Case Studies: Renal and Urologic Impairments Workshop

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AAIM Triennial October, 2012
Case #2 - Discussion

• Other than renal failure, other causes of elevated serum creatinine:
  – Race African American (higher avg. muscle mass)
  – Ingestion of cooked meat (transient elevation)
  – Body habitus (muscular build)
  – Medications (trimethoprim, cimetidine, and fibric acid derivatives reduce tubular secretion of cr)
  – Delay in centrifugation of specimen (temp. dependent, higher temp. results in higher elevations)
Case #2

• Delays in time to centrifuge cause serum creatinine to increase
  – Significant increase in serum cr occurs after 16 hour delay
  – By 24 hours, mean increase in serum cr 11%
  – By 48 hours, mean increase in serum cr 29%

Case #2

• Creatine supplementation
  – Increases phosphocreatinine levels in the muscles (up to 20%)
  
  – Only minimally affects serum creatinine concentrations and renal function in young healthy adults
  
  – Prolonged intake >10 g/day may increase serum creatinine concentrations
  
  – Upon discontinuation, muscle creatine concentrations and urinary creatinine excretions return to baseline within 3-4 weeks

BMJ Best Practice
• National Kidney Foundation

3 Simple tests to check for kidney disease

1) BP
2) UA - protein/cr ratio
   albumin/cr ratio
3) Glomerular Filtration Rate (GFR)
eGFR

• The estimated rate at which blood flows through and is filtered by the kidneys

• Can be measured by inulin, iohexol or iothalamate excretion

• Can be estimated by serum creatinine and formula
Creatinine Clearance

• Useful because creatinine is mostly filtered, only about 10% excreted. A good test to follow trends of kidney function.

• Normal range: men 85-125 mL/min
  women 75-112 mL/min

• Decreases by 1 mL/year at ages 50-75, 1.6/mL/year thereafter.

• Not simple or ideal, urine needs to be collected for specific time period.
Serum Creatinine

http://www.kidneys.org/professionals/doqi/kdoqi/figures.htm
eGFR

• Creatinine related to muscle mass

• In 6\textsuperscript{th} to 7\textsuperscript{th} decade of life, muscle mass tends to decrease

• Also a gradual loss of kidney function, estimated as 1 mL/min/1.73 m\textsuperscript{2} starting in the 2\textsuperscript{nd} or 3\textsuperscript{rd} decade
eGFR equations

• The Cockcroft-Gault equation is:
  \( eGFR = \frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{serum cr} \times (0.85 \text{ if female})} \)

• The MDRD 4 variable equation is:
  \( eGFR = 186 \times (\text{PCr}) - 1.154 \times (\text{age}) - 0.203 \times (0.742 \text{ if female}) \times (1.210 \text{ if African American}) \)

• The Mayo Formula, developed by Rule et al is:
  \( eGFR = \exp(1.911 + 5.249/\text{Scr} - 2.114/\text{Scr}^2 - 0.00686 \times \text{Age}) \)
  \( (-0.205 \text{ if female}) \). If SCr<0.8 mg/dL, use 0.8 for Scr.
• In general, the 4 variable MDRD performs better than the Cockcroft-Gault equation

• However, in older people and in people with GFR > 60 ml/min/1.73 m², the MDRD is
  – subject to bias
  – can underestimate GFR

CKD published by Royal College of Physicians, 2008, page 29
Cystatin C

• Desirable traits as marker of GFR
  – Filtered solely by the glomerulus
  – Not secreted by the renal tubules
  – Completely reabsorbed by the tubules and then catabolized
  – Generated at a constant rate by all cells in the body

www.kidney.org
Cystatin C

• Negative traits as marker of GFR

  – Not excreted in the urine

  – Substantial differences among assays used to measure cystatin C

www.kidney.org
Cystatin C Equations

• CKD-EPI cystatin equation not adjusted for age, sex, and race:
  \[ \text{eGFR} = 76.7 \times \text{CysC}^{−1.19} \]

• CKD-EPI cystatin equation adjusted for age, sex, and race:
  \[ \text{eGFR} = 127.7 \times \text{CysC}^{−1.17} \times \text{age}^{−0.13} \times 0.91 \text{ (if female)} \times 1.06 \text{ (if African American)} \]

