Chronic Kidney Disease

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Disclosures

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Topics

• Staging of chronic kidney disease (CKD)
  – How to assess GFR
• Blood pressure control
  – Optimal use of ACE-I and ARB
  • Treatment/prevention of hyperkalemia
• Anemia management
• CKD-MBD

Staging and GFR

Definition of Chronic Kidney Disease

• Kidney damage for ≥ 3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR manifest by either:
  – Pathological abnormalities; or
  – Markers of kidney damage, including abnormalities in the composition of blood or urine, or abnormalities in imaging tests
• GFR < 60 mL/min/1.73 m² for ≥ 3 months, with or without kidney damage

K-DOQI Staging of Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Kidney damage with normal GFR</td>
<td>≥ 90</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Kidney damage with mild decrease in GFR</td>
<td>60-89</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Moderate decrease in GFR</td>
<td>30-59</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Severe decrease in GFR</td>
<td>15-29</td>
</tr>
<tr>
<td>Stage 5</td>
<td>Kidney failure</td>
<td>&lt; 15 or dialysis</td>
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</table>
### Estimating GFR
- Serum creatinine alone is a poor predictor of GFR. Example: Thin elderly woman with creatinine of 2.0 mg/dL.
- The ideal substance for measuring GFR is one that is freely filtered at the glomerulus but is neither secreted nor reabsorbed.
- In research studies, clearance of iothalomate is the "gold standard" for measurement of GFR.

### Creatinine clearance
- Creatinine is freely filtered at the glomerulus and is not reabsorbed.
- 10-40% of urinary creatinine is derived from creatinine secretion in the proximal tubule, which can be affected by medications.
  - Trimethoprim
  - Cimetidine
- Creatinine clearance from 24-hour urine
  \[
  \text{Urine creatinine (mg/dL) x urine volume (mL)} \\
  \text{Serum creatinine (mg/dL) x 1440 min}
  \]

### Creatinine clearance example
- 40-year-old man
  - Urine volume: 2 liters
  - Urine creatinine: 88 mg/dL
  - Serum creatinine 1.1 mg/dL
  - \((88 \text{ mg/dL} \times 2000 \text{ mL})/(1440 \text{ min} \times 1.1 \text{ mg/dL})\)
  - Creatinine clearance 111 mL/min
  - Caveat: Creatinine excretion per day should be about 20-25 mg/kg of lean body weight for men and 15-20 mg/kg for women

### Cockroft-Gault Equation
\[
(140 \text{- age}) \times \text{weight in kg} \\
\text{Serum creatinine (mg/dL) x 72}
\]
Multiply x .85 for women
**MDRD Equation Simplified**

- $1.863 \times \text{PCr}^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$
- Caveat: Only validated for patients with CKD
- Equation from which automated eGFR estimates are derived.
- What to do with muscular young man with creatinine $1.4 \text{ mg/dL}$?

**Examples of MDRD and Cockroft-Gault**

- 40-year-old white man with a creatinine of $1.1 \text{ mg/dL}$
  - MDRD GFR 79 mL/min
  - Cockroft-Gault GFR 88 mL/min

**Pitfalls of the eGFR**

- The lower the serum creatinine, the less accurate the eGFR.
- 24-hour urine for creatinine clearance may be a better way of estimating GFR than the MDRD equation in this situation

**Blood pressure control in CKD**

Optimal Use of ACE-I/ARBs

**Importance of Blood Pressure Control**

- Retarding progression of kidney disease
- Reducing cardiovascular risk
- Recommended targets:
  - 130/80 (K-DOQI and JNC VII)
  - Will this recommendation hold?

**Indications for ACE-I/ARB**

- Diabetic kidney disease (type 1 and type 2)
- Proteinuric kidney diseases
- Hypertensive nephrosclerosis
- Microalbuminuria
Is there a GFR below which there is no benefit of ACE-I/ARB?

