Chronic Kidney Disease: What the Generalist Needs to Know

Primary Care Medicine: Principles and Practice

October 14, 2016
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KDIGO 2012 CKD Definition
Abnormalities of kidney function or structure > 3 months

- Markers of kidney disease
  - Albuminuria >30 mg/day or ACR > 30 mg/g creatinine
  - Urine sediment abnormalities
  - Electrolyte or other abnormalities due to tubular disorders
  - Abnormalities detected by histology
  - Structural abnormalities detected by imaging
  - History of kidney transplantation

OR
- Decreased eGFR < 60 mL/min/1.73 m²

Chronic Kidney Disease

- Definition of CKD
- Staging of CKD
- Relevance/Epidemiology
- Management
  - Metabolic acidosis
  - Electrolytes
  - HTN targets and agents
  - Proteinuria
  - DM nephropathy
- Referral to Nephrology

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

<table>
<thead>
<tr>
<th>Persistent albuminuria categories</th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
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<td>Description and range</td>
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<td>Normal to mildly increased</td>
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<td>Moderately increased</td>
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<td>Severely increased</td>
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GFR categories (ml/minute x 1.73 m²)

G1: Normal or high
G2: Mildly decreased
G3a: Moderately decreased
G3b: Moderately to severely decreased
G4: Severely decreased
G5: Kidney failure
Figure 2.2 Trends in prevalence of recognized CKD, by race, among Medicare patients aged 65+, 2000-2013

Data Source: Special analyses, Medicare 5 percent sample. Abbreviation: CKD, chronic kidney disease; Af Am, African American; Native Am, Native American.

Figure 3.1 Unadjusted and adjusted all-cause mortality rates (per 1,000 patient years at risk) for Medicare patients aged 66 and older, by CKD status and year, 2001-2013

(a) Unadjusted

(b) Adjusted


Figure 3.2 Unadjusted and adjusted all-cause mortality rates (per 1,000 patient years at risk) for Medicare patients aged 66 and older, by CKD status and stage, 2013

Data source: Medicare 5 percent sample. Adj: age/sex/race. Ref: all patients, 2013. See Table 4 for CKD stage definitions. Abbreviations: CHF, chronic heart failure; DM, diabetes mellitus; CKD stage undefined.

Figure 6.5 Per person per year expenditures on Parts A, B, and D services for the CKD Medicare population aged 65+, by DM, CHF, and year, 1993-2013

Data source: Medicare 5 percent sample. Abbreviations: CKD, chronic kidney disease; CHF, congestive heart failure; DM, diabetes mellitus; PPPY, per person per year.
Metabolic Acidosis in CKD

- Acid excretion as ammonium decreases in CKD → metabolic acidosis
- Prevalence of metabolic acidosis increases with CKD stage, up to 25% of CKD stage G5
- Increased anion gap due to retention of acidic anions such as PO₄, SO₄, urate, hippurate.
- Relevance of acidosis?
  - Association with increased mortality, progression of CKD
  - Bone resorption and osteopenia
  - Muscle protein catabolism
  - Worsening secondary hyperparathyroidism
  - Impaired myocardial contractility and heart failure

Treatment of Metabolic Acidosis in CKD

- CKD Stage 4, metabolic acidosis, serum bicarbonate 16-20 mEq/L
- Randomized to bicarbonate vs. no treatment x 2 years
  - Sodium bicarbonate 600 mg PO TID, dose titrated to serum bicarbonate ≥ 23
- Results
  - Slower decline in CrCl (1.88 vs. 5.93 mL/min/1.73 m² per year)
  - Lower risk of annual decline in CrCl ≥ mL/min/1.73 m² per (9 vs. 45%)
  - Lower risk of ESRD (6.5 vs. 33%)

Bicarbonate Therapy in CKD

- Bicarbonate patients more likely to develop edema and worsening HTN (not statistically significant)
  - Sodium bicarbonate does not expand volume as much as NaCl
  - CKD patients without acidosis may have smaller benefit
    - Kidney Int 2010, PMID 20445497
  - Alkaline diet may produce similar results to oral bicarbonate
    - CJASN 2013, PMID 23393104
  - Are other sources of bicarbonate, e.g. sodium citrate, calcium citrate, as effective?
Mineral Metabolism in CKD

- Hypocalcemia due to decreased vitamin D activation by kidney
- Secondary HPTH increases release of Ca x PO4 from bone, resulting in negative calcium balance, bone loss, and hyperphosphatemia
- Primary vs. Secondary Hyperparathyroidism
  - Hypercalcemia vs. Hypocalcemia
  - Normal/Mildly ↑ PTH vs. Moderately/Severely ↑ PTH

Bone density measured by DEXA can be unreliable in CKD/ESRD patients

- Difficult to diagnose osteoporosis/osteopenia in CKD/ESRD
- Decreased bone density on DEXA may be related to renal osteodystrophy (osteitis fibrosa cystica, adynamic bone disease, osteomalacia), not osteoporosis
- Bone biopsy may be necessary to differentiate, but procedure not readily available clinically.
- Bisphosphonates contraindicated in CKD, eGFR < 30-60 mL/min/1.73 m²

New oral agents to treat hyperkalemia

Zirconium cyclosilicate (ZS-9)
- Crystalline compound that exchanges Na/H for K in gut
- HARMONIZE trial, JAMA 2014: non-ESRD CKD, DM, heart failure, RAAS inhibitors, 28 day follow up
- NEJM 2015, adults with K 6 to 6.5 mmol/L, ~60% with CKD, ~60% with DM, ~48% with CHF, 48 hour trial
- Indication: Mild to moderate hyperkalemia
- Causes diarrhea
- Not FDA approved.