• CKD-EPI cystatin and creatinine equation adjusted for age, sex, and race:
  \[ \text{eGFR} = 177.6 \times \text{SCr}^{−0.65} \times \text{CysC}^{−0.57} \times \text{age}^{−0.20} \times 0.80 \text{ (if female)} \times 1.11 \text{ (if African American)} \]

www.kidney.org
• Defined as either kidney damage (proteinuria, hematuria or anatomical abnormality) or

• GFR <60 ml/min/1.73 m2 on at least 2 occasions for ≥ 3 months.
### NKF-KDOQI stages of chronic kidney disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (ml/min/1.73m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or increased GFR</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild reduction in GFR</td>
<td>60-89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate reduction in GFR</td>
<td>30–59</td>
</tr>
<tr>
<td>4</td>
<td>Severe reduction in GFR</td>
<td>15–29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 (or dialysis)</td>
</tr>
</tbody>
</table>
Prevalence of CKD

http://kidney.niddk.nih.gov/kudiseases/pub/kustats/#4

[Bar chart showing the percent of the population with Stage 3 CKD by age group and year.]

- Ages 20-39
  - NHANES III 1988-1994: 0.1%
  - NHANES 1999-2002: 0.3%
  - NHANES 2003-2006: 0.1%
  - NHANES 2001-2008: 0.2%

- Ages 60+
  - NHANES III 1988-1994: 18.8%
  - NHANES 1999-2002: 24.2%
  - NHANES 2003-2006: 24.5%
  - NHANES 2001-2008: 26.0%
CKD and Mortality

• Nondiabetic patients with CKD have increased prevalence of cardiovascular disease compared to the general population

• Cardiovascular disease is the leading cause of death in nondiabetic patients with CKD

• Cardiovascular mortality is more likely than development of renal failure in nondiabetic patients with CKD

http://www.kidneys.org/professionals/kdoqi/guidelines_ckd/p7_risk_g15.htm
Prevalence of CVS in CKD

Framingham Heart Study

Participants with elevated serum creatinine: Men 1.5- 3.0 mg/dL  
Women 1.4- 3.0 mg/dL

- Men: 17.9%
- Women: 20.4%

Participants with normal serum creatinine

- Men: 13.9%
- Women: 9.3%

Kidney Int 56:2214-2219, 1999
CKD and Mortality

• Ancillary analysis of Hypertension Detection and Follow-up Program (HDFP)
  
  – Involving nearly 11,000 patients
  
  – 58% of deaths in participants with serum cr > 1.7 mg/dL were secondary to cardiovascular causes

Hypertension 13: 180-193, 1989
## Table 2. Adjusted Hazard Ratio for Death from Any Cause, Cardiovascular Events, and Hospitalization among 1,120,295 Ambulatory Adults, According to the Estimated GFR.

<table>
<thead>
<tr>
<th>Estimated GFR</th>
<th>Death from Any Cause</th>
<th>Any Cardiovascular Event</th>
<th>Any Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60 ml/min/1.73 m²</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>45–59 ml/min/1.73 m²</td>
<td>1.2 (1.1–1.2)</td>
<td>1.4 (1.4–1.5)</td>
<td>1.1 (1.1–1.1)</td>
</tr>
<tr>
<td>30–44 ml/min/1.73 m²</td>
<td>1.8 (1.7–1.9)</td>
<td>2.0 (1.9–2.1)</td>
<td>1.5 (1.5–1.5)</td>
</tr>
<tr>
<td>15–29 ml/min/1.73 m²</td>
<td>3.2 (3.1–3.4)</td>
<td>2.8 (2.6–2.9)</td>
<td>2.1 (2.0–2.2)</td>
</tr>
<tr>
<td>&lt;15 ml/min/1.73 m²</td>
<td>5.9 (5.4–6.5)</td>
<td>3.4 (3.1–3.8)</td>
<td>3.1 (3.0–3.3)</td>
</tr>
</tbody>
</table>

* The analyses were adjusted for age, sex, income, education, use or nonuse of dialysis, and the presence or absence of prior coronary heart disease, prior chronic heart failure, prior ischemic stroke or transient ischemic attack, prior peripheral arterial disease, diabetes mellitus, hypertension, dyslipidemia, cancer, a serum albumin level of 3.5 g per deciliter or less, dementia, cirrhosis or chronic liver disease, chronic lung disease, documented proteinuria, and prior hospitalizations.

