OUTPATIENT MANAGEMENT OF CHRONIC KIDNEY DISEASE

Jeanie Park, MD MS
Assistant Professor
Renal Division
Emory University School of Medicine
Disclosures

- None
Goals

• Background and staging
• Strategies to slow progression of CKD
  • Proteinuria Control
  • Blood Pressure Control
  • Glycemic Control
  • Metabolic Acidosis Treatment
  • Hyperlipidemia Treatment
• Referral to Nephrologist
• Treatment of the Complications of CKD
  • Renal Osteodystrophy
  • Anemia
CHRONIC KIDNEY DISEASE

Background and Staging
CKD Definition (Previous K/DOQI)

Kidney Disease Outcomes Initiative (K/DOQI) Committee of the National Kidney Foundation (NKF)

CKD defined as:

• Glomerular Filtration Rate (GFR) < 60 ml/min for 3 or more months (with or without kidney damage)

• Presence of kidney damage for 3 or more months demonstrated by pathologic abnormalities or markers of kidney damage (blood, urine, or imaging tests)
CKD: Definition (KDIGO -2012)

- At least one of the following for ≥3 months:
  - Decreased GFR <60 ml/min
  - Markers of kidney damage
    - Albuminuria (>30 mg/g Cr)
    - Urine sediment abnormalities
    - Electrolyte and other abnormalities due to tubular disorders
    - Abnormal histology
    - Structural kidney abnormality by imaging
    - History of kidney transplant

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR (ml/min/1.73m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥ 90</td>
</tr>
<tr>
<td>2</td>
<td>60–89</td>
</tr>
<tr>
<td>3</td>
<td>30–59</td>
</tr>
<tr>
<td>4</td>
<td>15–29</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15 or dialysis</td>
</tr>
</tbody>
</table>

Must also have a marker of kidney damage
Revised Stages of CKD (KDIGO – 2012)

**G category**
- **GFR**
  - **G1**: >90 ml/min
  - **G2**: 60-89 ml/min
  - **G3a**: 45-59 ml/min
  - **G3b**: 30-44 ml/min
  - **G4**: 15-29 ml/min
  - **G5** Kidney Failure, <15 ml/min

**A category**
- **Albuminuria**
  - **A1**: <30 mg/g
  - **A2**: 30-300 mg/g
  - **A3**: >300 mg/g
CKD: Risk stratification

**Prognosis of CKD by GFR and albuminuria category**

<table>
<thead>
<tr>
<th>Persistent albuminuria categories Description and range</th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal to mildly increased</td>
<td>Normal to mildly increased</td>
<td>Moderately increased</td>
<td>Severely increased</td>
</tr>
<tr>
<td>&lt;30 mg/g</td>
<td>30-300 mg/g</td>
<td>&gt;300 mg/g</td>
<td></td>
</tr>
<tr>
<td>&lt;3 mg/mmol</td>
<td>3-30 mg/mmol</td>
<td>&gt;30 mg/mmol</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GFR categories (ml/min/1.73 m²) Description and range</th>
<th>G1</th>
<th>G2</th>
<th>G3a</th>
<th>G3b</th>
<th>G4</th>
<th>G5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal or high</td>
<td>G1</td>
<td>G2</td>
<td>G3a</td>
<td>G3b</td>
<td>G4</td>
<td>G5</td>
</tr>
<tr>
<td>≥90</td>
<td>60-89</td>
<td>45-59</td>
<td>30-44</td>
<td>15-29</td>
<td>&lt;15</td>
<td></td>
</tr>
</tbody>
</table>

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

Estimations of GFR

- **MDRD Equation**: underestimates GFR when renal function is close to normal
  \[ eGFR (\text{ml/min}) = 175 \times \text{SCr} \times (\exp[-1.154]) \times \text{Age} \times (\exp[-0.203]) \times (0.742 \text{ if female}) \times (1.21 \text{ if black}) \]

- **CKD-EPI Equation**: more precise in elderly and when renal function is near normal
  \[ eGFR = 141 \times \min(\text{Scr}/\kappa, 1)^\alpha \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018 \times \text{[if female]} \times 1.159 \times \text{[if black]} \]

- **24 hour urine creatinine clearance**: over-estimates GFR when renal function is poor
  - Average of 24 hour urine creatinine clearance and urea clearance gives a more accurate estimation of GFR when renal function is poor.
Prevalence of CKD

