Chronic Kidney Disease for the Internist
May 30, 2014, Alabama ACP Chapter Meeting

Errol D. Crook, MD
Abraham A. Mitchell Professor and Chair, Department of Medicine
University of South Alabama College of Medicine
Objectives

- At the end of this session the attendees should:
  - 1) Understand the definition of chronic kidney disease (CKD).
  - 2) Understand the epidemiology of CKD.
  - 3) Understand the common co-morbidities and complications of CKD.
  - 4) Understand better the basic treatment of complications of CKD.
Chronic Kidney Disease (CKD) Epidemiology

• CKD is common.

• Estimated that up to 31 million adults in US with chronic kidney disease.
  – 14% of US populations age 20 and older
  – (United States Renal Data System (www.usrds.org))
Chronic Kidney Disease (CKD) Epidemiology

• CKD mortality: 14/100,000 (9th leading cause of death)

• More than 82,000 people with endstage renal disease (ESRD) die each year.

• More than 470,000 people relying on dialysis or transplantation.

• More than 70,000 on waiting list for transplant. (Only ~17,000 will get a new kidney each year.)

*Per million U.S. population.

CDC MMWR, 53(39):918-920
## Cost of CKD

<table>
<thead>
<tr>
<th>Group</th>
<th>Cost (per person per year $’s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Medicare</td>
<td>$11,103</td>
</tr>
<tr>
<td>CKD</td>
<td>$23,128</td>
</tr>
<tr>
<td>Medicare no CKD, DM, CHF, ESRD</td>
<td>$8,245</td>
</tr>
<tr>
<td>CKD 4 or 5</td>
<td>$27,715</td>
</tr>
<tr>
<td>CKD 4 or 5 with CHF (White)</td>
<td>$37,794</td>
</tr>
<tr>
<td>CKD 4 or 5 with CHF (Black)</td>
<td>$40,650</td>
</tr>
</tbody>
</table>

Definition of Chronic Kidney Disease (CKD)

1. Kidney damage for at least 3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by either
   Pathological abnormalities; or
   Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests

2. GFR <60 mL/min/1.73 m² for at least 3 months, with or without kidney damage
JNC 7 Definition of CKD

Estimated GFR < 60 ml/min/1.73 m² or

Albuminuria 300 mg/d or
200 mg/g creatinine (spot urine)
# Stages of Renal Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>GFR &gt; 90 ml/min with presence of proteinuria or microalbuminuria</td>
</tr>
<tr>
<td>Stage 2</td>
<td>GFR between 60 - 89 ml/min (mild)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>GFR between 30 – 59 ml/min (moderate) (Stage 3b 30 – 44 ml/min)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>GFR between 15 – 29 ml/min (severe)</td>
</tr>
<tr>
<td>Stage 5</td>
<td>GFR &lt; 15 ml/min (Kidney failure, ESRD)</td>
</tr>
</tbody>
</table>
Complications of CKD by CKD Stage

- HTN
- Unable to walk 1/4 mile
- Ca++ < 8.5
- Hgb < 12
- Alb < 3.5
- PO4 > 4.5
Factors to Consider When Estimating Glomerular Filtration Rate

• Creatinine
• Age
• Weight (muscle mass)
• Gender
• Ethnicity (?)
• Is creatinine stable?
# Equations to Predict GFR

<table>
<thead>
<tr>
<th>Method</th>
<th>Equation</th>
</tr>
</thead>
</table>
| MDRD                                        | \[
GFR (\text{mL/min/1.73 m}^2) = 170 \times (S_{\text{Cr}})^{-0.999} \times (\text{age})^{-0.176} \times (\text{BUN})^{-0.170} \times (\text{albumin})^{+0.318} \times (0.762 \text{ if female}) \times (1.180 \text{ if black})
\] |
| Modified (abbreviated) MDRD                 | \[
\text{Estimated GFR (mL/min/1.73 m}^2) = 186 \times (S_{\text{Cr}})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})
\] |
| Cockcroft–Gault                             | \[
\text{Creatinine clearance (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight}) \times (0.85 \text{ if female})}{72 \times S_{\text{Cr}}}
\] |
| 24-hour urine collection                    | \[
\text{Creatinine clearance (mL/min)} = \frac{U_{\text{Cr}} \times \text{volume (in mL)}}{S_{\text{Cr}} \times 1440} \text{ (number minutes in 24 hours)}
\] |

$S_{\text{Cr}}$, serum creatinine in mg/dL, age in years, BUN in mg/dL, weight in kilograms, albumin in g/dL., $U_{\text{Cr}}$, urine creatinine in mg/dL.
# Prevalence of CKD by Stage of Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th># in millions</th>
<th>% of population</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Albuminuria, GFR ≥ 90 ml/min</td>
<td>~ 6.0</td>
<td>3.3</td>
</tr>
<tr>
<td>2</td>
<td>GFR 60 - 89</td>
<td>5.3</td>
<td>3.0</td>
</tr>
<tr>
<td>3</td>
<td>GFR 30 - 59</td>
<td>7.6</td>
<td>4.3</td>
</tr>
<tr>
<td>4</td>
<td>GFR 15 - 39</td>
<td>.4</td>
<td>0.2</td>
</tr>
<tr>
<td>5</td>
<td>GFR &lt; 15</td>
<td>.3</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Why Be Concerned About CKD?

