Clinical Approach to the Patient with Kidney Disease – Hematuria, Proteinuria, Elevated Serum Creatinine and Diabetic Nephropathy

THE FOUR QUESTIONS

1. Is there or is there not evidence of kidney (renal) parenchymal disease?

2. If kidney parenchymal disease is present, where within the kidney, is the primary pathology?

3. Is there evidence of reduced kidney function (i.e., reduction of glomerular filtration rate [GFR])?

4. Why is the detection of kidney disease and/or reduced kidney function important?
HOW DO WE DETECT KIDNEY DISEASE AND/OR REDUCED KIDNEY FUNCTION?

- Urinalysis
- Presence or absence of proteinuria
- Assessment of the kidney’s filtering ability, *i.e.*, glomerular filtration rate (GFR)
  - Serum creatinine
  - BUN
  - Mathematically estimated or measured GFR

HEMATUREIA

*Every Life Deserves World Class Care*
Hematuria: Definition

- Strictly defined, hematuria is “blood in the urine.”
  
  In conventional use, it means an abnormal number of red blood cells in the urine.

Hematuria: What is normal?

- <2 erythrocyte per high power field (? Higher in females) in a “urine sediment” re-suspended in a small volume (K0.5 mL) of an aliquot of a freshly-voided sample (10 mL) after light centrifugation (400G x 10 min) (Fogazzi, 1999)
Hematuria: Caveats

- 2nd morning voided (mid-stream) specimens are best.
- Always examine urine fresh (within 1-2 hrs., never stored in refrigerator).
- Avoid strenuous exercise before giving sample.
- Do not examine urine during menstruation in females.
- Catheterized samples of urine are unreliable.
- Urine should be concentrated and acidic.

Hematuria: “Dipstick”

- Commercial “dipsticks” detect 1-2 erythrocytes (in reality heme in erythrocytes) per HPF and are as sensitive as urinary sediment exams for detecting hematuria, BUT

• False negative for erythrocytes may occur with:
  - Consumption of large amounts of Vitamin C

• False positives for erythrocytes may occur with:
  - Semen contamination
  - Alkaline urine (pH > 8.0)
  - Oxidizing agent contamination (cleansing agents)
  - Hemoglobinuria or myoglobinuria
Pigmenturia

• Red or red-brown urine and negative dipstick may be seen in:
  – Porphyrinuria
  – Rhubarb, senna or beetroot ingestion
  – Aminopyrine, diphenylhydantoin, phenolsulfonphthalein, metronidazole, nitrofurantoin phenacetin, phenothiazine, rifampicin, salazosulfapyridine administration

Hemoglobinuria and Myoglobinuria: Clinical Differentiation

HEMOGLOBINURIA

• Urine red (alkaline) or red-brown (acid), heme-positive (diffuse not speckled); no erythrocytes in urine
• Plasma pink
• Serum haptoglobin levels decreased
• Serum creatine phosphokinase levels normal

MYOGLOBINURIA

• Urine red or reddish–brown; heme-positive (diffuse not speckled; no erythrocytes in urine
• Plasma clear
• Serum haptoglobin levels normal
• Serum creatine phosphokinase levels increased.
Hematuria: Sequencing of Tests

If dipstick is positive for blood, immediate microscopy of a fresh urinary sediment (not stored for later examination) is the most cost-effective approach.

(NHS-Office of Health Technology Assessment, 2006)

DIFFERENTIAL DIAGNOSIS OF RED URINE

1. Red supernatant
   - Negative dipstick
2. Red supernatant
   - Positive dipstick
   - Negative sediment
3. Positive dipstick
   - RBCs in sediment
4. RBC casts in sediment
   - Gu bleeding
   - Bleeding occurring in kidney parenchyma

Note:
- Negative supernatant (dipstick)
- Negative sediment (dipstick)
- Negative sediment (microscopic)
- No blood in urine
Causes of Hematuria

- Infections
  - Pyelonephritis cystitis

- Glomerular
  - Glomerulonephritis
  - Hereditary glomerular diseases line think basement membrane and Alport's disease
  - Vasculitis

- Vascular
  - Renal vein thrombosis
  - Atheroemboli
  - Malignant hypertension

- Malignancy
  - Renal cell carcinoma
  - Transitional cell carcinoma
  - Carcinoma of prostate

- Interstitial
  - AIN
  - PKD
  - Papillary necrosis

- Malignancy
  - Renal cell carcinoma
  - Transitional cell carcinoma
  - Carcinoma of prostate