US Renal Data System (2011)

- 31 million Americans (10% of US population) have CKD

- 9 out of 10 people with CKD Stage III do not know it
Incidence of Advanced CKD Varies by Race and Ethnicity

Primary Diagnosis For Patients Who Start Dialysis

- Diabetes: 50.1%
- Hypertension: 27%
- Glomerulonephritis: 13%
- Other: 10%

United States Renal Data System. Annual data report 1984-2010

No of Patients Projection 95% CI

- 243,524
- 281,355
- 520,240

R² = 99.8%
Prevalence by Stage of CKD

- NHANES: Prevalence by staging of CKD
  - Stage I: 1.8%
  - Stage II: 3.2%
  - Stage III: 7.7%
  - Stage IV: 0.35%
  - Stage V: 0.03%

CKD and Mortality Risk

- Both reduced renal function and proteinuria are independent risk factors for CV disease and mortality.

- CVD is the leading cause of mortality in patients with CKD, accounting for 50% of deaths in this population. End-stage renal disease (ESRD) patients are at 10-20 times greater risk for cardiac mortality.

- CKD patients are more likely to die of CVD than to reach ESRD.
Epidemiology of CV Disease in CKD

Go et al. NEJM 2004;351:1296-305
Epidemiology of CV Disease in CKD

A All-cause mortality; eGFR

B All-cause mortality; ACR

C Cardiovascular mortality; eGFR

D Cardiovascular mortality; ACR

Chronic Kidney Disease Prognosis Consortium. Lancet 2010;375:2073
CKD

Slowing the Progression of CKD
Cost of Treating Kidney Disease

• In 2009, overall Medicare expenditures for people with CKD totaled $33.8 billion.

• The savings to Medicare for EACH kidney disease patient who does not progress on to dialysis is estimated to be $250,000.
General Management of CKD

- Determine etiology and avoid further insults (stop nephrotoxic drugs, NSAIDS)
- Adjust drug doses for the level of eGFR
- Slow the progression of CKD
- Treat the complications of CKD
- Refer to Nephrologist when appropriate
### Monitoring Renal Function

#### Guide to Frequency of Monitoring (number of times per year) by GFR and Albuminuria Category

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</tr>
<tr>
<td>&lt;30 mg/g &lt;3 mg/mmol</td>
<td>30–300 mg/g 3–30 mg/mmol</td>
<td>&gt;300 mg/g &gt;30mg/mmol</td>
<td></td>
</tr>
</tbody>
</table>

#### GFR categories (ml/min/1.73 m²) Description and range

<table>
<thead>
<tr>
<th>G1</th>
<th>Normal or high</th>
<th>≥90</th>
<th>1 if CKD</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>G2</td>
<td>Mildly decreased</td>
<td>60–89</td>
<td>1 if CKD</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>G3a</td>
<td>Mildly to moderately decreased</td>
<td>45–59</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>G3b</td>
<td>Moderately to severely decreased</td>
<td>30–44</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>G4</td>
<td>Severely decreased</td>
<td>15–29</td>
<td>3</td>
<td>3</td>
<td>4+</td>
</tr>
<tr>
<td>G5</td>
<td>Kidney failure</td>
<td>&lt;15</td>
<td>4+</td>
<td>4+</td>
<td>4+</td>
</tr>
</tbody>
</table>

Slowing Progression of CKD

- Reducing Proteinuria
- Blood Pressure Control
- Glycemic Control in Diabetics
- Treatment of Metabolic Acidosis
- Treatment of Hyperlipidemia
Importance of Proteinuria in Renal Prognosis

Proteinuria is the most important independent factor associated with progressive renal failure

Importance of Proteinuria in Renal Prognosis

Case

60 year-old Black male with longstanding type II diabetes has CKD Stage IIIIB, with 3.5 grams of proteinuria/gCr. He is being treated with Amlodipine 10mg daily, and Lisinopril 40mg daily. His blood pressure is 153/95 mm Hg.
Which of the following is NOT correct?