- There is a significant risk of progression to Endstage Renal Disease (ESRD) among those with CKD Stage 3b, 4, and 5.
- There is a higher risk of death from cardiovascular disease among those with CKD Stage 3 and higher.
- There is a significant risk of metabolic complications in patients with CKD 3b, 4, 5.
CKD Risks

CKD3: 20X more likely to die of CV event than reach ESRD

Age ≤ 45 yrs
CKD 4/5

CKD 4/5 and > 65

Risk of Death

Risk of Progression to ESRD

In general, the risk of Death from CV event increases as kidney function declines.
Chronic Kidney Disease (CKD) and Death

• Only 0.5% of general population progress to ESRD raising concerns that premature death occurs in a large part of the CKD population.

• Patients with diagnosis of diabetes and CKD are 5 times more likely to die before reaching ESRD than those without diagnosis.
  – 150 times more likely to die than reach ESRD within 1 year of follow-up in general Medicare population (> 65 yrs). (USRDS 2002)
Screening For CKD, Who’s at Highest Risk

• Diabetes
• Hypertension
• Family History of CKD (especially ESRD)
• African American, Hispanic, Native American
• Increased Age
• Low income or education
• Low birth weight
Figure 6. DM & HTN ESRD Incidence Rates by Race/Ethnicity (1999; per million, adjusted for age, gender)

DM = Diabetes Mellitus
HTN = Hypertension

DM & HTN ESRD Incidence Rates by Race/Ethnicity (1999; per million, adjusted for age, gender)
During 2004, 104,364 new dialysis and transplant patients began ESRD therapy. (Amer J Kid Dis vol 49, suppl 1)
Screening for CKD: How

• Urinalysis: proteinuria, hematuria
  – If UA positive for protein: urine protein-to-creatinine ratio (<0.2 is normal, >/= 3 is nephrotic range proteinuria)
  – If have diabetes or hypertension and UA negative for protein, consider urine for microalbuminuria

• Serum creatinine with estimation of GFR
Major Complications of Chronic Kidney Disease

• Cardiovascular Disease
  – Hypertension, diabetes mellitus, metabolic syndrome, dyslipidemia
  – myocardial infarction, congestive heart failure, stroke
Major Complications of Chronic Kidney Disease

- Anemia
- Mineral Bone Disease
- Nutrition
- Acid – base disturbance
- Electrolyte disturbances
- Altered drug metabolism and/or clearance
Other Complications of Chronic Kidney Disease

• Other hematologic
  – Platelet and leukocyte dysfunction

• Endocrine
  – Less clearance of insulin
  – Increased aldo

• Erectile dysfunction

• Neurologic
  – Neuropathies
  – Cognitive deficits
Most Effective, and Perhaps Most Important, Treatment Consideration in CKD

• Treatment of Hypertension
  – Strong association between blood pressure level and rate of progression of kidney disease.
  – Strong association between blood pressure level and likelihood of having CV event in patients with CKD.
Increasing Systolic BP Linked to End-Stage Renal Disease Risk: MRFIT

Reasons to be Aggressive in Treatment of Hypertension in CKD

1) The adverse outcomes of CKD (kidney failure, cardiovascular disease, premature death) can be prevented or delayed.

2) Treatment of earlier stages of CKD is effective in retarding progression to kidney failure and in preventing the systemic complications that develop during the course of progressive CKD.

