CHRONIC KIDNEY DISEASE
UPDATE: WHAT THE GENERALIST NEEDS TO KNOW

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Outline
- Definition and Complications
- New CKD Staging 2013
- Screening for CKD
- Treatment of CKD
- Introduction to Cystatin C
- When to refer to nephrologist

Question 1: Which of these patients has CKD?

- Heart failure patient in ED with creatinine of 2.0
- Diabetes patient with albumin/creatinine of 100 mg/g, creatinine= 1.0 mg/dL
- 35 year old African American man with creatinine of 1.5
- All of the above
**DEFINITION & CLASSIFICATION OF CHRONIC KIDNEY DISEASE**
KDIGO 2012 Clinical Practice Guideline (CPG) for the Evaluation and Management of Chronic Kidney Disease

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**Introduction**

- Chronic Kidney Disease (CKD):
  - Defined in 2002 with original CKD staging
  - Replaced earlier terms “chronic renal insufficiency”, “chronic renal failure”, or “high creatinine”
  - Previous 5 CKD stages were developed by an expert panel
  - Most CKD epidemiology research has been conducted since the 5 stages were defined

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**Definition and Complications**

- Overall CKD definition unchanged
- Chronic kidney disease: >3 month duration of either:
  - Decreased kidney function (eGFR<60)
  - Injury/damage to the kidney (e.g. albuminuria, cysts, stones)
- Etiology of CKD:
  a) Common diseases treated by generalists: diabetes, hypertension, cardiovascular disease, heart failure
  b) Other systemic diseases typically treated by specialists: systemic lupus erythematosus, HIV, urological diseases
  c) Primary kidney disease: polycystic kidney disease, glomerular disease

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**Complications of CKD**

- Kidney failure (end-stage renal disease)
- Death
- Other chronic disease:
  a) Atherosclerotic Cardiovascular Disease
  b) Heart failure
  c) Osteoporosis/fracture
  d) Cognitive impairment/dementia
  e) Frailty
- Treatment Complications:
  a) Medications
  b) Procedures
Question 2: A 75 yr. old White male with CAD and HF has an eGFR=25. What is he at most risk for?

- Death
- Dialysis

Prognosis by eGFR and Albuminuria

- Key meta-analysis published in 2010 in Lancet
- Evaluated prognosis by eGFR and albuminuria
- 21 studies, 1.2 million patients
- Predictor:
  - eGFR categories
  - Albuminuria (ACR categories)
- Outcome: mortality risk

CKD Complications

Keith et al., Arch Int Med, 2004

- Design: Northwest Kaiser database
- 5 year follow-up
- Death and ESRD outcomes

<table>
<thead>
<tr>
<th></th>
<th>eGFR 30-60 N=11,728</th>
<th>eGFR 15-30 N=777</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>72</td>
<td>74</td>
</tr>
<tr>
<td>ESRD (%), 5 yrs</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>Death (%), 5 yrs</td>
<td>24</td>
<td>45</td>
</tr>
</tbody>
</table>

Albuminuria and eGFR grid


Conclusion: CKD staging must integrate eGFR and albuminuria together

Age, sex, race and cardiovascular risk factor adjusted hazard ratio for all-cause mortality

- CKD by low GFR
- CKD by albuminuria

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Q3: What is the current definition of Stage 3 CKD?

- 1+ proteinuria or ACR > 30
- GFR 30-60
- GFR 45-60
- There’s no such thing

CKD Stages and Prevalence

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>Estimated GFR (mL/min per 1.73 m²)</th>
<th>U.S. Prevalence N (1000’s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD Stage 1</td>
<td>90+*</td>
<td>3,200 (1.6)</td>
</tr>
<tr>
<td>CKD Stage 2</td>
<td>60-89*</td>
<td>6,500 (3.2)</td>
</tr>
<tr>
<td>CKD Stage 3</td>
<td>30–59</td>
<td>15,500 (7.7)</td>
</tr>
<tr>
<td>CKD Stage 4</td>
<td>15–29</td>
<td>700 (0.4)</td>
</tr>
<tr>
<td>CKD Stage 5</td>
<td>&lt;15 (or dialysis)</td>
<td>400 (0.2)</td>
</tr>
</tbody>
</table>

*With evidence of kidney damage, e.g. albuminuria

KDOQI Guidelines, AJKD, Feb. 2002

Problems with Old Staging

- Stages 1 and 2 were the same
- Stage 3 (30-60) was too broad; eGFR of 30-45 is very different from 45-60
- Did not address levels of albuminuria; and only used albuminuria for Stages 1 and 2
**Classification of CKD**

- It is recommended that CKD be classified by:
  - Cause
  - GFR category
  - Albuminuria category

- This is collectively referred to as “CGA Staging”

- Represents a revision of the previous KDOQI CKD guidelines, which included staging only by level of GFR

**Screening for CKD**

- CKD guidelines do not address when or how to screen
- Other guidelines have disease-specific recommendations (hypertension, diabetes, CVD)
- The following are my suggestions.
Who and When to Check Creatinine?