1. Addition of losartan will further decrease proteinuria and improve renal outcomes.

2. Addition of spironolactone can decrease proteinuria by 40%.

3. Statins have been shown to decrease proteinuria.

4. Reducing blood pressure will lead to a reduction in proteinuria.

5. His blood pressure goal is <130/80 mm Hg.
Strategies to Reduce Proteinuria in CKD

- Dietary salt restriction 90mmol (2 g) per day of sodium
- Weight loss if overweight or obese
- Reducing dietary protein intake to 0.7 g/kg ideal body weight
- Smoking cessation
- Control of blood pressure
- Suppression of the renin-angiotensin system with ACE inhibitors (ACEi) or angiotensin receptor blockers (ARBs)
- Aldosterone antagonists in some patients

ACEi and Renoprotection: Diabetic Patients with Proteinuria

Percentage with Doubling of Base-Line Creatinine

Years of Follow-up

Placebo
Captopril

P = 0.007
ACEi and Renoprotection: Nondiabetic Patients with Proteinuria

Lancet 1999; 354:359-364
ARBs and Renal Protection

A. Risk reduction, 16%  
P = 0.02

B. Risk reduction, 25%  
P = 0.006

C. Risk reduction, 28%  
P = 0.002

D. Risk reduction, 20%  
P = 0.01

What about combination therapy with ACEi and ARBs?

**KDIGO**: There is insufficient evidence to recommend combining an ACE-I with ARB to prevent progression of CKD.

No proven benefit of combination therapy on renal outcomes, and possible adverse effects

**ONTARGET** *(Circulation 2011;123:1098 and NEJM 2008;358:1547)*
- Combination therapy did not reduce the risk of cardiovascular disease or death
- Combination therapy was associated with a significant increase in incidence of ESRD and doubling of serum creatinine
Aldosterone Receptor Blockers Reduce Proteinuria

Kidney International 2006; 70: 2116
Should we use ACE or ARB in Advanced CKD?


<table>
<thead>
<tr>
<th>Group</th>
<th>No. at Risk</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, benazepril</td>
<td>102 96 84 40</td>
<td></td>
</tr>
<tr>
<td>2, benazepril</td>
<td>107 96 73 32</td>
<td></td>
</tr>
<tr>
<td>2, placebo</td>
<td>108 88 59 22</td>
<td></td>
</tr>
</tbody>
</table>
Blood Pressure Control and CKD Progression

2012 KDIGO Clinical Practice Guidelines

- Goal blood pressure ≤140/90 mm Hg for CKD patients without albuminuria.

- Goal BP ≤130/80 mm Hg for patients with CKD (with or without diabetes) and micro- or macroalbuminuria.
Blood Pressure Control and CKD Progression

JNC 8 Blood Pressure Goals

- Goal BP <140/90 mm Hg in patients younger than 60, and all diabetics, and CKD patients regardless of age.

- Goal BP < 150/90 in patients >60 years without CKD or DM
Blood Pressure Control and CKD Progression: Differs According to Proteinuria

Stage III CKD

Stage IV CKD

Study 1

Study 2

Mean Rate of GFR Decline (ml/min/yr)

Base-Line Urinary Protein (g/day)

n = 420  n = 104  n = 54  n = 136  n = 63  n = 32

<1  1–<3  3  <1  1–<3  3

Summary: Proteinuria and BP Goals

- ACEi and ARBs are the most effective treatments for proteinuria in CKD
- The combination of ACEi with ARBs should generally not be used
- ACEi and ARBs may slow progression of renal disease in advanced CKD (Stage IV) and may be initiated with careful monitoring
- ACEi and ARBs have no benefit over other antihypertensive drugs in nonproteinuric CKD patients
- The addition of spironolactone or eplerenone may further reduce proteinuria in CKD patients
- BP goal is <140/90 in nonproteinuric CKD, and <130/80 in CKD with proteinuria
Glycemic Control and Progression of CKD

- Glycemic control reduces the progression of renal disease as judged by the mitigation of albuminuria in both type 1 and type 2 diabetics.

- DCCT Trial (Kidney International 1995; 47:1703-20): In Type I DM, strict glycemic control compared with usual control lessened the progression from microalbuminuria to macroalbuminuria.

