

• STD’s or IVDA

• NSAID(s) (particularly combination)

• ACE-I, ARBs, diuretics (reversible)
Exposures

- Herbal remedies (aristolochic acid, Ma Huang or Ephedra, ayurveda)

- Arsenic #1 heavy metal contaminant in over 50% of about 250 randomly sampled Chinese herbs (Australia), mercury, Cd, Pb all present

- Complementary and alternative medication use soaring (40% between 30-70)
Promoters of Progression

• Higher levels of proteinuria (nephrotoxic)
• Poorly controlled blood pressure
• Poorly controlled sugars
• Elevated cholesterol
• Cigarette smoking
• Nephrotoxins
• High protein diets?
Slow Progression

- Control HTN
- Avoid nephrotoxins, adjust medications
- Early treatment of obstruction, infections
- Tight sugar control in diabetics
- Protein restriction?
- Cholesterol control?
Clinical Consequences

- Fluid Overload
- Hypertension
- Electrolyte abnormalities
- Metabolic acidosis
- Hyperparathyroidism
- Anemia
- Accelerated CV disease
- Malnutrition
Clinical Consequences

• Prevalence increases significantly once GFR < 45 ml/min
• CKD stages 3b, 4, 5
Fluid Overload

- Ability to excrete salt and water is limited
- Restrict oral salt intake
- Because thiazide diuretics alone are often ineffective in CKD, high doses of loop blocking diuretics are required
- Goal is a negative salt balance
- Lasix best dosed b.i.d.
Hypertension

- Both a cause and complication of CKD
- Diuretics, fluid mgmt are the cornerstone
  - Often mediated by volume retention
- ACE-I or ARBs if no renovascular disease
- BP goal (KDOQI/KDIGO):
  - < 130/80 mmHg if proteinuric (> 500mg/day)
  - < 140/90 mmHg if not proteinuric
Hypertension

- Conservative measures
- Individualize the treatment depending upon clinical scenario
Hyperkalemia

- Maintain K⁺ homeostasis until GFR < 25 ml/min
- ACE-I, ARBs, NSAIDs, K sparing diuretics, non-selective beta-blockers, digoxin
- Treat metabolic acidosis
- Limit oral intake
- Loop diuretics
- Exchange resins
Metabolic Acidosis

- Once GFR < 25 ml/min
- Impaired renal NH3 production
- Reduced bicarbonate reabsorption
Metabolic Acidosis

• Treat with oral alkali
  – Maintain serum CO\textsubscript{2} normal
  – 1 meq/kg maintenance

• Options: NaHCO\textsubscript{3}, baking soda, NaCitrate

• New studies suggest treating may reduce progression of CKD

• Less fluid overload with NaHCO\textsubscript{3} in recent study
Metabolic Bone Disease

- Manifest as bone pain, pathologic fractures and decreased bone density
- Hyperphosphatemia
  - From decreased GFR
  - Reduced renal synthesis of 1,25-dihydroxy D3
- Hypocalcemia
  - From vitamin D deficiency
Metabolic Bone Disease

- Elevation of PTH may start in Stage 2 CKD
  - Secondary hyperparathyroidism (HPTH)
- Many forms of metabolic bone disease
- Diagnose by bone bx (rarely done)
- High turnover bone disease (HPTH) requires treatment
# PTH Goal

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>KDOQI iPTH target (pg/mL)</th>
<th>KDIGO iPTH target (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>35-70</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>70-110</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>150-300</td>
<td>2-9 X ULN</td>
</tr>
</tbody>
</table>
HPTH Treatment Options

- **Vitamin D receptor agonists:**
  - Calcitriol 0.25mcg/day starting dose
  - Doxercalciferol 0.5mcg/day starting dose
  - Paracalcitriol 1mcg/day starting dose

- Repeat iPTH, calcium and phos in one month after starting therapy

- Watch for hypercalcemia, stop therapy if CaxPhos > 80
## Calcium and Phosphorous

<table>
<thead>
<tr>
<th></th>
<th>KDOQI</th>
<th>KDIGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>8.4-9.5 mg/dL</td>
<td>Normal range</td>
</tr>
<tr>
<td>Phosphorous</td>
<td>2.7-4.6 mg/dL in CKD stage 3-4</td>
<td>Normal range CKD stage 3-5</td>
</tr>
<tr>
<td>Calcium intake</td>
<td>&lt; 2000 mg/day including supplements in CKD stage 5</td>
<td></td>
</tr>
<tr>
<td>Phosphorous intake</td>
<td>800-1000 mg/day in CKD stage 5</td>
<td></td>
</tr>
</tbody>
</table>
Hyperphosphatemia