- Begin screening:
  - Age >40 lower-risk populations
  - Age >30 Blacks, Native Americans
  - Diagnosis of hypertension, diabetes, cardiovascular disease, heart failure
- Frequency of creatinine monitoring (no evidence)
  - No risk factors: 3-5 years
  - Risk factors: 1-2 years
- Creatinine cost: $0.20

GFR Estimation from Creatinine

- Estimated GFR:
  - Automatic reporting by most labs
  - Equations are rough
  - <60 concerning for kidney disease, but not diagnostic of kidney disease
  - > 60- imprecise
- 3 equations in current use:
  - Cockroft-Gault (Nephron, 1976)- used by FDA and pharmacies
  - MDRD (Annals, 1999)- used for most automated reporting
  - CKD-EPI (Annals, 2009)- favored by researchers

Question 4: Which of the following is true about creatinine GFR estimates?

a) More accurate in older populations than middle-aged because prevalence of kidney disease is higher
b) They have been validated in most ethnic groups
c) They are more likely to be accurate in healthy persons than in persons with chronic illness
d) All of the above

Pros and Cons of Estimated GFR

- Pros:
  - Indexes creatinine for demographic characteristics
  - Forces us to think in terms of GFR and kidney function
- Cons:
  - Mostly validated in younger patients with kidney disease
  - Huge assumption that demographic characteristics alone can define muscle mass
  - Only developed in Whites and Blacks
  - Estimated GFR ≠ GFR
Who to Screen with Urine Albumin?

- Primary prevention screens:
  - Diabetes - annual
  - Hypertension
  - Elderly
- CKD Staging:
  - Urine albumin will be important part of CKD staging
  - Should be measured and documented in all CKD patients
    - Repeat annually in diabetics
    - every 2-3 years in non-diabetics

How to Measure Urine Albumin

- Often listed as “microalbumin panel”
- Focus on albumin/creatinine ratio (ACR):

<table>
<thead>
<tr>
<th>ACR (mg/g)</th>
<th>OLD</th>
<th>NEW</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30</td>
<td>Normal</td>
<td>Normal or mildly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>elevated</td>
</tr>
<tr>
<td>30-300</td>
<td>Microalbuminuria</td>
<td>Moderately</td>
</tr>
<tr>
<td></td>
<td></td>
<td>elevated</td>
</tr>
<tr>
<td>&gt;300</td>
<td>Macroalbuminuria</td>
<td>Severely elevated</td>
</tr>
</tbody>
</table>

- Dipstick: “trace” is abnormal
- If dipstick is abnormal, quantify ACR

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Question 5: Which of the following treatment options will not slow the progression of kidney disease?

A. ACE/ARB treatments
B. Blood pressure control
C. Glucose control
D. Statins

- ACE/ARB: 6%
- Blood pressure: 79%
- Glucose: 13%
- Statins: 2%
CKD Treatment

- **Goals:**
  - Prevent progression to ESRD
  - Prevent CKD complications

- **Treatments:**
  - ACE/ARB therapy
  - Blood Pressure Control
  - Glucose Control in Diabetes
  - Statins

ACE/ARB’s in Diabetic CKD

- Diabetic CKD- nearly always has albuminuria
- Diabetic CKD- ACE/ARB essential for:
  - Type I or II diabetes
  - Moderate albuminuria (ACR 30-300)
  - Severe albuminuria (ACR > 300)
- ACE/ARB’s do not appear to be helpful to prevent onset of albuminuria

Shlipak, Clinical Evidence 2009

ACE/ARB’s in Non-Diabetic CKD

- Meta-analysis- 1,860 CKD patients
  - RCTs of ACE vs. other HTN agents
  - Overall RR 0.67 (0.53-0.84) for kidney outcomes
- Subgroup analysis:
  - No benefit in group without proteinuria (< 500 mg/g)

Are ACE/ARB’s for All CKD Patients?

- ALLHAT Hypertension Trial –
  - Subgroup analysis of CKD (eGFR< 60)
  - Compared lisinopril, amlodipine, and chlorthalidone
- ACE not different from thiazides or CCB’s for kidney decline or ESRD (Rahman, Arch Intern Med, 2005)
- Low eGFR without albuminuria- choice of blood pressure agent may not matter
ACE-I in Advanced CKD

- 224 patients with creatinine 3.1-5.0 mg/dL
- Mean eGFR 25; mean urine prot – 1.6g/day
- Benazepril 20 mg daily vs. placebo
- Primary end point: doubling of creatinine, ESRD, death

Findings:
- 43% reduction in primary end point
- 52% reduction in proteinuria
- Effects independent of blood pressure
- Adverse events rare

ACE/ARB Combination?

