# Proteinuria and Hematuria

- **Proteinuria (including Albuminuria)**
  - **Qualitative Testing** (dye-impregnated paper strip- “dipstick”) - 1-4+
  - **Quantitative Testing**
    - Urine protein to creatinine ratio (UPCR) (gm/gm) in a “spot” urine sample or a timed collection
    - Urine albumin to creatinine ratio (UACR) (mg/mg) in a “spot” urine or a timed collection
    - Urine albumin concentration (mg/dL) (UAC)
    - Urine albumin excretion rate (mg/d or μg/min (UAER) in timed urinary collection
    - Urine protein excretion rate (UPER) in a timed urinary collection-usually 24 hours

  *(UACR or UAC preferred)*

# Proteinuria and the Nephrotic Syndrome: Definitions

**Proteinuria:**
- **Overt** - Urinary excretion of >300mg total protein/d or a UPCR of >200mg/gm
- **Covert** - (microalbuminuria) UAER of 30-300mg albumin/d (20-200μg/min or a UACR of 17-250mg/gm (M) or 25-355mg/gm (F)

**Nephrotic Syndrome:**
- Urinary excretion of >3.5gm total protein/d or a UPCR of >3.0gm/gm (Adult) +
- Hypoalbuminemia (Edema and Hyperlipidemia are variable)
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
- Myoglobin and Hemoglobin can give a + test

**Dipsticks:**
- Negative - <10mg/dL
- Trace - 10mg/dL
- 1+- - 30mg/dL
- 2+- - 100mg/dL
- 3+- - 300mg/dL
- 4+- - >1000mg/dL

**Dipstick Proteinuria and UPCR**

![Graph showing urine protein/creatinine ratio (mg/g) vs. dipstick value](image)
Probability (%) of Detecting UPCR >500mg/gm
Dipstick and Specific Gravity

<table>
<thead>
<tr>
<th></th>
<th>1005</th>
<th>1010</th>
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<tr>
<td>0</td>
<td>5.5</td>
<td>5.5</td>
<td>3.0</td>
<td>1.7</td>
<td>1.2</td>
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<tr>
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<td>27</td>
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<td>1+</td>
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<td>98</td>
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<tr>
<td>3+</td>
<td>100</td>
<td>100</td>
<td>98</td>
<td>98</td>
<td>97</td>
<td>100</td>
<td>100</td>
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Gross Hematuria and Proteinuria
(From Fairley and Becker, 2001)

<table>
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<tr>
<th>Blood (ml/L)</th>
<th>0.5</th>
<th>1</th>
<th>4</th>
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<th>7</th>
<th>10</th>
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<tbody>
<tr>
<td>Protein</td>
<td>-</td>
<td>-</td>
<td>-/Tr</td>
<td>Tr/1+</td>
<td>1+</td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
<td>4+</td>
<td>4+</td>
<td>4+</td>
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</table>

Proteinuria: Evaluation Caveats

- Concentration of urine (SG or Osm) must be taken into account in the evaluation of overt proteinuria by Dipsticks
- Fever, vigorous exercise, urinary infection can 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 (unless substantial hemolysis contributes hemoglobin to proteinuria)
Microalbuminuria: 

**Evaluation**

- Increased urinary excretion of albumin below the level reliably detected by semi-quantitative means (Dipsticks) but above the normal level of excretion (20-300mg/d) = microalbuminuria
- Microalbuminuria is associated with an increased risk of CVD, Hypertension and CKD
- In Diabetics (Type 1 and 2) it is often predictive of the eventual development of overt Diabetic Nephropathy

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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 (see Lambers-Heerspink et al JASN 21:1355-1360, 2010)
- However, both albumin excretion (UA) and creatinine excretion (C) contribute to risk – in opposite directions (similar to Kt/V) (see Kestenbaum B, de Boer J. JASN 21:1243-1244, 2010)

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<table>
<thead>
<tr>
<th>Baseline albuminuria measures</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macroalbuminuria (UAE)</td>
<td>9.3 (3.6-23.4)</td>
</tr>
<tr>
<td>Microalbuminuria (UACR)</td>
<td>3.0 (2.00-3.96)</td>
</tr>
<tr>
<td>Low-normal Creatinine clearance (g/d)</td>
<td>2.28 (1.19-4.38)</td>
</tr>
<tr>
<td>Low-normal Creatinine clearance (g/d)</td>
<td>1.69 (1.00-2.88)</td>
</tr>
<tr>
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</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.48 (1.30-2.60)</td>
</tr>
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<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.48 (1.30-2.60)</td>
</tr>
</tbody>
</table>
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
The HUNT-II Study-
Adjusted 10 year risk of ESRD according to
eGFR and Albuminuria
(Hallan S, et al JASN 20:1069-1077, 2009)