Patiromer
- Organic polymer resin, exchanges Ca for K in gut
- OPAL-HK Trial, NEJM 2015, PMID 25415805
  - Stage 3-4 CKD patients on RAAS inhibitors, K 5.1 to 6.4 mEq/L
  - Outcome: Serum K at 4 weeks
  - Constipation was major adverse event
  - Mean ΔK was 1 mEq/L
New oral agents to treat hyperkalemia

Conclusions for Zirconium and Patiromer
- Indication: Outpatient chronic moderate hyperkalemia
- Caveats
  - Zirconium not FDA approved.
  - Patiromer causes constipation.
  - Utility in acute or severe hyperkalemia?
  - Long term safety and efficacy?

HTN Targets in CKD
- SPRINT TRIAL, NEJM 2015
- Patients: 9361 adults ≥ 50 years old, high CV risk (CV disease, Framingham score ≥15%, eGFR 20-60 mL/min/1.73 m², or older age ≥ 75 years)
- Exclusion criteria: DM or prior CVA
- Intervention: 120 mm Hg vs. 140 mm Hg SBP target
- Primary outcome: MI, ACS, CVA, heart failure, CV death
- Intensive vs. Conventional Group hazard ratio for primary outcome 0.75
- Complications in Intensive Group: hypotension, syncope, electrolyte abnormalities, and AKI
- Comment: Primary endpoint did not include renal outcomes (doubling of serum creatinine, ESRD)

ACCORD Trial, NEJM 2010
- Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus
- The ACCORD Study Group
ACCORD Trial

- T2DM patients at high CV risk
  - T2DM with HbA1c ≥ 7.5%
  - Age ≥ 40 with CV disease OR Age ≥ 55 with atherosclerosis, albuminuria, LVH, or at least 2 additional CV risk factors (dyslipidemia, HTN, smoking, obesity)
- Intervention: Intensive (120 mmHg) vs. Standard (140 mmHg) SBP
- Primary endpoint: non-fatal MI or CVA, CV death
- Endpoint did not include renal outcome
- Results: No difference in primary endpoint or annual death rates, but lower annual rate of CVA in intensive group

HTN Target in CKD

- SPRINT Trial suggests systolic target of 120 mmHg for CV (non-renal) outcomes in non-DM patients, some with moderate CKD
- ACCORD Trial found no CV benefit in high risk T2DM patients (some with albuminuria)
- JNC 8 Guidelines
  - Goal <140/90 mmHg for patients < 60 years, DM, or CKD
  - Goal <150/90 mmHg for patients ≥ 60 years
- BP goal in non-DM CKD patients with proteinuria?
  - Few trials with primary renal outcomes
  - Limited evidence for BP target < 140/90 mmHg

ACR and ARB in CKD

- ACE or ARB are preferred agents in CKD patients with HTN
- ACE and ARB slow the progression of DM kidney disease
  - Captopril trial in IDDM, NEJM 1993
  - RENAAL and IDNT trials T2DM in 2001
- ACE effective in non-DM CKD
  - Benazepril trial, NEJM 1996; REIN Trial, Lancet 1997; AASK Trial JAMA 2001
- ACE remain effective even in advanced CKD
  - Benazepril in patients with creatinine 3-5 mg/dL, NEJM 2006
- Goal urine protein: < 1000 mg/day, roughly equivalent to spot urine P:C ratio < 1 or 1000 mg/g creatinine

Diabetic Nephropathy

- Hallmark is albuminuria, ACR > 30 mg/g creatinine or 24 hour urine albumin 90 mg/day
- May have hyperfiltration in early stages, glomerular hypertrophy, and enlarged kidneys
- Consider non-diabetic kidney disease if:
  - Abrupt onset of kidney disease/dysfunction
  - T1DM patients: Duration < 5 years or absence retinopathy and neuropathy
  - T1DM patient >20-25 years without nephropathy now presents with kidney disease
- Active urine sediment (dysmorphic RBCs and RBC casts)
Risk Factors of DM Nephropathy

- Genetics: Family Hx
- Race: African Americans, Mexican-Americans, Pima Indians
- Age: Older age and duration of DM
- Obesity
- Glycemic control
- HTN
- GFR: Hyperfiltration (increased GFR) in early stages of DM nephropathy
- Smoking

Treatment of DM Nephropathy

- In T1DM and T2DM, nephropathy can regress with glycemic control, HTN therapy, and ACE or ARB.
  - Spontaneous regression can occur
  - Glycemic control
    - Can reverse glomerular hypertrophy and hyperfiltration
    - Can delay development of albuminuria/DM nephropathy
    - Can stabilize or reduce albuminuria (may take years)
    - Can slow progression of eGFR/CKD

- Proteinuria reduction
  - IDNT and RENAAL Trials: dose response relationship between proteinuria reduction and greater risk reduction in risk of kidney failure
  - Combination ACE/ARB therapy will decrease proteinuria more than monotherapy with ACE or ARB alone, but does not improve renal outcomes.