- Proteinuria reduction from ACE inhibitors and ARBs is similar.
- Combination of ACE/ARB has additional reductions in proteinuria.
  

- However, ACE/ARB combination carries higher risk of adverse events
  

- Given added risk of hyper-kalemia and uncertain benefit, I do NOT recommend combination therapy.

Blood Pressure Target in CKD

- SBP control extremely important and often requires 3-4 meds at full dose


The Challenge of Blood Pressure Control in CKD

- Since CKD often in older patients with stiff arteries, an SBP<130 rarely attainable.

- In large health screening study, we found one-third of CKD patients had SBP > 150 (Peralta CA, Arch Intern Med, 2012)

- Guidelines on blood pressure control in CKD:
  
  - JNC-7 target < 130
  - New KDIGO-CKD HTN guideline: suggests <130 recommends <140

- Evidence-based treatment: <140 for most CKD patients
Glycemic Control in Diabetic CKD

- Type I Diabetes- tight glucose control slows kidney disease progression: OR= 0.34 (0.20-0.58)
- Type II Diabetes- ADVANCE trial *(NEJM, 2008, 2560-72)*
  - Tight glucose control (HbA1c 6.5 vs. 7.3): 20% lower risk of "new or worsening nephropathy"
  - RR= 0.8; 4.1 vs. 5.2% (p = 0.006)
- In Type II Diabetes, risks of tight glucose control may offset kidney benefits
- Tailor A1C treatment goal to the individual patient

Statins in CKD- beneficial for CVD

- Meta-analysis, 26 studies, statins vs. placebos in CKD
  - cardiovascular deaths *(20 studies, 18,746 patients)*
    - RR 0.80 (95% CI: 0.70,0.90)
    - Navaneethan et al. Cochrane Review. April, 2009
- SHARP Trial: RCT of 9,500 patients with CKD
  - Simvastatin/ezetimide vs. placebo- RR= 0.83 (95% CI: 0.74-0.94) for CVD
- No benefits of statins in patients with ESRD

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Cystatin C

- Cystatin C is a blood test of kidney function that is an alternative to creatinine
- Because cystatin C is not related to muscle mass (or age, sex, and race), it has major advantages over creatinine
- Cystatin C is a reliable, standardized, and inexpensive ($4/test) measure that is available for clinical use.
GFR Equations using Cystatin C

- 2 recent studies in major journals developed GFR equations for cystatin C
  1. **CKD-EPI** *(NEJM July 2012)*
     - eGFRcys, eGFRcys-cr
     - Best GFR by creatinine + cystatin C
     - Cystatin C has no race bias, so same eGFR formula for Blacks and Whites
  2. **Berlin Study** *(Ann Intern Med November 2012)*
     - In elderly persons, cystatin C much better than creatinine
     - Best estimate also uses creatinine + cystatin C

“Cystatin C versus Creatinine in Determining Risk based on Kidney Function”

- Meta-analysis of all available observational studies and clinical trials with creatinine and cystatin C
- Compared associations of eGFRcr, eGFRcys, and eGFRcr-cys with death
- Determined proportions reclassified by cystatin C in each eGFRcr subgroup and impact on risk associations

**eGFR Distributions and CKD Prevalence**


**All-Cause Mortality**

*12,351 events*

Reclassification by eGFRcys and associated risk

KDIGO 2012 Clinical Practice Guideline (CPG) for the Evaluation and Management of Chronic Kidney Disease

Guideline Statements Relevant to Cystatin C

KDIGO Suggestion #1 (2B)

- Estimating GFR:
  1. Use creatinine eGFR
  2. Are you confident that this is accurate?
  3. If no, use either:
     - Cystatin C
     - Direct measure GFR

KDIGO Suggestions #2 (2C)

Confirming CKD:
- Your patient’s eGFRcr is 45-60 and is not known to have kidney disease:
  1. Measure cystatin C
  2. If eGFR <60 by cystatin C, CKD
     >60 by cystatin C, no CKD
KDIGO Suggestion #3 (2C)

• When using cystatin C:
  • Use eGFR equation
  • Use standardized measure

KDIGO Recommendation (1C)

• For medical dosing of potentially toxic agents, use cystatin C or direct measure GFR

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Reasons to Consider Referral to Nephrologist

- Combined hematuria and proteinuria
  - Indicates concern for glomerulonephritis
- Estimated GFR < 30
  - Need to start planning for dialysis
- Nephrotic proteinuria
  - Potential for treatable condition
- Mineral metabolism management:
  - High phosphate/high PTH
- Anemia of CKD
  - Hemoglobin target ~10
Thank you!
Any Questions?