- Others
  - Calculi
  - Hypercalcemia
  - Hypercalciuria
  - Hyperuricemia
  - Coagulopathy
  - Cytoxan

CAUSES OF HEMATURIA BY AGE AND SEX

<table>
<thead>
<tr>
<th>Age</th>
<th>Disease</th>
</tr>
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<tbody>
<tr>
<td>0-20 yrs</td>
<td>glomerulonephritis urinary tract infection (more common in females)</td>
</tr>
<tr>
<td>20-49 yrs</td>
<td>calculi bladder and renal cell carcinoma</td>
</tr>
<tr>
<td>40-60 yrs</td>
<td>urinary tract infection (more common in females)</td>
</tr>
<tr>
<td>Over 60 yrs</td>
<td>Males: BPH Bladder and renal cell carcinoma Urinary tract infections</td>
</tr>
<tr>
<td></td>
<td>Females: Urinary tract infections Bladder and renal cell carcinoma</td>
</tr>
</tbody>
</table>
Simple cyst

Complex cyst (wall calcification, wall thickening)
Cystic clear cell carcinoma

Polycystic kidney dz MRI with contrast
U/S of Kidney Stone in renal pelvis of right kidney

Staghorn calculus
Hematuria:

Glomerular vs. Non-glomerular

• Glomerular disease is strongly associated with excretion of small (MCV <70 fL), misshapen (dysmorphic) poorly hemoglobinized (∧ MCHC) erythrocytes and excretion of erythrocyte containing casts

• Non-glomerular (urinary tract) disease is strongly associated with excretion of normal sized (MCV >90fL), normal-shaped (iso-or normomorphic), well hemoglobinized erythrocytes

• Glomerular disease is strongly associated with an increase in the urinary albumin to total protein ratio (on a “spot” urine)

Erythrocyte Morphology in Urine
(Phase contrast microscopy)

Dysmorphic

Isomophic

Gai M, et al. NDT 17:1533, 2002

Urine sediment showing free red cells and a red cell cast that is tightly packed with red cells. It is more common for red cell casts to have fewer red cells trapped within a hyaline or granular cast. Red cell casts are virtually diagnostic of glomerulonephritis or vasculitis. 

Courtesy of Harvard Medical School.

CAUSES OF RED CELL AND HEMOGLOBIN CASTS

1. Acute and subacute glomerulonephritis (GN)
   - Acute post streptococcal GN
   - Subacute bacterial endocarditis
   - Rapidly progressive glomerulonephritis (RPGN)
   - Focal nephritis (benign recurrent hematuria)
   - ? Viral infection, streptococcal infection, staph aureus septicemia
2. SLE
3. Vasculitides (e.g., periarteritis nodosa, hypersensitivity angitis, Henoch-Schönlein syndrome, Wegener’s granulomatosis, Goodpasture’s syndrome)
4. Malignant nephrosclerosis
5. Acute tubular necrosis
6. Acute arterial embolism or thrombosis
7. Renal vein thrombosis
8. Trauma to kidney (including renal biopsy), violent exercise
Major Causes of Acute Nephritis

<table>
<thead>
<tr>
<th>LOW serum complement level*</th>
<th>NORMAL serum complement level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SYSTEMIC DISEASES</strong></td>
<td><strong>SYSTEMIC DISEASES</strong></td>
</tr>
<tr>
<td>Lupus erythematosus (focal ≥75%, diffuse ≥ 90%)*</td>
<td>Polyarteritis nodosa group</td>
</tr>
<tr>
<td>Subacute bacterial endocarditis (≥ 90%)</td>
<td>Hypersensitivity vasculitis</td>
</tr>
<tr>
<td>“Shunt” nephritis (≥ 90%)</td>
<td>Wegener’s granulomatosis</td>
</tr>
<tr>
<td>Cryoglobulinemia (≥ 85%)</td>
<td>Henoch-Schönlein purpura</td>
</tr>
<tr>
<td></td>
<td>Goodpasture’s syndrome</td>
</tr>
<tr>
<td></td>
<td>Visceral abscess</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th><strong>RENAL DISEASES</strong></th>
<th><strong>RENAL DISEASES</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute poststreptococcal glomerulonephritis (GN) (≥90%)</td>
<td>IgG-IgA nephropathy</td>
</tr>
<tr>
<td>Membranoproliferative GN</td>
<td>Idiopathic RPGN</td>
</tr>
<tr>
<td>Type I (≥ 50 – 80%)</td>
<td>Antiglomerular basement membrane disease</td>
</tr>
<tr>
<td>Type II (≥ 80 – 90%)</td>
<td>Immune-complex disease</td>
</tr>
<tr>
<td></td>
<td>Negative immunofluorescence findings</td>
</tr>
</tbody>
</table>

* Percentages indicate the approximate frequencies of depressed C3 or hemolytic complement levels.