<table>
<thead>
<tr>
<th>&gt;60</th>
<th>45-59</th>
<th>30-44</th>
<th>15-29</th>
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<tbody>
<tr>
<td>Normal UACR</td>
<td>1.00</td>
<td>23.4</td>
<td>51.9</td>
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<tr>
<td>Microalbuminuria</td>
<td>27.3</td>
<td>146.5</td>
<td>448.9</td>
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<tr>
<td>Macroalbuminuria</td>
<td>196.3</td>
<td>641.1</td>
<td>2036.0</td>
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Albuminuria and the Risk of CVD and ESRD: PREVEND Study
(Gansevoort RT, de Jong P JASN 20:465-468, 2009)

Dipstick Proteinuria and Risk of Rapid Progression of CKD

- Rapid kidney function decline (RKFD) defined as loss of eGFR >5% per year (2754 community living adults with median FU of 7 years)
- One of 40 of screened individuals (2.5%) had ≥100mg/dL (≥2+) at baseline—1 of every 2.6 such patients had RKFD
- Screening for ≥2+ proteinuria detect 91% of those with RKFD (TP), misses 8% with eventual RKFD (FN) and mislabels 1% as likely to develop RKFD (FP)
- Serial eGFR measurements should focus on those with ≥2+ proteinuria in an office visit
**ALBUMINURIA:**
*New Definitions- KDIGO-2012*

<table>
<thead>
<tr>
<th>UACR*</th>
<th>Dipstick</th>
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<tr>
<td>Normal</td>
<td>&lt;10</td>
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<tr>
<td>High Normal</td>
<td>10-29</td>
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<tr>
<td>High</td>
<td>30-299</td>
</tr>
<tr>
<td>Very High</td>
<td>300-2999</td>
</tr>
<tr>
<td>Nephrotic</td>
<td>3000+</td>
</tr>
</tbody>
</table>

(*UACR=mg Albumin/gm Creatinine*)

Microalbuminuria term is strongly discouraged—High albuminuria preferred

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<table>
<thead>
<tr>
<th>Albuminuria Stages, Description and Range (mg/g)</th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
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</thead>
<tbody>
<tr>
<td>optimal to high-normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>high</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>very high to nephrotic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
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<td>10-29</td>
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<tr>
<td>30-299</td>
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<td></td>
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<tr>
<td>300-2999</td>
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<tr>
<td>&gt;2000</td>
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<table>
<thead>
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<th>A3</th>
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<tr>
<td>&gt;105</td>
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<tr>
<td>90-104</td>
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<td></td>
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<tr>
<td>G2 low-normal</td>
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<td>75-89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G3a mild-moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45-59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G3b moderate-severe</td>
<td></td>
<td></td>
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<tr>
<td>G4 severe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G5 kidney failure</td>
<td></td>
<td></td>
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<tr>
<td>&lt;15</td>
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**Proteinuria:**
*Categories*

- Glomerular
- Tubular
- Overflow
- Tissue
- Physico-chemical
Glomerular Proteinuria

- Abnormal urinary excretion of protein due to an abnormality of glomerular permeability (often plus some abnormality of tubular reabsorption)

- Two subtypes: Selective (albumin predominates); Non-selective (albumin + high molecular weight proteins, such as IgG)

- Amounts excreted vary widely— from slightly above normal to >20gms/d

Glomerular Proteinuria: Does the Quality Count? (Bazzi C, D’Amico NephSAP 4:111, 2005)

- Poorly selective proteinuria (High FE IgG, high IgG excretion rate) is associated with a poor response to therapy and a tendency for progression to ESRD

- High Beta2 microglobulin urinary excretion (?tubular origin) is associated with a poor response to therapy and a poor prognosis (especially in IMN)
**Tubular Proteinuria**

- Abnormal urinary excretion of proteins (usually low molecular weight [LMW] + albumin) normally filtered by the glomerulus due to defective proximal tubular reabsorption
- Diagnosed by electrophoresis of urine proteins + greatly elevated β2m/albumin excretion ratio
- Usually <2.0gms/d

**Tubular Proteinuria: Causes**

- With Fanconi Syndrome
  - Heavy metals (Pb, Cd)
  - Outdated Tetracycline
  - Interstitial nephritis
  - Cystinosis
  - Multiple myeloma (with crystals in PT)
  - Dent’s disease
- Without Fanconi Syndrome
  - Immerslund-Grasbeck Disease (Cubulin deficiency)