† This group served as the reference group.
Case #3- Proteinuria

• Urine protein to creatinine ratio:
  – Normal ratio <0.2 grams protein/g of cr (correlates with 0.2 g protein/day)
  – Nephrotic ratio 3.5 (correlates with 3.5 g protein)

• Urine albumin to creatinine ratio:
  – Normal is <30 mg/g of cr
  – Microalbuminuria: 30-300 mg albumin/g of cr
  – Macroalbuminuria >300 mg albumin/g of cr
Case #3 – Proteinuria

• Proteins normally excreted in urine consist of:

  – Immunoglobulins (20%)
  – Albumin (40%)
  – Tamm-Horsfall mucoproteins (40%)
Proteinuria

• Benign Causes:
  – Fever
  – Intense activity or exercise
  – Dehydration
  – Acute illness
  – Orthostatic disorder
### Classification of Proteinuria

<table>
<thead>
<tr>
<th>Type</th>
<th>Pathologic Features</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerular</td>
<td>Increased glomerular capillary permeability to protein</td>
<td>Primary or secondary glomerulopathy</td>
</tr>
<tr>
<td>Tubular</td>
<td>Decreased tubular reabsorption of proteins in glomerular filtrate</td>
<td>Tubular or interstitial disease</td>
</tr>
<tr>
<td>Overflow</td>
<td>Increased production of low molecular weight proteins</td>
<td>Monoclonal gammopathy or leukemia</td>
</tr>
</tbody>
</table>

AFP Vol. 62/No. 6 (Sept. 15, 2000)
# Proteinuria

## Cause of proteinuria by quantity:

<table>
<thead>
<tr>
<th>Daily protein excretion</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.15 - 2 grams</td>
<td>Mild glomerulopathies</td>
</tr>
<tr>
<td></td>
<td>Tubular proteinuria</td>
</tr>
<tr>
<td></td>
<td>Overflow proteinuria</td>
</tr>
<tr>
<td>2.0 – 4 grams</td>
<td>Usually glomerular</td>
</tr>
<tr>
<td>&gt;4.0 grams</td>
<td>Always glomerular</td>
</tr>
</tbody>
</table>

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Proteinuria- Glomerular Causes

• Primary Glomerulopathy:
  – Minimal change disease
  – Idiopathic membranous glomerulonephritis
  – Focal segmental glomerulonephritis
  – Membranoproliferative glomerulonephritis
  – IgA nephropathy

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Proteinuria – Glomerular Causes

• Secondary glomerulopathy
  – Diabetes Mellius
  – Collagen vascular disease (i.e. lupus nephritis)
  – Amyloidosis
  – Preeclampsia
  – Infection (HIV, hepatis B and C, syphilis, etc)
  – GI and lung cancers
  – Lymphoma, chronic renal transplant rejection

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Proteinuria – Tubular Causes

• Hypertensive nephrosclerosis
• Tubular interstitial disease due to:
  – Uric acid nephropathy
  – Acute hypersensitivity interstitial nephritis
  – Fanconi syndrome
  – Heavy metals
  – Sickle cell disease
  – NSAIDs, antibiotics

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Proteinuria – Overflow causes

- Hemoglobinuria
- Myoglobinuria
- Multiple myeloma
- Amyloidosis
## Table 2. Distribution of protein/creatinine ratio values by age group

<table>
<thead>
<tr>
<th>P/C ratio (g/g)</th>
<th>Population distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age 20 to 59</td>
</tr>
<tr>
<td>&lt;.11 (ref)</td>
<td>95.6%</td>
</tr>
<tr>
<td>.11 to .20</td>
<td>3.1%</td>
</tr>
<tr>
<td>.21 to .50</td>
<td>1.0%</td>
</tr>
<tr>
<td>.51 to 1.0</td>
<td>0.2%</td>
</tr>
<tr>
<td>&gt;1.0</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

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Proteinuria and Mortality

Figure 1. Mortality ratios for protein/creatinine ratio bands, by age group

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