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PROTEINURIA

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PROTEINURIA
vs. ALBUMINURIA
vs. MICROALBUMINURIA
**PROTEINURIA and ALBUMINURIA**

- Normal urine protein excretion
  <100 – 150 mg/day
- Most normal urine protein is albumin
- Normal urine albumin excretion is:
  
  \[
  <15 \text{ – } 20 \, \mu g/min
  \]
  \[
  <30 \text{ mg/day}
  \]

**Microalbuminuria: Evaluation**

- Increased urinary excretion of albumin below the level reliably detected by semi-quantitative means (dipsticks) but above the normal level of excretion (20-300 mg/d) = *microalbuminuria*
- Microalbuminuria is associated with an increased risk of CVD, hypertension and CKD
- In diabetics (Type 1 and 2) it is predictive of the eventual development of overt diabetic nephropathy
Proteinuria: Evaluation

- Spot morning second voided urine samples are best – **UAC or UACR or UPCR**
- Dipstick testing is only semi-quantitative and is influenced by urine concentration (specific gravity or osmolality)
- Dipstick tests are relatively insensitive for globulins and light-chains
- False positive dipsticks with alkaline urine and after contrast agent or cephalosporins
**Proteinuria: Evaluation**

**DIPSTICKS**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Protein Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>&lt;10 mg/dL</td>
</tr>
<tr>
<td>Trace</td>
<td>10 mg/dL</td>
</tr>
<tr>
<td>1+</td>
<td>30 mg/dL</td>
</tr>
<tr>
<td>2+</td>
<td>100 mg/dL</td>
</tr>
<tr>
<td>3+</td>
<td>300 mg/dL</td>
</tr>
<tr>
<td>4+</td>
<td>&gt;1000 mg/dL</td>
</tr>
</tbody>
</table>

**Proteinuria: Evaluation Caveats**

- Concentration of urine (SG of OSM) must be taken into account in the evaluation of overt proteinuria by dipsticks.
- Fever, vigorous exercise, urinary infection can all transiently increase protein excretion.
- Protein excretion is greatest during upright ambulation (orthostatic proteinuria).
- Gross (or microscopic) hematuria due to urinary tract bleeding does not give more than a 1+ protein on dipstick.
Albuminuria (UACR) as a Prognostic Tool: Caveats

• Numerous cross-sectional studies have shown a strong association between UACR and subsequent all-cause mortality, CV events and progressive CKD (Lamers-Heerspink, et al: *J Am Soc Nephrol* 21:1355, 2010.)

• However, both albumin excretion (UA) and creatinine excretion (C) contribute to risk – in opposite direction (similar to KT/V) (Kestenbaum B, de Boer J. *J Am Soc Nephrol* 21:1243, 2010.)
• Since U Cr decreases with age, loss of muscle mass, vegetarian and low-protein diets – UACR may increase without any absolute increase in AER.

• Since U Cr increases with body building, high red-meat diets and acute muscle breakdown, UACR may not increase despite an increase in absolute AER.

**PROTEINURIA**

• Abnormal
• Indicates kidney disease (rare exceptions)
• Qualitatively detected by routine urinalysis-dipstick and several other methods.
• Quantitatively determined by:
  — “spot” urine specimen (protein/creatinine ratio)
  — 24-hour urine collection
• 65% of total urine protein consists of albumin
When bubbles settle on the surface of the urine, they indicate disease of the kidneys and that the complaint will be protracted.