NEJM June 2016

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fichtet, M.D., Maximilian von Eynatten, M.D., Michaela Matheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D., Hans J. Woehrle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D., for the EMPA-REG OUTCOME Investigators*
EMPA-REG OUTCOME Trial

- T2DM patients, eGFR ≥ 30 mL/min/1.73 m²
- Empagliflozin: Na-glucose cotransporter 2 inhibitor
- Intervention: empagliflozin vs. placebo
- Endpoint: incident or worsening nephropathy (progression to macroalbuminuria, doubling of serum creatinine, initiation of dialysis, death from renal disease) and incident albuminuria
- Results:
  - Incident/worsening nephropathy: Empagliflozin 12.7% vs. Placebo 18.8%
  - Doubling of serum Cr: 1.5% vs. 2.6%
  - Dialysis Initiation: 0.3% vs. 0.6%
  - No difference in incident albuminuria

What NOT to do in DM Nephropathy

- **Combination ACE/ARB Therapy**
  - **VA NEPHRON-D Trial**, NEJM 2013; PMID 24206457
    - T2DM with ACR ≥ 300 mg/g, eGFR 30-90 mL/min/1.73 m²
    - Losartan +/- Lisinopril, similar primary endpoint of 50% decline in eGFR, ESRD or death, but combination therapy associated with hyperkalemia and AKI requiring or during hospitalization
  - **ONTARGET Trial**, Lancet 2008; PMID 18707986
    - Patients ≥ 55 years with atherosclerotic vascular disease OR DM with end organ damage
    - Telmisartan and/or Ramipril: Combination therapy increased primary endpoint of death, ESRD and doubling of serum creatinine

What NOT to do in DM Nephropathy, cont.

- **Renin inhibitor Aliskiren with ACE or ARB**
  - **ALITUDE Trial**, NEJM 2012; PMID 23121378
    - Aliskiren with ACE or ARB in T2DM, primary endpoint CV death, arrest, non-fatal MI or CVA, heart failure hospitalization, ESRD, uremic death, doubling of serum creatinine
    - Aliskiren patients more likely than placebo patients to reach primary endpoint (18.3 vs. 17.1%) although similar renal endpoints (6% vs 5.9%)
  - **Antioxidant inflammatory modulator Bardoxolone with ACE or ARB**
    - BEACON Trial, NEJM 2013; PMID 24206459
    - Similar primary endpoint of ESRD and CV death, but bardoxolone had more CV events (CV death, heart failure hospitalization, non-fatal CVA/MI)

Referral to Nephrology

- **Unknown etiology of CKD**
- **eGFR < 30 mL/min/1.73 m²**
- **Rapidly progressive CKD**
- **Albuminuria > 300 mg/g creatinine**
- **Non-urological hematuria**
- **Resistant HTN**
- **Complicated CKD** (hyperkalemia, anemia of CKD requiring ESA, mineral metabolism, CKD and CHF)
- **Known or suspected hereditary CKD**
**KDIGO 2012 CKD Definition**
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**Causes for Late Referral to Nephrology**
- Lack of consensus when to refer to nephrology
  - eGFR < 30 mL/min/1.73 m² and/or albumin > 300 mg/g creatinine?
- Definition of late referral: Referral 1-6 months prior to requiring RRT
  - Regional and international differences in late referral patterns
  - System issues: Health insurance, healthcare access, health literacy, other structural barriers
  - Patient factors: socioeconomic issues, substance use, denial, etc.

**Consequences of Late Referral**
- Metabolic abnormalities: Acidosis, hyperkalemia, hyperphosphatemia, hypoalbuminemia, anemia
- Lack of preparation for renal replacement therapy (RRT)
  - HD > PD, In Center > Home, temporary > tunneled catheters, Catheter > AVF/AVG, Increased hospitalizations for RRT initiation
- Late referral to kidney transplantation
  - Less likely to get primary transplant (transplant without preceding RRT), longer time on RRT waiting for transplant, increased morbidity of ESRD/RRT, higher mortality
- Increased Mortality: All cause and one year mortality

**Final Thought**
- Recommendations to elderly patients starting dialysis?
  - You will feel better, have more energy, eat more, etc.
  - Recent data suggest otherwise
  - NEJM 2009; PMID 19828531
Quality of Life pre/post Dialysis Initiation

[Graph showing metrics over time]