3) Initiation of therapy for cardiovascular risk factors at earlier stages of CKD can be effective in reducing the very high cardiovascular morbidity and mortality of these patients.
Recommendations for Treatment of Blood Pressure in Patients with CKD (2014)

- Diabetes or Proteinuria:
  - Target level of Blood pressure is < 130 / 80 mm Hg
- Without Proteinuria or Diabetes
  - Target is < 140 / 90 mm Hg
- Age 70 yrs and older.
  - Target is < 150 / 90 mm Hg.
## BP Recommendations in CKD, Previous vs. Current

<table>
<thead>
<tr>
<th></th>
<th>JNC 7, NKF, others (Pre JNC 8)</th>
<th>Hypertension Guidelines 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Mellitus</td>
<td>&lt; 130/80</td>
<td>&lt; 130/80</td>
</tr>
<tr>
<td>Non-Diabetes, + proteinuria</td>
<td>&lt; 130/80, &lt; 125/75</td>
<td>&lt; 130/80, &lt; 135/85</td>
</tr>
<tr>
<td>Non-Diabetes, no proteinuria</td>
<td>&lt; 140/90, &lt; 130/80</td>
<td>&lt; 140/90</td>
</tr>
<tr>
<td>Older (&lt; 60, &lt; 70)</td>
<td>As above, individualize</td>
<td>&lt; 150/90</td>
</tr>
</tbody>
</table>
Which Blood Pressure Lowering Medicines Are Recommended for Treatment of Blood Pressure in Patients with CKD?

• Proteinuria or Diabetes
  – ACE inhibitor or Angiotensin Receptor Blocker

• No proteinuria
  – ACE inhibitor or ARB, Thiazide diuretic, Calcium Antagonist
Level of baseline GFR and # of BP Meds to Achieve BP Goal

Multiple Agents Usually Required to Achieve BP Goals in Diabetic Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Agents Needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>RENAAL (&lt;140/90)</td>
<td>3</td>
</tr>
<tr>
<td>IRMA2 (&lt;135/85)</td>
<td>3.1</td>
</tr>
<tr>
<td>IDNT (&lt;135/85)</td>
<td>3</td>
</tr>
<tr>
<td>UKPDS</td>
<td>2.7</td>
</tr>
<tr>
<td>ABCD</td>
<td>2.8</td>
</tr>
<tr>
<td>MDRD</td>
<td>3.6</td>
</tr>
<tr>
<td>HOT</td>
<td>3.3</td>
</tr>
<tr>
<td>AASK</td>
<td>3.8</td>
</tr>
</tbody>
</table>

Blood Pressure Level is Much More Important than Blood Pressure Medication!!!
Chronic Kidney Disease and Cardiovascular Disease
Community Based Sample from HMO (Kaiser) (Go et. al. NEJM (2004) 351:1296)
There is Higher Cardiovascular Disease Risk in Patients with CKD

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>5-year Death Rate from CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>19.5%</td>
</tr>
<tr>
<td>3</td>
<td>24.3%</td>
</tr>
<tr>
<td>4</td>
<td>45.7%</td>
</tr>
</tbody>
</table>

Kid Internat (2008) 73:1310
CCJM (2014) 81: 289
CVD risk factors that are strongly associated with renal disease.

- Diabetes
- Hypertension
- Obesity
- Lipid abnormalities (esp. proteinuric)
- Insulin Resistance
- CHF
- Renal Disease
- LVH, Elevated Uric Acid, albuminuria, hyperphosphatemia
Anemia of CKD

- Erythropoietin Deficiency
- Shortened erythrocyte survival
- Uremic inhibitors of erythropoiesis
- Hemolysis
- Bleeding
- Loss of blood on dialysis
- Iron deficiency
Erythropoietin – Hemoglobin Relationship

Graph showing the relationship between Hemoglobin (g/dL) and EPO (mU/ml). The graph indicates a decrease in EPO levels as Hemoglobin levels increase, with a distinction between Renal Disease and Basal states.
Anemia of CKD

• Treatment
  – Goal: Avoid need for transfusions
  – Erythropoiesis-Stimulating Agents (ESA’s)
    • EPO, epoetin alfa, darbepoetin
  – Adequate Iron
    • IV formulations are now more safe
Bone Mineral Disorders of CKD

- Can start to be clinically apparent by CKD Stage 3.
  - Secondary Hyperparathyroidism
  - Hyperphosphatemia
  - Hypocalcemia (usually in advanced CKD (Stages 4 or 5)
Pathophysiology of Bone Mineral Disorders of CKD

• Decreased eGFR results in:
  – Decreased production of 1,25-dihydroxyvitamin D
  – Decreased clearance of phosphorous in urine
  – PO4 (2-) binds to Ca (2+) in blood giving transient lowering of Ca2+
  – These events lead to increase in PTH and abnormal bone metabolism.
    • weakened bone matrix and more calcium and phosphorous efflux from bone (renal osteodystrophy).
### K/DOQI Guidelines for Bone Metabolism Disease in CKD