— Hippocrates

NEPHROTIC SYNDROME

Nephrotic syndrome is a clinical entity having many causes and characterized by increased glomerular membrane permeability manifested by massive proteinuria and excretion of fat bodies. There is variable edema, hypoproteinemia, and hyperlipedemia. Protein excretion usually greater than 3.5 gm/24 hrs/1.73 m² of body surface if GFR is normal.
DEFINITIONS

A. Nephrotic syndrome is defined as any one of the following:
   1. Urine protein of 4 gm/day or more
   2. Urine protein of 3.5 gm/1.73 m² or more

B. “No response” is more than 2 gm proteinuria/day after several months of specific antiproteinuric therapy.

C. “Partial response” is between 2 – 150 mg proteinuria/day (inclusive)

D. “Complete response” is <150 mg proteinuria/day

E. Relapse is an increase in urine protein in a patient with a complete response to >150-200 mg/day; or in a patient with a partial response to >2 gm/day.

F. Steroid dependence is a relapse on two or more occasions within one year when corticosteroid therapy is reduced or discontinued.

COMMON CAUSES OF HEAVY (nephrotic range) PROTEINURIA (>3.5 gm/day)

1. Idiopathic nephrotic syndrome
   - FSGS
   - membranous
   - membranoproliferative
   - minimal change
2. Intercapillary glomerulosclerosis
3. Amyloidosis
4. Multiple myeloma and other dysproteinemias
5. Acute and chronic glomerulonephritis (GN)
6. Rapidly progressive GN (RPGN)
7. SLE
8. HIV
### COMMON CAUSES OF HEAVY (nephrotic range) PROTEINURIA (>3.5 gm/day), cont.

9. Hepatitis B + C  
10. Vasculitides (*e.g.*, periarteritis)  
11. Malignant nephrosclerosis  
12. Renal venous congestion  
13. Drugs  
   - NSAIDs
   - penicillamine
   - gold
   - pamidronate
14. Morbid obesity

### Causes of Moderate Proteinuria (0.5 - 3.5 gm/day)

1. Any of the causes of “heavy proteinuria”
2. Latent or chronic glomerulonephritis  
3. Nephrosclerosis and/or  
4. Pyelonephritis/interstitial nephritis
### Causes of Minimal or Intermittent Proteinuria

(<0.5 gm/day)

1. Latent glomerulonephritis, healing APSGN or focal nephritis
2. Obstruction
3. Chronic pyelonephritis
4. Benign nephrosclerosis
5. Polycystic kidney disease
6. Hypercalcemia; potassium depletion
7. Tubular syndromes (Fanconi, TRA, etc.)
8. Neoplasms, stones malformations
9. “Benign” proteinurias (often intermittent)
   a. Functional proteinuria
   b. Postural (orthostatic) proteinuria

### Orthostatic Proteinuria

**Definition:** protein excretion <150 mg/day when recumbent, but >150 mg/day when upright

1. “Persistent” proteinuria (5-10%*)
   - Present during BOTH the recumbent and upright postures
2. “Transient” orthostatic proteinuria (75-80%*)
   - Present inconstantly from day to day
3. “Fixed” orthostatic proteinuria (15%*)
   - Present consistently on separate days

* Routine urinalysis in healthy young males → proteinuria
ORTHOSTATIC PROTEINURIA, continued

**CLINICAL CHARACTERISTICS**
1. Healthy adolescents and young adults (3-5%)
2. Routine health examination
3. Clinical and laboratory examination normal except for the proteinuria
4. Total daily protein excretion usually < 1.0 g/day
5. Prognosis - good

**RENAL HISTOLOGY (patients with “fixed” orthostatic proteinuria)**
- 8% - definite abnormalities
- 45% - subtle alternations of glomerular structure
- 47% - normal biopsy

- Clinical significance of abnormal biopsy not clear.
- Little histological data for patients with “transient” orthostatic proteinuria

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**FUNCTIONAL PROTEINURIA**

1. Fever
2. Exercise (e.g., athletic exertion)
3. Exposure to heat or cold
4. Emotional stress
5. Congestive heart failure
RENAL DISEASE OCCURRING IN THE ABSENCE OF PROTEINURIA

1. Acute and chronic pyelonephritis
2. Obstructive nephropathy
3. Nephrolithiasis
4. Nephropathies of hypercalcemia and potassium depletion
5. Benign nephrosclerosis
6. Polycystic kidney disease (PKD)
7. Tumors, congenital malformations

