Update on the Management of Chronic Kidney Disease (CKD) in Adults: Focus on Blood Pressure and Proteinuria

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Disclosure
• Kevin Roeder has no actual or potential conflicts of interest to report

Objectives for Pharmacists
• Describe the underlying pathophysiology of chronic kidney disease (CKD).
• Understand the common laboratory tests that are used to assess CKD.
• Describe non-pharmacologic interventions used for the management of CKD.
• Distinguish the various pharmacologic treatments used to manage CKD.
• Apply treatment recommendations to develop a care plan when given a clinical scenario.

Objectives for Pharmacy Technicians
• Identify common causes of CKD.
• Identify medications commonly used in the management of CKD.
• Understand non-pharmacologic treatments of CKD.

Abbreviations
• CKD- chronic kidney disease
• ESRD- end-stage renal disease
• CGA- cause, GFR, albuminuria staging
• GFR- glomerular filtration rate
• PER- protein excretion rate
• AFR- albumin excretion rate
• PCR- protein : creatinine ratio
• ACR- albumin : creatinine ratio
• BP- blood pressure
• SBP- systolic blood pressure
• DBP- diastolic blood pressure
• ACEI- angiotensin converting enzyme inhibitor
• ARB- angiotensin receptor blocker

Kidney Disease / Improving Global Outcomes
Physiology of the Kidney

What is CKD?
- Abnormalities of kidney structure or function, present >3 months, with implications for health.
- Either of the following for >3 months
  - Decreased GFR <60 ml/min
  - Markers of kidney damage
    - Albuminuria
    - Urine sediment abnormalities
    - Electrolyte and other abnormalities due to tubular disorders
    - Structural abnormalities detected by imaging
    - History of a kidney transplant

Why do we care?
- Estimated 25 million Americans have CKD (13%)
  - Not including ESRD patients
- In 2010, there were 593,086 patients with ESRD, including 116,946 new cases
  - 415,725 patients receiving dialysis
  - 179,361 patients with a functioning kidney after transplant
  - African Americans, Native Americans, Hispanics > Caucasians
  - Medicare cost for ESRD: $32.9 billion
    - 8% increase from previous year and 6% of the total budget
- Area of focus in Healthy People 2020

What are the stages of CKD?
- Stages 1-5 based on GFR
  - CGA staging
    - Cause
    - GFR
    - Albuminuria

Causes of CKD

<table>
<thead>
<tr>
<th>Location within the kidney</th>
<th>Examples of systemic diseases</th>
<th>Examples of primary kidney disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerular disease</td>
<td>Diabetes, systemic autoimmune disease, amyloidosis</td>
<td>Proliferative glomerulonephritis</td>
</tr>
<tr>
<td>Tubulointerstitial disease</td>
<td>Drugs, toxins, myeloma, autoimmune</td>
<td>UTI, stones, obstruction</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>Atherosclerosis, hypertension, cholesterol emboli, systemic vasculitis</td>
<td>ANCA renal-limited vasculitis</td>
</tr>
<tr>
<td>Cystic and congenital</td>
<td>Polycystic kidney disease</td>
<td>Renal dysplasia</td>
</tr>
</tbody>
</table>

Stages of GFR

- GFR categories in CKD
  - G1 >90 Normal or high
  - G2 60-89 Mildly decreased
  - G3a 45-59 Mildly to moderately decreased
  - G3b 30-44 Moderately to severely decreased
  - G4 15-29 Severely decreased
  - G5 <15 Kidney failure

- Threshold of GFR <60 ml/min (>3 months) to indicate CKD
  - <50% of "normal"
  - Easily detected by routine labs and current equations for estimating GFR
  - GFR <60 ml/min associated with higher rates of complications
    - Drug toxicity, metabolic/endoctrine, CVD/Death


Data collected from 1996-2000 (n=1,120,295) showed a graded association between reduced GFR and rate of cardiovascular events and hospitalizations.