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>eGFR</th>
<th>PO4 $^{2-}$</th>
<th>Ca $^{2+}$</th>
<th>Ca$^{++}$ X PO4$^{2-}$</th>
<th>Intact PTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>30 – 59</td>
<td>2.7 – 3.6</td>
<td>8.4 – 10.2</td>
<td>35 – 70</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>15 – 29</td>
<td>2.7 – 3.6</td>
<td>8.4 – 10.2</td>
<td>70 – 110</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>&lt; 15, dialysis</td>
<td>3.5 – 5.5</td>
<td>8.4 – 9.5</td>
<td>&lt; 55</td>
<td>150 - 300</td>
</tr>
</tbody>
</table>
Bone Metabolism Disease of CKD

• Treatment Strategies
  – Restrict dietary phosphorous
    • 800 – 1000 mg/day
    • Diary, nuts, beer, chocolate
  – Keep calcium in normal range
  – Assure adequate vitamin D
  – Suppress PTH
Bone Metabolism Disease of CKD

• Control of phosphorous
  – Dietary restriction
  – Calcium based phosphate binders (with meals)
    • Calcium acetate, calcium carbonate
    • Increased coronary (arterial) calcium
  – Non-aluminum, non-calcium phosphate binders
    • Sevelamer (cross-linked poly-allylamine HCl)
    • Lanthanum carbonate
    • Less vascular calcification
    • GI side effects
    • $$$$$
Bone Metabolism Disease of CKD

- Vitamin D
  - Often lower in patients with CKD
    - Lack of sunlight due to chronic illness
    - Poor oral intake
    - Decreased skin production
    - Loss in urine in patients with nephrotic range proteinuria
Bone Metabolism Disease of CKD

• Suppression on PTH
  – Vitamin D analogues (Give for PTH > 300 pg/ml)
    • 1, 25 (OH)2 vitamin D calcitriol
    • Active Vitamin D analogues
    • Paricalcitol
    • Doxercalciferol
    • Alfacalcitol
    • 22-oxacalcitriol
  – Mechanism: Decrease PTH by binding to vitamin D receptor on Parathyroid. Results in lower PTH, increased serum calcium and increased serum phosphorous.
Bone Metabolism Disease of CKD

• Suppression on PTH
  – Calcimimetics
    • Cinacalcet
  – Mechanism: Decrease PTH by binding to calcium sensing receptor (CaSR) on Parathyroid (Calcium receptor-sensing agonist). Results in lower PTH, but does not increase phosphorous or calcium.
  – Side Effect: hypocalcemia
Major Complications of Chronic Kidney Disease

• **Nutrition**
  – Pre-ESRD: moderate protein intake
  – ESRD – dialysis: higher protein intake needed

• **Acid – base disturbance**
  – Acidosis (low bicarb)
  – Contributes to bone disease, anemia, hyperkalemia

• **Electrolyte disturbances**
  – Hyperkalemia
When Do I Refer to Nephrologist?

- Estimated GFR < 60 ml/min
- Proteinuria (urine protein-to-creatinine ratio > .5)
Considerations In Patients Progressing Toward ESRD

• Risk of developing ESRD and needing renal replacement therapy increases significantly once patient reaches Stage 4 CKD.

• Considerations for the preservation of GFR are important
  – Avoid nephrotoxins (prescribed and OTC’s)
  – Avoid contrasted studies if possible
  – Reevaluate dosing for all meds (adjust for eGFR)
Considerations In Patients Progressing Toward ESRD

- The Primary Care Physician should participate in choices for renal replacement therapy to the degree that he/she and patient feel comfortable.

- Early decisions regarding modality or renal replacement therapy are important, particularly with development of AV Fistulas.
  - Protect the non-dominant arm
Considerations In Patients Progressing Toward ESRD

- Renal Replacement Therapy Options
  - Incenter Hemodialysis
    - Nocturnal
  - Peritoneal Dialysis
  - Renal Transplantation
    - Preemptive with living donor
    - Cadaveric (long wait times)
  - Home Hemodialysis
### Summary: It’s Not the Creatinine, It’s the Estimated GFR!

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>GFR &gt; 90 ml/min with presence of proteinuria or microalbuminuria</td>
</tr>
<tr>
<td>Stage 2</td>
<td>GFR between 60- 89 ml/min (mild)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>GFR between 30 – 59 ml/min (moderate)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>GFR between 15 – 29 ml/min (severe)</td>
</tr>
<tr>
<td>Stage 5</td>
<td>GFR &lt; 15 ml/min (Kidney failure, ESRD)</td>
</tr>
</tbody>
</table>
## Summary: Complications of CKD by Stage

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>CVD</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Mineral Bone DZ</td>
<td></td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
<td>++</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Electrolyte D/O</td>
<td></td>
<td></td>
<td>+</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Acidosis</td>
<td></td>
<td></td>
<td>+</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Nutrition</td>
<td></td>
<td></td>
<td>+</td>
<td>+++</td>
<td></td>
</tr>
</tbody>
</table>