- Low phosphorous diet, 800-1000mg/day
- Phosphorous binders with meals if dietary intervention ineffective
  - Tums, Phoslo 667mg, Renagel 800mg, Renvela 800mg, Fosrenol 500mg (all with meals)
  - Aluminum and magnesium binders avoided
- Ca x Phos product < 55 mg/dL
Calcimimetic Therapy

- Cinacalcet (*Sensipar*)
- Binds to transmembrane domain of the calcium sensing receptor in the parathyroid gland and renal tubules
- For the treatment of HPTH
- Ca and Phos levels decline (as opposed to vitamin D therapy)
Vitamin D

- 25-hydroxyvitamin D level should be monitored initially if PTH elevated
- Supplement if < 30 ng/mL with Ergocalciferol (KDOQI guideline) in stages 3-4
- Recommendation based upon opinion
Anemia

- Normocytic normochromic anemia
- Reduced erythropoietin production from interstitial cells
- Shortened RBC survival, iron and folate deficiencies contribute
- Clinical manifestations include fatigue, dyspnea, depression, etc.
Anemia

- Exclude other causes first
- Treatment with ESAs:
  - Recombinant human erythropoietin 80-120U/kg/week, other options now available darbopoeitin, etc
  - Essentially all require iron supplementation
- Watch blood pressure with procrit therapy
- Goal Hgb 10-11 g/dL
Erythropoietin Stimulating Agents

**Risks**

- Exacerbation of HTN
- Thromboembolism
- CV events

**Benefits**

- Reduction in transfusions (important prior to transplant)
- Surveys show improved QOL
CV disease

• Abnormal lipids can be treated with:
  – Dietary intervention
  – Achieve desirable body weight
  – HMG CoA reductase inhibitor

• CKD accelerates CV disease

• Proteinuria is a risk factor for CV disease
CV disease

- ESRD patients are at 20x the risk of CV disease as age matched controls
- CV disease accounts for ~ 50% of deaths of ESRD patients
- 15% of ESRD patients have normal LVs (by echo)
Malnutrition

- Multiple serum markers of nutrition: albumin, cholesterol, SGA, nPCR
- *Serum albumin correlates with mortality in ESRD patients*
- CKD patients benefit from regularly seeing dietitians
Protein Restriction

- Studies vary, controversial
- NIH guidelines suggest:
  - GFR 25-55 ml/min 0.8 g/kg/day
  - GFR 13-25 ml/min 0.6 g/kg/day
- Proteinuric patients may benefit most
- Must be done under guidance of RD
- Correlation of low albumin with mortality
Nephrotoxins

- Contrast dye
- NSAIDs and COX-2 inhibitors
- OTCs (herbals, supplements)
- Select antimicrobial and antifungal agents
  - Aminoglycosides, amphotericin B
- Immunomodulators
  - Cyclosporine, tacrolimus
Cholesterol

- Statins are agents of choice
  - May reduce proteinuria
  - Mesangial cell modifications
  - No strong data to suggest preservation or improvement in GFR
- LDL < 100 is goal
- Some data suggest that fasting triglycerides ≥ 500 should be treated
Management

- Identify reversible causes of CKD
- Control known factors that lead to progression of CKD
- Many aspects of treatment are not specific to the cause of the renal disease
# Clinical Action Plan for CKD

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR (ml/min)</th>
<th>Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt;90</td>
<td>Diagnosis and treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slow progression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CVD risk reduction</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
<td>Estimating progression</td>
</tr>
<tr>
<td>3</td>
<td>30-59</td>
<td>Evaluating and treating</td>
</tr>
<tr>
<td></td>
<td></td>
<td>complications</td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>Preparation for RRT</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15</td>
<td>RRT if uremic</td>
</tr>
</tbody>
</table>
Nephrology Referral?

• NIH suggested to refer when Scr > 1.5 mg/dL in women and > 2.0 mg/dL in men
• VHA suggests to refer if CrCl < 25 ml/min or Scr > 4 mg/dL
• Clinical practice guidelines suggest referral when GFR < 30 ml/min or stage 4 CKD
• Lower threshold for referral when nephrotic (pathology changes mgmt 86%)
Nephrology Referral?

- Risk factors for progression:
  - Proteinuria > 500 mg/day
  - Uncontrolled or difficult to control progression

- Identify trend in creatinine, stability may allow for monitoring without referral
Early Referral

- **Avoids:**
  - urgent dialysis
  - severe metabolic abnormalities
  - fluid overload
  - catheter access
  - delay in transplant referral

- **Provides:**
  - lowers initial hospital cost
  - patient choice of modality
  - lower 1 year mortality
  - Education on modality
  - Access placement
Conclusions/Summary

• Qualify & quantify primary renal disease
• Slow the progression
• Identify the clinical consequences
• Prevent and or treat the clinical consequences
• Modify the diet
• Watch medications, avoid nephrotoxins
Questions?