**Stages of Albuminuria**
- Clinical terminology shifting toward “albuminuria” vs. “proteinuria”
- Albumin is the principal component of urinary protein
- Current classification based on albuminuria
- Levels of urinary albumin have been strongly correlated with risk (CKD and CVD)

**Albuminuria categories in CKD**

<table>
<thead>
<tr>
<th>Category</th>
<th>AER (mg/24 hrs)</th>
<th>ACR (mg/g)</th>
<th>Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>&lt;30</td>
<td>&lt;30</td>
<td>Normal to mild</td>
</tr>
<tr>
<td>A2</td>
<td>45-59</td>
<td>30-300</td>
<td>Moderate</td>
</tr>
<tr>
<td>A3</td>
<td>60-89</td>
<td>&gt;300</td>
<td>Severe</td>
</tr>
</tbody>
</table>

- Threshold of AER ≥30mg/24 hours or ACR ≥30mg/g to indicate CKD
  - >3 times ULN
  - Lowest threshold that can be detected as “trace” on dipstick
  - Increased risk for complications above these thresholds

**Albuminuria vs. Proteinuria and Conversions**

<table>
<thead>
<tr>
<th>Categories</th>
<th>Measure</th>
<th>Normal to mildly increased</th>
<th>Moderately increased</th>
<th>Severely increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>AER (mg/24h)</td>
<td>&lt;30</td>
<td>30-300</td>
<td>&gt;300</td>
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<tr>
<td>FFR (mg/24h)</td>
<td>&lt;150</td>
<td>150-500</td>
<td>&gt;500</td>
<td></td>
</tr>
<tr>
<td>ACR (mg/mmol)</td>
<td>&lt;3</td>
<td>2-30</td>
<td>&gt;30</td>
<td></td>
</tr>
<tr>
<td>ACR (mg/g)</td>
<td>&lt;30</td>
<td>30-300</td>
<td>&gt;300</td>
<td></td>
</tr>
<tr>
<td>PCR (mg/mmol)</td>
<td>&lt;15</td>
<td>15-50</td>
<td>&gt;50</td>
<td></td>
</tr>
<tr>
<td>Protein reagent strip</td>
<td>Negative to trace</td>
<td>Trace to +</td>
<td>or greater</td>
<td></td>
</tr>
</tbody>
</table>

**GFR, Albinurinaria, and Prognosis**

- Risk of progression indicated by color
- Numbers indicate recommended number of follow-up visits per year

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[References]


Risk Factors for CKD Progression

- Cause of CKD
- Level of GFR
- Level of albuminuria
- Age
- Gender
- Race/ethnicity
- Elevated BP
- Hyperglycemia
- Dyslipidemia
- Smoking
- Obesity
- CVD
- Continued exposure to nephrotoxic agents

Relative weights of these risk factors is unknown. There is no well-validated risk calculator/model.

Lifestyle Interventions in CKD

- **Protein Intake**
  - Reduce to 0.8 g/kg/day if GFR <30 ml/min (G4-G5)
  - Avoid >1.3 g/kg/day if at risk for progression (esp. non-dairy animal protein)
- **Low carbohydrate diet in diabetic patients with CKD**
  - HbA1c ~7.0%, or above with comorbidities / short life expectancy
  - RBC life is shorter in CKD patients, leads to falsely low HbA1c
- **Salt Intake**
  - <2 g sodium per day (5 g NaCl), unless contraindicated
- **Limit alcohol**
  - Increases BP

Assessment Question 1
Which of the following defines chronic kidney disease (CKD)?

a. Abnormalities of kidney structure or function, present >3 months, with implications for health
b. Any GFR <90 ml/min
c. Albuminuria for >1 week
d. None of the above

Assessment Question 2
Which of the following is a recommended component of KDIGO CKD staging?

a. Cause of CKD
b. GFR
c. Albuminuria
d. All of the above

e. Race/ethnicity, cardiovascular disease

Assessment Question 3
Which of the following is reversible risk factor(s) for CKD progression?

a. Cause of CKD
b. Elevated blood pressure, hyperglycemia, dyslipidemia
c. Age, gender
d. Race/ethnicity, cardiovascular disease
Assessment Question 4
The presence of albuminuria and decreased GFR have been associated with which of the following?
- a. Higher hospitalization rates
- b. Increased mortality risk
- c. Increased risk of cardiovascular events
- d. All of the above