NEPHRITIC vs. NEPHROTIC

<table>
<thead>
<tr>
<th>Proteinuria</th>
<th>Variable amount</th>
<th>“heavy” (&gt;3.5 gm/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine sediment</td>
<td>RBCs + RBC casts</td>
<td>Lipiduria (OFBs, free fat, fatty casts, Maltese crosses)</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>Less common</td>
<td>Common</td>
</tr>
<tr>
<td>Edema</td>
<td>Acute ↓ GFR Preserved tubular function ↑ reabsorption of NA and H₂O</td>
<td>Consequence of hypoalbuminemia→ ↑ISF ↑ reabsorption of NA and H₂O</td>
</tr>
</tbody>
</table>
Identification and Staging of CKD: Diagnosis and Classification

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CREATININE VS GLOMERULAR FILTRATION RATE
BLACK AREA INDICATES 95% LIMITS
**Glomerular Filtration Rate (GFR)**

- GFR is the clearance by the kidney of a marker (either endogenous or exogenous) in plasma, expressed as the volume of plasma completely cleared of that marker per unit time:

\[ C = \frac{UV}{P} \]

- Reported in ml/min/1.73 m²

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**Filtration Markers**

<table>
<thead>
<tr>
<th>Endogenous</th>
<th>Exogenous</th>
</tr>
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<tbody>
<tr>
<td>Creatinine</td>
<td>Inulin</td>
</tr>
<tr>
<td>Urea</td>
<td>⁵¹Cr-EDTA</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>⁹⁹mTc-DTPA</td>
</tr>
<tr>
<td></td>
<td>¹²⁵I-ithalamate</td>
</tr>
<tr>
<td></td>
<td>“Cold” iothalamate</td>
</tr>
<tr>
<td></td>
<td>Iohexol</td>
</tr>
</tbody>
</table>
**Why do we care about GFR?**

- GFR is the best overall measure of kidney function
- Chronic kidney disease is a public health problem → by 2030 more than 2 million people in USA will need dialysis or transplantation
- The definition and classification system for CKD is based on level of GFR → accurate estimation of GFR is central to the detection, evaluation and management of CKD

**Estimation of GFR – K/DOQI**

- The level of GFR should be estimated from prediction equations that take into account the SCr concentration and some or all of the following variables: age, gender, race, and body size:
  - Cockcroft-Gault equation
  - MDRD Study equation / re-expressed MDRD equation
- The GFR may be measured directly (e.g., iothalamate)
- The SCr concentration alone should not be used to assess the level of kidney function

K/DOQI Clinical Practice Guidelines, AJKD 2002;39(suppl 1)
SUSPECT REDUCED KIDNEY FUNCTION,  
(*i.e., DECREASED GFR*) **IF**…

- S Creat > 0.9 to 1.0 mg/dL (women)
- S Creat > 1.3 mg/dL (men)

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**Definition of CKD – 3 Components**

1. **Anatomical or structural**: with/out decreased GFR:
   - pathologic abnormalities
   - markers of kidney damage, including abnormalities in the composition of the blood or urine or abnormalities in imaging tests

2. **Temporal component**: > 3 months of abnormality

3. **Functional component on its own**: eGFR <60 ml/min/1.73 m², with or without kidney damage
Estimation of GFR drives the staging of CKD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>eGFR (ml/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or - GFR</td>
<td>&gt;90</td>
</tr>
<tr>
<td>2</td>
<td>Mild ↓ GFR</td>
<td>60-89*</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30-59</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ GFR</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 or dialysis</td>
</tr>
</tbody>
</table>

* may be normal for age

AJKD 2002

Automated Reporting of GFR
Current Recommendations by NKF and NKDEP

- eGFR by *current* abbreviated MDRD equation should be reported automatically on all SCr measured by a clinical lab, independent of SCr assay calibration
- Results should be interpreted in the context of the CKD definition
- If patient has CKD → appropriate action/specialist referral
#### US Adults Age >20

<table>
<thead>
<tr>
<th>GFR (mL/min/1.73 m²)</th>
<th>N*</th>
<th>Prevalence (95% CI)</th>
<th>Millions of Individuals (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90+</td>
<td>10,183</td>
<td>64% (63–66)</td>
<td>114 (106–122)</td>
</tr>
<tr>
<td>60–89</td>
<td>4,404</td>
<td>31% (30–33)</td>
<td>55.3 (50–61)</td>
</tr>
<tr>
<td>30–59</td>
<td>961</td>
<td>4.3 % (3.8–4.7)</td>
<td>7.6 (6.5–8.6)</td>
</tr>
<tr>
<td>15–29</td>
<td>52</td>
<td>0.2% (0.1–0.3)</td>
<td>0.4 (0.2–0.5)</td>
</tr>
</tbody>
</table>

GFR estimated from serum creatinine using MDRD Study equation based on age, gender, race and calibration for serum creatinine.