Benazepril is beneficial in patients with advanced CKD

The hyperkalemia “perfect storm”
- Pre-existing CKD
- Volume depletion
- ACE-I
- NSAIDs
- Trimethoprim-sulfamethoxazole

Risk Factors for Hyperkalemia with the Use of Drugs That Interfere with the Renin–Angiotensin–Aldosterone System

The Renin–Angiotensin–Aldosterone System and Regulation of Potassium Excretion in the Kidney

Association Between Hospital Admission Involving Hyperkalemia and Recent Antibiotic Use
Treatment of Chronic Hyperkalemia
- Dietary K+ restriction: Refer to nutrition for dietary counseling
- Treat metabolic acidosis associated with type 4 RTA
- Loop diuretic
- Sodium polystyrene sulfonate

Loop diuretics
- Act in the thick ascending limb of the nephron
- Block the furosemide sensitive co-transporter
- Induce loss of sodium and potassium

Anemia in CKD
- Decreased production of erythropoietin
- Direct marrow suppression by uremic toxins
- Shortened red blood cell survival
- Increased blood loss
- Iron and folate deficiency
- Resistance to erythropoietin

Benefits of anemia management in chronic kidney disease
- Improved functional status and sense of well being
- Relief of uremic symptoms
- Reduction in macular edema in diabetic patients
- Increased cognitive function
- Reduction in left ventricular mass
- Improved sleep pattern

Pathophysiology
- Iron management
  - Iron saturation between 20 and 50%
  - Ferritin between 100 and 800 ng/mL
  - IV iron therapy as needed
    - Iron sucrose (Venofer®)
    - Ferric gluconate (Ferrlecit®)
    - Ferumoxytol (Feraheme®)
    - Iron dextran (Infed®)
  - Significant rate of adverse reactions including a 1.7% risk of anaphylactoid reactions
Erythropoiesis stimulating agents

- Erythropoietin (Procrit® and Epogen®) and darbepoetin (Aranesp®) are currently available ESPs.
- Darbepoetin has a longer half-life and requires less frequent administration.
- ESPs are generally given subcutaneously in pre-dialysis patients and intravenously or subcutaneously to dialysis patients.

FDA Label for Procrit® (2007)

• WARNINGS:
  - INCREASED MORTALITY, SERIOUS CARDIOVASCULAR EVENTS, THROMBOEMBOLIC EVENTS, STROKE and INCREASED RISK OF TUMOR PROGRESSION OR RECURRENCE

FDA Label for Procrit® (2007)

• Chronic Renal Failure:
  - In clinical studies, patients experienced greater risks for death, serious cardiovascular events, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target hemoglobin levels of 13 g/dL and above.
  - Individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL.

FDA changes to the ESA label June 2011

• For patients with CKD not on dialysis:
  - Consider initiating ESA treatment only when the hemoglobin level is less than 10 g/dL and the following considerations apply:
    - The rate of hemoglobin decline indicates the likelihood of requiring a red blood cell transfusion; and
    - Reducing the risk of alloimmunization and/or other red blood cell transfusion-related risks is a goal.
    - If the hemoglobin level exceeds 10 g/dL, reduce or interrupt the dose of ESA and use the lowest dose of ESA sufficient to reduce the need for red blood cell transfusions.

FDA changes to the ESA label June 2011

• For patients with CKD on dialysis:
  - Initiate ESA treatment when the hemoglobin level is less than 10 g/dL
  - If the hemoglobin level approaches or exceeds 11 g/dL, reduce or interrupt the dose of ESA.
  - When initiating or adjusting therapy, monitor hemoglobin levels at least weekly until stable, then monitor at least monthly.
  - For patients who do not respond adequately over a 12-week escalation period, increasing the ESA dose further is unlikely to improve response and may increase risks.

Renal Bone Disease

CKD-MBD
Renal Bone Disease

Renal Disease

GFR (< 30 ml/min)

Phosphate

Calcium

1,25(OH)2D3

Osteomalacia

Renal Osteodystrophy

Management of bone disease in CKD patients

- Dietary phosphate restriction
- Phosphate binders
  - Calcium carbonate
  - Calcium acetate (PhosLo ®)
  - Sevelamer (Renagel ®)
  - Lanthanum carbonate (Fosrenol®)
- Vitamin D analogues
  - Calcitriol (Rocaltril ®)
  - Paracalcitol (Zemplar ®)
  - Doxercalciferol (Hectorol ®)
- Cinacalcet (Sensipar ®)
- Parathyroidectomy

Target PTH in CKD

<table>
<thead>
<tr>
<th>CKD STAGE</th>
<th>GFR RANGE</th>
<th>TARGET INTACT PTH</th>
<th>OPINION OR EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>30-59</td>
<td>35-70</td>
<td>OPINION</td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>70-110</td>
<td>OPINION</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15 or dialysis</td>
<td>150-300</td>
<td>EVIDENCE</td>
</tr>
</tbody>
</table>

Vitamin D deficiency in CKD

- Vitamin D deficiency is common in patients with CKD.
- Correcting vitamin D deficiency may lower PTH in patients with hyperparathyroidism.