“Blood Pressure” and CKD (not hypertension)
- Strong association between blood pressure and CKD
  - Each can aggravate the other
- Emphasis on individualized BP targets
- BP-lowering medication may be used for other indications

Populations of Interest
- Adults with CKD ND – DM
- Adults with CKD ND + DM
- Adults with CKD ND + transplant (CKD T)
- Children with CKD ND
- Elderly with CKD ND

Adults with CKD +/- DM
- Blood pressure target depends on albuminuria
  - AER ≤30 mg/24 hours: ≤140/90
  - AER >30 mg/24 hours: ≤130/80
  - Remember, BP targets should be individualized
  - This is an area of controversy
- Prefer ACE(I) or ARB as first line agents AER >30 mg/24 hours
- If AER <30 mg/24 hours: ACE(I) or ARB?
  - Clinically, we usually start with an ACE(I) or ARB in the absence of contraindications

ACE(I) and ARB
- ACE(I) and ARBs can be used interchangeably
- Arterial vasodilation, efferent > afferent arteriole dilation decreases intra-glomerular pressure
  - Decreased GFR (reversible) and albuminuria
- Reductions in BP and albuminuria do not always correlate, but each is associated with risk reduction independent of the other.
- Reduced secretion of aldosterone
  - “Aldosterone breakthrough” in ~50% of patients
- Use cautiously or avoid in bilateral renal artery stenosis and certain acute care settings
- ACE(I) + ARB combination is controversial
Aldosterone Antagonists
- Established role in resistant hypertension / hyperaldosteronism, CHF
- Shown to reduce albuminuria ~50% at 12 weeks when used in combination with an ACE(I)
  - Interpret cautiously due to limited data
- Unclear long-term effect on renal function
- Increased risk of hyperkalemia when used with ACE(I) or ARB
  - Monitor!
- Clinically, aldosterone antagonists are useful for add-on therapy in the setting of albuminuria already being treated with ACE(I) or ARB
- Gynecomastia with spironolactone, more common at high doses

Calcium Channel Blockers
- Dihydropyridines (amlodipine)
  - Act on L-type calcium channels
  - Found predominantly on the afferent arteriole, increases intra-glomerular pressure
  - Can increase albuminuria
  - Avoid with albuminuria, especially if not being treated with ACE(I) or ARB
- Non-dihydropyridines (diltiazem, verapamil)
  - Act on T-type calcium channels
  - Found on afferent and efferent arterioles, decreases intra-glomerular pressure
  - Can decrease albuminuria
- Problematic lower extremity edema (especially dihydropyridines), otherwise consider CCBs as “CKD neutral”

Other Antihypertensives
- Loop diuretics—VOLUME!
- Thiazides—may potentiate benefits of ACE(I) and ARB
  - Reduced efficacy at CrCl <30 mL/min
  - Metolazone—only for loop-refractory volume overload
- Potassium-sparing diuretics (amiloride, triamterene)—Liddle’s Syndrome
- Beta-blockers—atenolol and bisoprolol accumulate in CKD
- Central alpha-agonists—caution in the elderly, otherwise safe in CKD
- Alpha-blockers—hypertension = BPH, no renal dose adjustments
- Direct vasodilators (hydralazine)—generally safe, but limited value in CKD

Kidney Transplant Recipients (CKD T)
- BP target is ≤130/80 regardless of albuminuria
- Choice of agent depends on:
  - Time after transplant
    - Often avoid ACE(I) and ARB for ~3-4 months post-transplant
  - Use of calcineurin inhibitors
  - Presence or absence of persistent albuminuria
- Co-morbid conditions / “compelling indications”
- Limited evidence supporting DHP CCBs
  - MOA: may counteract afferent arteriole constriction caused by CNIs
  - Reduced risk of graft loss (RR 0.75, CI 0.57-0.99)
  - Improved GFR (MD 4.5 mL/min, CI 2.2-6.7)
- Drug interaction with tacrolimus?
**Management of BP in the Elderly**

- BP treatment tailored to the individual
- "J-shaped" relationship between CKD and BP in the elderly, both treated and not treated, and associated with increased mortality
  - Lowest prevalence
    - SBP 120-159mmHg and DBP 80-99mmHg
  - Higher prevalence
    - SBP ≥160 OR <120mmHg
    - DBP ≥100 OR <80mmHg
  - Slow treatment escalation
- Isolated high systolic blood pressure