*N is based on number of individuals in each listed GFR range in NHANES III, 1988–1994. Prevalence and number of individuals estimated by extrapolation to population of US adults age ≥20 (N = 177 million). Based on one-time assessment of estimated GFR.

Coresh et al, AJKD 2002

### Prevalence of CKD by eGFR Stage and Persistent Albuminuria

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥ 90</td>
<td>* 5,900,000</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
<td>* 5,300,000</td>
</tr>
<tr>
<td>3</td>
<td>30-59</td>
<td>7,600,000</td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>400,000</td>
</tr>
<tr>
<td>5</td>
<td>&lt; 15 or dialysis</td>
<td>300,000</td>
</tr>
</tbody>
</table>

* Persistent albuminuria for eGFR stages 1 and 2.

Relationship Between iGFR and GFR Estimated by MDRD Equation

\[
\text{MDRD} = 186 \times \text{SCr}^{-1.154} \times \text{Age}^{-0.203} \times [0.742 \text{ if Female}] \times [1.212 \text{ if AA}]
\]

“Normal” GFR vs. Age

\[
\text{GFR ml/min/1.73 m}^2
\]

Inulin (Davies 1949)

NHANES III Estimated GFR (median, 5th, 95th %iles)
Screening for CKD with eGFR: Doubts and Dangers


Uses and misuses of eGFR: Screening and diagnosis of CKD

- Correct or Incorrect?
- Can you apply an estimation model developed in patients with a known condition (*i.e.*, CKD) to screen for such condition in subjects that will unlikely have the disease (*i.e.*, general population)?
Classifications of CKD (KDOQI) based on MDRD-eGFR will be *WRONG* when compared to a gold-standard mGFR in *one of every three instances*

**MDRD-eGFR: The Future?**

- Ancestry- and geography–specific coefficients – (a “universal MDRD equation is impossible)
- Adjustments for body habitus, customary dietary intake (meat/vegetable protein)
- Calibration to a universal (global) “gold standard” creatinine
- Repeated measurements (≥3 months apart) to define chronicity
- Combination of eGFR (MDRD) and Cystatin C eGFR (?)
- Abandonment for diagnostic/epidemiologic purposes (?)
Staging of CKD

- Subjects (of any age) with eGFR* <5th percentile for age/sex but without any corroborating evidence of kidney damage (macroalbuminuria, glomerular hematuria, imaging or histology) would be labeled as:

“RedUced Renal Function of Uncertain Significance” (RUFUS) NOT Chronic Kidney Disease

(*Ancestry/Geography specific)


Conclusions

- Global prevalence rates of CKD have been greatly overestimated due to inherent flaws in the K/DOQI construct and the eGFR (MDRD) formula

- Even with “bona-fide” Stage 3 CKD the risk of surviving and receiving ESRD treatment (in developed countries) is very low and inversely related to age (0.2-0.4% per year; greater in males than females), despite higher mortality in males from CVD

- The combination of reduced eGFR and dipstick positive proteinuria greatly increases the risk of progression to ESRD (proteinuria more predictive than eGFR). eGFR and proteinuria are poorly correlated with each other
When bubbles settle on the surface of the urine, they indicate disease of the kidneys and that the complaint will be protracted.

— Hippocrates

DIABETIC NEPHROPATHY

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Pathogenesis of Diabetic Nephropathy

**Hemodynamic alterations**

**Biochemical alterations**

- HSPG
- Type IV collagen ↑

Courtesy of Lewis EJ, Pers Comm 2005
Diabetes
*The Most Common Cause of ESRD*

**Primary diagnosis for patients who start dialysis**

- **Diabetes**: 50.1%
- **Glomerulonephritis**: 13%
- **Hypertension**: 27%
- **Other**: 10%

**No. of patients**

<table>
<thead>
<tr>
<th>Year</th>
<th>Diabetes</th>
<th>Hypertension</th>
<th>Glomerulonephritis</th>
<th>Other</th>
</tr>
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<tbody>
<tr>
<td>1984</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<tr>
<td>1992</td>
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<tr>
<td>1996</td>
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<tr>
<td>2000</td>
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<tr>
<td>2004</td>
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<tr>
<td>2008</td>
<td></td>
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</tr>
</tbody>
</table>

**Projected no. of patients**

- 243,524
- 281,355
- 520,240

r$^2$ = 99.8%

**No. of dialysis patients (thousands)**

- 1984: 700
- 1988: 281,355
- 1992: 520,240

ESRD, end-stage renal disease.
United States Renal Data System. USRDS 2000 Annual Data Report.

