CHRONIC KIDNEY DISEASE
UPDATE: WHAT THE
GENERALIST NEEDS TO KNOW

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Disclosures
- I am on the Scientific Advisory Boards with stock option compensation for the following companies:
  - TAI Diagnostics
  - Cricket Health, Inc.

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

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**Question 1: Which of these patients has CKD?**

- a) Heart failure patient in ED with creatinine of 2.0
- b) Diabetes patient with albumin/creatinine of 100 mg/g, creatinine = 1.0 mg/dL
- c) 35 year old African American man with creatinine of 1.5
- d) All of the above

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**Definition & Classification of Chronic Kidney Disease**

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

*Kidney Inter., Suppl. 2013; 3: 1–150*

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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 (GFR<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
Complications of CKD

- Kidney failure (end-stage renal disease)
- Death
- Other chronic disease:
  - Atherosclerotic Cardiovascular Disease
  - Heart failure
  - Osteoporosis/fracture
  - Cognitive impairment/dementia
  - Frailty
- Treatment Complications:
  - Medications
  - Procedures

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

**Albuminuria and eGFR grid**


<table>
<thead>
<tr>
<th>eGFR (mL/min/1.73m²)</th>
<th>Albuminuria Classes (mg/g)</th>
<th>&lt;10</th>
<th>10-29</th>
<th>30-300</th>
<th>&gt;300</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;105</td>
<td></td>
<td>1.0</td>
<td>1.4</td>
<td>2.1</td>
<td>4.4</td>
<td>1.2</td>
</tr>
<tr>
<td>90-104</td>
<td></td>
<td>1.0</td>
<td>1.3</td>
<td>1.3</td>
<td>3.1</td>
<td>1.6</td>
</tr>
<tr>
<td>75-89</td>
<td></td>
<td>0.9</td>
<td>1.2</td>
<td>1.7</td>
<td>2.3</td>
<td>1.9</td>
</tr>
<tr>
<td>60-74</td>
<td></td>
<td>0.8</td>
<td>1.0</td>
<td>1.4</td>
<td>2.1</td>
<td>1.7</td>
</tr>
<tr>
<td>45-59</td>
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<td>1.0</td>
<td>1.5</td>
<td>1.4</td>
<td>3.6</td>
<td>2.8</td>
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<tr>
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<td>1.2</td>
<td>2.1</td>
<td>2.6</td>
<td>4.0</td>
<td>4.2</td>
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<tr>
<td>15-29</td>
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<td>1.7</td>
<td>2.7</td>
<td>4.2</td>
<td>6.0</td>
<td>5.0</td>
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<td>10</td>
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<td>6.0</td>
<td>10.0</td>
<td>7.6</td>
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*P<0.05

**ESRD Risk**


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*P<0.05
Outline

- Definition and Complications
- New CKD Staging 2013
- Screening for CKD
- Introduction to Cystatin C
- Treatment of CKD
- Hyperkalemia

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

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

From Old to New Staging

<table>
<thead>
<tr>
<th>Cause</th>
<th>GFR (mL/min per 1.73 m²)</th>
<th>Albuminuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Diabetic ( A1 (ACR&lt;30) )</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>Hypertensive ( G2 (60-89) )</td>
<td>( A2 ) (ACR 30-300)</td>
</tr>
<tr>
<td>Polycystic Disease</td>
<td>( G3a (45-59) )</td>
<td>( A3 ) (ACR &gt; 300)</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>( G3b (30-44) )</td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td>( G3c (20-29) )</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>( G5 (&lt;15) )</td>
<td></td>
</tr>
</tbody>
</table>

"CKD" is an inadequate descriptor (like diabetes)
CGA Staging for CKD

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


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Screening for CKD

- International CKD guidelines do not address when or how to screen
  - No RCT evidence for or against
  - Relative costs of screening vary by region
- Hypertension, Diabetes, and CVD guidelines all recommend some form of CKD screening.
- The following are my suggestions for primary care:

Who to Screen with Urine Albumin?

- Primary prevention screens:
  - Diabetes- annual
  - Hypertension
  - Elderly
- CKD Staging:
  - Urine albumin is now 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 elevated</td>
</tr>
<tr>
<td>30-300</td>
<td>Microalbuminuria</td>
<td>Moderately 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

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

Question 3: 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

GFR Estimation from Creatinine

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

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Question 4: Which of the following is true of cystatin C?