- ACCORD Study (Lancet 2010; 376 (9739): 419-30): Transitions to microalbuminuria and macroalbuminuria were diminished by stringent glycemic control.
Metabolic Acidosis and CKD Progression

- Total ammonium excretion starts to fall when the GFR is < 40-50 mL/min, leading to retention of hydrogen ions

- Consequences of metabolic acidosis in CKD
  - Bone resorption and osteopenia
  - Increased muscle protein catabolism
  - Worsening secondary hyperparathyroidism
  - Impaired myocardial contractility
  - Inflammation
  - *Progression of chronic kidney disease*

- Treatment with bicarbonate therapy
  - Progression of chronic kidney disease
  - Bone health
  - Nutritional Status
Metabolic Acidosis is Associated with Progressive Renal Dysfunction

Bicarbonate Supplementation may slow the progression of CKD
Metabolic Acidosis in CKD

- **KDIGO (2012)**: suggest that in people with CKD and serum bicarbonate concentrations of < 22 mmol/l treatment with oral bicarbonate supplementation be given to maintain serum bicarbonate within the normal range (23-29 meq/L), unless contraindicated.
Dyslipidemia and CKD Progression

• LDL
  • Renal inflammation
  • Profibrotic changes in the kidney

• Dyslipidemia may be associated with progression of renal disease
  • Helsinki Heart Study showed that a LDL to HDL ratio > 4.4 was associated with a 20% faster decline than a ratio <3.2
  • The Physicians Health Study showed that dyslipidemia was significantly associated with an increased risk of developing renal dysfunction in men

• Statins may improve renal outcomes and reduce proteinuria
CHRONIC KIDNEY DISEASE
Referral to Nephrologist
Referral to a Nephrologist

- All patients with severely decreased GFR (eGFR<30 mL/min/1.73 m2, GFR Stage 4) should be referred to a nephrologist.

- Late referral to a nephrologist (<3-12 months before start of dialysis therapy) is associated with higher mortality after initiation of dialysis.
Referral to a Nephrologist

- There is less consensus about referral for patients with higher eGFR

Consider early referral for:
- Glomerular hematuria
- Proteinuria > 300mg/gCr
- Unclear etiology of CKD
- Progressive decline in renal function (>5 ml/min/year)
- Uncontrolled blood pressure
Referral to a Nephrologist

- Co-management with the primary care provider is a common strategy at early stages of CKD, and may be associated with improved outcomes.
# Prevalence of CKD Complications by GFR category

<table>
<thead>
<tr>
<th></th>
<th>&gt;90%</th>
<th>60-89%</th>
<th>45-59%</th>
<th>30-44%</th>
<th>&lt;30%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anemia</strong></td>
<td>4%</td>
<td>4.7%</td>
<td>12.3%</td>
<td>22.7%</td>
<td>51.5%</td>
</tr>
<tr>
<td><strong>HTN</strong></td>
<td>18.3</td>
<td>41.0</td>
<td>71.8%</td>
<td>78.3%</td>
<td>82.1</td>
</tr>
<tr>
<td><strong>Vitamin D Deficiency</strong></td>
<td>14.1</td>
<td>9.1</td>
<td>10.7%</td>
<td>10.7%</td>
<td>27.2</td>
</tr>
<tr>
<td><strong>Acidosis</strong></td>
<td>11.2</td>
<td>8.4</td>
<td>9.4%</td>
<td>18.1%</td>
<td>31.5</td>
</tr>
<tr>
<td><strong>High phos</strong></td>
<td>7.2</td>
<td>7.4</td>
<td>9.2%</td>
<td>9.3%</td>
<td>23%</td>
</tr>
<tr>
<td><strong>High PTH</strong></td>
<td>5.5</td>
<td>9.4</td>
<td>23%</td>
<td>44%</td>
<td>72.5</td>
</tr>
</tbody>
</table>

Potential benefits of early referral to Nephrologist

- Earlier management of complications
- Slower progression to end-stage renal disease
- Timely placement of dialysis access
- Timely and informed selection of renal replacement therapy modality
- Nonemergent initiation of dialysis
- Lower morbidity/mortality and improved survival
- Lower cost and decreased hospitalization
Potential benefits of early referral to Nephrologist

<table>
<thead>
<tr>
<th>Variable</th>
<th>Early Referrals</th>
<th>Late Referrals</th>
<th>Risk Ratio or Difference</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mortality (%)</td>
<td>11 (3)</td>
<td>23 (4)</td>
<td>1.99 (1.66-2.39)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Duration of hospitalization at initiation of RRT (days)</td>
<td>13.5 (2.2)</td>
<td>25.3 (3.8)</td>
<td>12 (8–16.1)</td>
<td>0.0007</td>
</tr>
<tr>
<td>1-year mortality (%)</td>
<td>13 (4)</td>
<td>29 (5)</td>
<td>2.08 (1.31-3.31)</td>
<td>0.028</td>
</tr>
</tbody>
</table>
Potential benefits of early referral to Nephrologist