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**Course of Diabetic Nephropathy**

- **Pre-Clinical Nephropathy**
- **Incipient Nephropathy**
- **Overt Nephropathy**

- Proteinuria
- Persistent Microalbuminuria

**GFR (mL/min)**

- 0 to 160

**Protein Excretion (g/day)**

- 0 to 4

**Years After Onset of Diabetes Mellitus**

- 0 to 20

Factors in Progressive Renal Disease

- PGE\textsubscript{2}
- ↑ Glycemia
- ↑ Dietary Protein
- ↑ Systemic BP
- A-II
- NE
- Sym N.S.
- Cytokines
- TGF-β
- Fibrosis
Strategies for Preventing Progressive Nephropathy in Type 2 Diabetes

- Major treatment strategies
  - BP control
  - Renoprotection
    - potential specific benefits of RAS blockade
  - glycemic control
  - low-protein diet
- Reduction in proteinuria predicts slower decline in GFR

RAS, renin-angiotensin system; GFR, glomerular filtration rate.


Effect of Antihypertensive Treatment on Kidney Function in Diabetic Nephropathy

Do Certain Antihypertensive Agents Have Unique Renal Effects in Diabetes?

Effect of Captopril on Doubling of SeCreat in Type 1 Diabetic Nephropathy

Risk reduction = 51.1%

P=0.004

Effect of Captopril on End-Stage Renal Disease or Death in Type 1 Diabetic Nephropathy

Risk reduction = 50.5%
P = 0.006


Stability of Renal Function in a Patient with Type I Diabetic Nephropathy

<table>
<thead>
<tr>
<th>Year</th>
<th>1993</th>
<th>‘94</th>
<th>‘95</th>
<th>‘99</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iothalmate GFR (ml/min/1.73 m²)</td>
<td>15.6</td>
<td>16.7</td>
<td>13.2</td>
<td>13.0</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>3.3</td>
<td>3.4</td>
<td>3.9</td>
<td>4.6</td>
</tr>
<tr>
<td>Urinary protein (mg/day)</td>
<td>522</td>
<td>355</td>
<td>343</td>
<td>--</td>
</tr>
</tbody>
</table>

CCF Patient Data, 1993-1999
Angiotensin Converting Enzyme Inhibitors (ACEi) and Angiotensin II Receptor Blockers (ARBs)

**Lingering Questions**

1. Have the intrarenal effects of ACE inhibitors been observed with the ARBs?
2. Which experimental models?
3. Which ARBs?

**Mechanisms of Protection: ACEI and AIIRA**

- Effects on glomerular hemodynamics and permselectivity
- Effects on proteinuria, sclerosis, and structural injury
- Effects on pro-sclerosing mediators
- Role of combined ACEI plus AIIRA
Recent Nephrology Trials in Type 2 Diabetes

IRMA II/MARVAL RENAAL/IDNT
Microalbuminuria Proteinuria ESRD
Cardiovascular Morbidity and Mortality

Early Stage Late Stage End Stage

Kidney Disease

IRMA 2
Study Design

- 590 subjects with hypertension, type 2 diabetes, microalbuminuria (albumin excretion rate 20–200 µg/min), and normal renal function

Screening/enrollment

Double-blind treatment

Placebo

Irbesartan 150 mg/d

Irbesartan 300 mg/d

Up to 5 weeks Follow-up: 2 years

Adjunctive antihypertensive therapies (excluding ACE inhibitors, angiotensin II receptor blockers, and dihydropyridine calcium channel blockers) could be added to all groups to help achieve equal BP levels.

IRMA 2 Primary Endpoint

Time to Clinical Proteinuria

- **Placebo (n=201)**
- **Irbesartan 150 mg/d (n=195)**
- **Irbesartan 300 mg/d (n=194)**

RRR = 70%

P < 0.001

**Subjects (%)**

**Follow-up (mo)**

0 3 6 12 18 24

RRR, relative risk reduction.