**Labs for JR on 8/26/13**

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<th>08/26/13</th>
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<td>138</td>
</tr>
<tr>
<td>K (mEq/L)</td>
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<td>4.7</td>
</tr>
<tr>
<td>Cl (mEq/L)</td>
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<td>CO2 (mEq/L)</td>
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<tr>
<td>BUN (mg/dL)</td>
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<td>34</td>
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<tr>
<td>Hct/SCr</td>
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<td>29</td>
</tr>
<tr>
<td>SCR (mg/dL)</td>
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</tr>
<tr>
<td>eGFR (mL/min)</td>
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<td>28</td>
</tr>
<tr>
<td>PCR (mg/g)</td>
<td>200</td>
<td>N/A</td>
</tr>
<tr>
<td>FeNa</td>
<td>N/A</td>
<td>1.6%</td>
</tr>
<tr>
<td>FeUrea</td>
<td>N/A</td>
<td>0.9%</td>
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**Clinical Course for JR**

- Discontinued metoprolol, no compelling indication and not first line
- Decreased spironolactone to 25mg once daily, then D/C on 9/30/13
- Followed home blood pressure readings and local labs

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<td>200</td>
<td>100</td>
<td>N/A</td>
<td>N/A</td>
</tr>
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</table>

**Summary of Blood Pressure Management**

- Blood pressure goals should be individualized
  - Albuminuria (-): ≤140/90
  - Albuminuria (+): ≤130/80
  - CKD T: ≤130/80
- Geriatrics:
  - Over-treating and under-treating BP are BOTH HARMFUL
  - ACE(I) and ARB are preferred, especially in the presence of albuminuria or diabetes
  - Titration based on blood pressure AND albuminuria
  - Aldosterone antagonists can further reduce albuminuria when used with an ACE(I) or ARB
- Other antihypertensives can be useful if additional BP lowering is needed, or if co-morbid conditions are present (i.e. CHF and beta-blockers)

**Managing BP in the Elderly: Patient Case**

- JR is a 70 y/o Caucasian female who presents for follow-up for "stage 3" CKD and hypertension.
- PMH: HTN (2° to CKD), DM2, COPD, anemia, omeprazole-induced interstitial nephritis, SLE with nephropathy (1976)
- Medications related to blood pressure and CKD:
  - Losartan 50mg BID
  - Spironolactone 25mg BID
  - Metoprolol tartrate 25mg BID
  - FHE: non-contributory
  - SLE: EtOH (-), smoking (+)
- Vitals:
  - BMI: 35 kg/m²
  - Supine: BP- 108/66 mmHg P- 88 BPM
  - Upright: BP- 90/64 mmHg P- 96 BPM

**Managing BP in the Elderly: Patient Case**

- What stage of CKD would JR correspond to, per KDIGO guidelines?

**Managing BP in the Elderly: Patient Case**

- What are the risk factors for progression of CKD in JR?
- What could be the underlying cause of the decline in her renal function?
**Assessment Question 5**
The blood pressure goal for both diabetic and non-diabetic CKD patients who have clinically significant albuminuria (≥30 mg/24 hours or equivalent) is:

a. ≤140/80
b. ≤130/80
c. ≤140/90
d. ≤120/80

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**Assessment Question 6**
In diabetic and non-diabetic CKD patients with albumin excretion rates >300 mg/24 hours (or equivalent), the first line agent for the treatment of elevated blood pressure is:

a. ACE inhibitor
b. Thiazide diuretic
c. Beta-blocker
d. Both A and B are first-line agents

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**Assessment Question 7**
True or False: In the absence of an absolute contraindication (such as hypersensitivity, bilateral renal artery stenosis, etc.) all patients with diabetes should be given an ACE inhibitor or angiotensin receptor blocker.

- True
- False

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**Assessment Question 8**
True or False: In the absence of an absolute contraindication (such as hypersensitivity, bilateral renal artery stenosis, etc.) all patients with CKD should be given an ACE inhibitor or angiotensin receptor blocker.

- True
- False

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**Questions?**
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