**Early Referral**

- Decreased mortality
- Decreased duration of hospitalization (by 8.8 days)
- Increased initiation of peritoneal dialysis
- Decreased use of temporary vascular access
- Improved hgb levels and increased use of ESA

Complications of CKD

- Mineral Bone Disease/Renal Osteodystrophy
- Anemia
- Hypertension
- Acidosis
- Hyperkalemia
- Cardiovascular disease
- Volume Overload
- Uremia
Pathogenesis of CKD-MBD

- Renal Phosphate Retention
- Decreased 1,25 dihydroxyvitamin D
- Decreased free ionized Calcium
- Increased secretion of parathyroid hormone (PTH)
- Increased fibroblast growth factor 23 (FGF23)
Renal Osteodystrophy

- Osteitis Fibrosa Cystica (secondary hyperparathyroidism)

- Adynamic Bone Disease (oversuppression of PTH)

- Osteomalacia (Vitamin D deficiency and aluminum toxicity)
Approach to Renal Osteodystrophy

- Treat Vitamin D deficiency
  - Goal 25-OH Vitamin D Level > 30
  - Ergocalciferol or cholecalciferol

- Treat Hyperphosphatemia
  - Goal PO$_4$ level in CKD Stage III and IV is 2.7-4.6 mg/dL
  - Calcium x phos product goal <55
  - Dietary phosphorus restriction and phosphorus binders

- Treat Persistent Secondary Hyperparathyroidism
  - Activated Vitamin D analogs (calcitriol, hectorol, zemplar)
  - Calcium Receptor Binder (Cinacalcet)
Anemia of CKD

• The primary etiology of the anemia of chronic kidney disease is decreased production of erythropoietin by the kidney.
  • Others: iron deficiency, vitamin deficiencies, blood loss, & chronic inflammation/uremia.

• Treatment
  • Iron (oral or IV)
  • Erythropoietin Stimulating Agents (ESAs) (darbepoetin, erythropoietin)
ESA Treatment Goals

- No difference in mortality, cardiovascular events, or renal events between the high hgb group versus low hgb group

- Increased risk of stroke in the high hgb group
FDA (ESAs – Anemia Treatment)

- FDA released an update in June 2011 on dosing guidelines for ESA use to treat anemia in CKD.

- Patients with CKD should be considered for starting ESA treatment when hemoglobin level < 10 g/dL.

- If hemoglobin level exceeds 10 g/dL, reduce or interrupt the dose of ESA.

- The provider should individualize dosing and use the lowest dose of ESA sufficient to reduce the need for RBC transfusions.

Summary of Key Points

• CKD is highly prevalent. Patients with CKD are at significantly higher risk of cardiovascular mortality.

• Strategies to slow progression of CKD include control of proteinuria, hyperglycemia, blood pressure, metabolic acidosis, and hyperlipidemia.

• All proteinuric patients should be treated with an ACE-I or ARB, with a goal BP <130/80 mm Hg, and referred to a nephrologist.

• Consider early referral to a nephrologist. Indications include unknown etiology, poorly controlled blood pressure, hematuria, proteinuria, progressive decline in renal function, eGFR<30cc/min,
Evaluation

- Please take < 90 seconds to evaluate this session.
- Time permitting, speaker will take questions following evaluation.
- Responses are not displayed and are important in maintaining high quality education.
The overall performance of the speaker:

1. Poor
2. Fair
3. Average
4. Good
5. Excellent

- 79% Excellent
- 21% Good
- 0% Average
- 0% Fair
- 0% Poor
How well were the learning objectives met?

1. Poor
2. Fair
3. Average
4. Good
5. Excellent

92% Excellent
Did speaker present a balanced view of therapeutic options?

1. Yes
2. No
3. N/A
How useful will this session be in your practice?

1. Poor
2. Fair
3. Average
4. Good
5. Excellent
As a result of this program, do you intend to change your patient care?

1. Yes
2. No
Thank you!