Preventing and treating renal osteodystrophy

- Control serum phosphorous (diet and phosphate binders)
- Measure intact PTH and vitamin D level
- If PTH is above target for stage of CKD and vitamin D level is < 30 ng/mL, vitamin D should be repleted.
- If PTH is above target for stage of CKD and vitamin D level is > 30 ng/mL, therapy with an activated form of vitamin D (calcitriol, doxercalciferol, or paracalcitol) is indicated.

Vitamin D repletion

<table>
<thead>
<tr>
<th>Serum 25 (OH)D (ng/mL)</th>
<th>Ergocalciferol dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>50000 units po weekly x 12 weeks, then monthly</td>
<td>6 months</td>
</tr>
<tr>
<td>5-15</td>
<td>50000 units po weekly x 4 doses, then 50000 units monthly</td>
<td>6 months</td>
</tr>
<tr>
<td>16-30</td>
<td>50000 units po monthly</td>
<td>6 months</td>
</tr>
</tbody>
</table>
Summary and Take-Home Points-1
• Use the K-DOQI CKD staging system to guide the treatment plan.
• The MDRD equation is the preferred method for estimating GFR in patients with CKD. It should be used with caution in patients with “normal” creatinines.

Summary and Take-Home Points-2
• Blockade of the renin-angiotensin system is important for patients with a range of chronic kidney diseases:
  – Diabetic nephropathy
  – Non-diabetic proteinuric kidney disease
  – Hypertensive nephrosclerosis in African-Americans
  – Hypertensive patients with microalbuminuria

Summary and Take-Home Points-3
• ESAs are an important therapeutic tool in the treatment of anemia; however, overshooting hemoglobin targets is detrimental.
• Patients with CKD are at high risk for development of hyperkalemia with RAS blockade. This hyperkalemia can often be traced to medications, notably NSAIDs and trimethoprim.

Summary and Take-Home Points-4
• Bone disease (CKD-MBD) is a common complication of kidney disease, and its treatment often requires dietary phosphate restriction, phosphate binders, vitamin D analogues and/or cinacalcet.
Question 1

A 70-year-old woman develops dysuria from a UTI with *E. coli*. She is prescribed trimethoprim-sulfamethoxazole. Her creatinine, which had been 1.0 mg/dL, increases to 1.3 mg/dL. She has no rash, eosinophilia, or eosinophiluria. Her dysuria resolves with treatment, and she has no other symptoms. After completing the course of TMP-SMX, her creatinine is re-checked, and it is back down to 1.0 mg/dL.

Which of the following most likely explains the increase in serum creatinine?

- A) Acute kidney injury due to volume depletion
- B) Acute kidney injury due to interstitial nephritis
- C) The creatinine has risen with no change in GFR due to the effects of trimethoprim on creatinine secretion.
- D) Acute kidney injury due to pyelonephritis

Question 1 Explanation

There is nothing in the history that suggests volume depletion. She has no signs of interstitial nephritis: rash, fever, eosinophilia, or eosinophiluria. Her symptoms are limited to the lower urinary tract; there is no evidence of pyelonephritis. The best is answer is therefore C. (See Slide 10.)

Question 2

A 60-year-old man with CKD stage 4 from diabetic nephropathy complains of fatigue limiting his ability to play golf. He is anemic with a hemoglobin of 11 g/dL and hematocrit of 33%. His iron saturation is 9%.

Which of the following would be appropriate next steps in this patient’s management?

- A) Administer erythropoietin subcutaneously weekly to achieve a hemoglobin of 13 g/dL
- B) Administer darbepoietin monthly to achieve a hemoglobin of 13 g/dL
- C) Administer IV iron
- D) Check for occult gastrointestinal bleeding
- E) Both C and D

Question 2 Explanation

Choices A and B are both incorrect because the target for hemoglobin with either erythropoietin or darbepoietin would be 10-12 g/dL. This patient is iron deficient, so it would be appropriate to check for occult gastrointestinal blood loss and to administer IV iron.
References

• Palmer BF. N Engl J Med 2004;351:585-592

Disclosures

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  – Baxter Healthcare