- a) Better marker of GFR than creatinine
- b) Better marker of glomerular injury than albumin
- c) Has not been studied in African Americans, but approved for use in Whites
- d) Only used outside the U.S.
- e) All of the above

Cystatin C

- Cystatin C is a blood test of kidney function that is an alternative better version of 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 automated measure that is available for clinical use.
Comparisons of eGFR Using Creatinine, Cystatin C, or both with All-Cause Mortality


Reclassification by eGFRcys and associated risk

International Guidelines Support Use of Cystatin C


KDIGO Suggestion #1 (2B)

- Estimating GFR:
  1. Use creatinine eGFR
  2. Are you confident that this is accurate?
  3. If not, use either:
     - Cystatin C
     - Direct measure GFR

KDIGO Suggestion #2 (2C)

Confirming CKD:
Your patient’s eGFRcr is 45-60 and is not known to have kidney disease:
- Measure cystatin C
- If cystatin C eGFR <60: patient has CKD
- If cystatin C eGFR >60: patient does NOT have CKD

KDIGO Recommendation (1C)

- For medical dosing of potentially toxic agents, use cystatin C or direct measure GFR
- Potential examples — novel, oral anti-coagulants, chemotherapeutics, metformin
- Major challenge — FDA has dosing based on creatinine clearance
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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 and Non-Diabetic CKD

- Diabetic CKD - nearly always has albuminuria
- Diabetic CKD - ACE/ARB essential for:
  - Moderate albuminuria (ACR 30-300)
  - Severe albuminuria (ACR > 300)
- ACE/ARB’s do not appear to be helpful to prevent onset of albuminuria
- In non-diabetic CKD, ACE benefit limited to persons with proteinuria
  - Rahman M, Arch Intern Med, 2005
- Conclusion: For patients with reduced eGFR but normal levels of albuminuria - choice of blood pressure agent probably does not matter

Two Guidelines, Two Opinions

- The new JNC-8 Guideline: ACE/ARB should be used in all patients with CKD (eGFR<60)
  - James PA et al. JAMA 2014
- KDIGO-CKD Hypertension Guideline: ACE/ARB only necessary if ACR > 30

Prevention

ESRD

CVD

Death

CKD
**Frequently Asked ACE/ARB Questions**

- **Question 1:** How much increase in creatinine is safe?
  - **Answer 1:** ↑ of creatinine >30% is common; worry about the potassium

- **Question 2:** Do we stop the ACE in advanced CKD?
  - **Answer 2:** Only if the potassium is un-manageable

- **Question 3:** Is there a reason to combine ACE + ARB?
  - **Answer 3:** No, might decrease proteinuria, but increased potassium risks too high

**Blood Pressure Target Uncertain in CKD**

- Modern RCTs **HAVE NOT** proven that tighter BP control reduces **CKD PROGRESSION**
- Current guidelines on blood pressure control in CKD:
  - JNC-7 target < 130 (contrast with <140)
  - KDIGO-CKD HTN guideline: <140, though <130 considered optimal.
  - JNC-8 target < 140 (contrast with < 150)

**Does SPRINT apply to CKD patients?**

- SPRINT Trial: SBP <120 (Intensive) vs. <140 (Standard)
- Primary Outcome (CVD composite): HR 0.75 (0.64 – 0.89)
- CKD subset (N = 2,646)
  - Primary CVD outcome: 0.82 (0.63-1.07) (interaction p=0.36)
  - Composite renal outcome: 1.4 vs. 1.5 events
  - Impact an kidney injury – TBD
- **Summary:** Impact of intensive BP lowering appear similar in persons with or without CKD.
- Participants without CKD at baseline had higher incidence of incident CKD (<60 ml/min and 30% decline)
  - 127 vs. 37 events; HR = 3.49 (2.44 – 5.10)

**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 0.80; p=0.006)
  - Low rates: 4.1 vs. 5.2%
- In Type II Diabetes, risks of tight glucose control probably offset kidney benefits in older patients.
Statins in CKD - beneficial for CVD

- CKD patients have very high CVD Risk
- Statins lower CVD risk in CKD patients:
  - Meta-analysis of 20 early studies (N=18,746 patients) found RR 0.80 (95% CI: 0.70, 0.90)
  - SHARP RCT: (N=9,500) simvastatin/ezetimide vs placebo
    RR = 0.83 (95% CI: 0.74-0.94)
- No effect on CKD progression
- No benefits of statins in patients with ESRD

Question 5

- In a stable patient on an ACE or ARB, I will tolerate K levels up to the following without stopping the ACE/ARB:
  a) 5.1
  b) 5.3
  c) 5.5
  d) 5.9

Question 6

- Your patient with diabetic nephropathy (eGFR<40, ACR 150) has serum K of 5.3 on repeat measures over 6 months. She is asymptomatic and has a normal physical exam except for symmetric decreased sensation to the ankle. What should you do next?
  a) Change to losartan as it causes less hypokalemia
  b) Increase her furosemide to lower the K
  c) Educate her about situations that would elevate her K further
  d) Stop the lisinopril

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A New Era for the Treatment of Hyperkalemia?

Hyperkalemia is in the Eye of the Beholder

Julie R. Ingelfinger, M.D. - Deputy Editor

- Mild hyperkalemia: 5.0-5.9
- Moderate hyperkalemia: 6.0-7.0
- Severe hyperkalemia: >7.0

New Agent to Treat Hyperkalemia in CKD (Patiromer) Weir MR, NEJM 2015

- FDA approved
- Subjects: CKD and mild/moderate hyperkalemia (5.0-5.6) eGFR:
- Intervention:
  - patiromer (4.2g or 8.4mg BID)
- Adverse effect: constipation – 11%
- Other concern: short-term only

Baseline: 5.7
1 week: 4.9
Day 3: 5.2

Thank you!
Any Questions?