---

**Irbesartan Diabetic Nephropathy Trial (IDNT): Rationale**

- Inhibition of angiotensin II was shown to have beneficial effects in patients with nephropathy caused by type 1 diabetes


- No published study had addressed the issue of renoprotection in patients with type 2 diabetes


- IDNT was designed to determine whether use of an ARB or a CCB would provide protection against progression of nephropathy due to type 2 diabetes beyond that attributable to lowering of blood pressure

ARB = angiotensin II receptor blocker; CCB = calcium channel blocker.
**IDNT**

**Time to Doubling of Serum Creatinine**

- **Irbesartan**: RRR 37% \( P<0.001 \)
- **Amlodipine besylate**: RRR 33% \( P=0.003 \)
- **Placebo (control)**

Subjects (%)

Follow-up (months)


---

**IDNT**

**Time to Doubling of Serum Creatinine, ESRD, or Death**

- **Irbesartan**: RRR 23% \( P=0.006 \)
- **Amlodipine besylate**: RRR 20% \( P=0.02 \)
- **Placebo (control)**

ESRD, end-stage renal disease; RRR, relative risk reduction.

IDNT: Impact of Quartile of Achieved Mean Systolic Blood Pressure on Time to Renal Endpoint

Simultaneous impact of quartile of achieved SBP and treatment modality on the relative risk for reaching a renal endpoint*

* doubling of baseline Scr or ESRD, defined as Scr > 6.0 mg/dl or renal replacement therapy
IDNT
Adverse Outcomes

<table>
<thead>
<tr>
<th>Adverse Outcome</th>
<th>Irbesartan</th>
<th>Amlodipine</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early serum creatinine rise</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>D/C due to hyperkalemia</td>
<td>11 (1.9)</td>
<td>3 (0.5)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Stopped study medicine</td>
<td>134 (23)</td>
<td>133 (23)</td>
<td>140 (25)</td>
</tr>
<tr>
<td>SAEs/1000 days on drug</td>
<td>2.0</td>
<td>2.5</td>
<td>2.3</td>
</tr>
</tbody>
</table>


RENAAL
Time to Doubling of Serum Creatinine, ESRD, or Death

**Components of the Primary End Point**

Doubling of Serum Creatinine  

<table>
<thead>
<tr>
<th>Months</th>
<th>Subjects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>36</td>
<td>30</td>
</tr>
<tr>
<td>48</td>
<td>40</td>
</tr>
</tbody>
</table>

**ESRD**

<table>
<thead>
<tr>
<th>Months</th>
<th>Subjects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
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<td>24</td>
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<tr>
<td>36</td>
<td>30</td>
</tr>
<tr>
<td>48</td>
<td>40</td>
</tr>
</tbody>
</table>

**RR=25%**  
**P=0.006**

**RR=28%**  
**P=0.002**

ESRD, end-stage renal disease; RRR, relative risk reduction.  

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**End-Organ Protection With ARBs**

**Summary**

- BP control is crucial to slow the progression of diabetic renal disease
- Renoprotective benefits has been demonstrated with RAS inhibition and angiotensin II receptor blockade, beyond the effects of BP lowering
- ARBs have been proven to slow the progression of type 2 diabetic renal disease

RAS, renin-angiotensin system; ARB, angiotensin II receptor blocker.
ADA Guidelines: Management of Diabetic Nephropathy

In the treatment of albuminuria/nephropathy, ACE inhibitors and ARBs are recommended as follows:

- In hypertensive type 1 diabetic patients with any degree of albuminuria, ACE inhibitors have been shown to delay the progression of nephropathy.
- In patients with type 2 diabetes, hypertension, macroalbuminuria, and renal insufficiency..., ARBs have been shown to delay the progression of nephropathy.

ACE = angiotensin-converting enzyme; ADA = American Diabetes Association; ARB = angiotensin II receptor blocker.


WHAT ARE OPTIMAL BLOOD PRESSURE TARGETS FOR CARDIO/RENAL PROTECTION?
Independent and Additive Impact of Blood Pressure Control and Angiotensin II Receptor Blockade on Renal Outcomes in the Irbesartan Diabetic Nephropathy Trial: Clinical Implications and Limitations


Impact of Achieved Blood Pressure on Cardiovascular Outcomes in the Irbesartan Diabetic Nephropathy Trial

SUMMARY

• Lowering BP, particularly SBP, is clearly renal and cardio-protective, but below certain levels of SBP and DBP risk may occur in selected populations.

• BP of 120-125/80-85 appears to be ideal target.

• Inhibiting/blocking the RAS benefits both heart and kidney.