**Overflow Proteinuria**

- Abnormal urinary excretion of protein due to the appearance of low-molecular weight (LMW) proteins in excess in the circulation
- No abnormality of glomerular permselectivity is required but maximum capacity of tubular reabsorption must be exceeded
- Diagnosed by identification of protein in serum or urine (e.g. Freelite, electrophoresis, immunofixation, etc)
- May range from a few hundred mg/d to >10gm/d (pseudo-nephrotic syndrome)
**Overflow Proteinuria**

*Causes*

- Monoclonal Light Chains (LCDD, Amyloidosis, Multiple Myeloma)
- Hemoglobin (after haptoglobin binding capacity exceeded)
- Myoglobin
- Lysozyme
- Mucoproteins from Malignant Tumors

**Tissue Proteinuria**

- Abnormal protein excretion due to secretion of proteins (such as IgA) from mucosal surfaces into urine (usually bladder or upper urinary tract origin)
- Often associated with inflammation or infiltration of tissue
- *Seldom greater than 500mg/d*

**Physico-Chemical Proteinuria**

- Abnormal urinary excretion of protein due to a physico-chemical alteration of a normal plasma protein leading to increased trans-glomerular passage or reduced tubular reabsorption or both
- Usually <300mg/d
- Best example is *glycated albumin* in poorly controlled DM
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?

- Less than 2 erythrocyte per high power field (about 0.5μL) in a “urine sediment” resuspended in a small volume (<0.5mL) of an aliquot of a freshly-voided urine sample (10 mL) after light centrifugation (400G x 10 min) [Fogazzi, 1999]

- Less than 8,000 erythrocytes per mL of centrifuged urine (back calculated to the original volume of urine or less than 13,000 erythrocytes per mL of uncentrifuged urine Using a Fuchs-Rosenthal hemacytometer chamber) (Fairley, 1984)

HEMATURIA Caveats

- Second morning voided (mid-stream) specimens are best
- Always examine urine fresh (within 1-2 hours, never stored in refrigerarator)
- 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 high power field and are as sensitive as urinary sediment exams for detecting hematuria but

- False negatives (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

A negative Dipstick does not completely exclude significant hematuria

A positive Dipstick should always be confirmed by examination of urinary sediment microscopically

<table>
<thead>
<tr>
<th>Dipstick Results</th>
<th>Erythrocytes/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0-10⁴ 10⁵ &gt;10⁵</td>
</tr>
<tr>
<td>Trace</td>
<td>428 37 1</td>
</tr>
<tr>
<td>1+</td>
<td>56 76 1</td>
</tr>
<tr>
<td>2+</td>
<td>1 12 31</td>
</tr>
<tr>
<td>3+</td>
<td>4 24 2</td>
</tr>
<tr>
<td>4+</td>
<td>0 15 9</td>
</tr>
</tbody>
</table>

False Positive Dipstick- 62/490 = 12%
False Negative Dipstick- 38/466 = 8%
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)

“PSEUDO-HEMATURIA”

- Red or Reddish-brown urine does not always mean hematuria
  - Red urine + positive Dipstick for heme + no erythrocytes in urine = hemoglobinuria or myoglobinuria (alkaline urine)
  - Red-brown urine + positive Dipstick for heme + no erythrocytes in urine = hemoglobinuria or myoglobinuria (acid urine)
  - Red or Red-brown urine + negative dipstick = Pigmenturia

Pigmenturia

- Red or Red-brown urine and negative Dipstick may be seen in:
  - Porphyrinuria
  - Rhubarb, senna or beetroot ingestion
  - Aminopyrine, diphenylhydantoin, phenosulfonphthalein, 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 increased
  - 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

**Abbreviated Etiologic Classification**

(108 Causes; Glassock, 2001)

- **Renal Parenchymal Disease** (52 causes)
  - Glomerular
  - Vascular
  - Tubulo-interstitial

- **Urinary Tract Diseases** (44 causes)
  - Renal pelvis
  - Ureter
  - Bladder
  - Prostate
  - Urethra

- **Systemic Coagulation Disorders** (9 causes)

- **Other** (2 causes)

- **Surreptitious (malingering)**

HEMATURIA

**Patterns**

- **Gross** (macroscopic)- visible to the naked eye- a “urocrit” of >0.1% (1mL of blood per liter of urine).
  - with clots- always of urinary tract origin
  - without clots- renal parenchymal or urinary tract origin

- **Covert** (microscopic)- only detectable by microscopic examination of urine (2->200 erythrocytes per high power field)

- **Persistent**- seen on all or nearly all examinations of the urine over an extended period of time (weeks/months/years)

- **Episodic** (Recurrent)- seen only on some examinations with intervals of normal urine

- **Cyclic**- seen at regularly occurring intervals- menstruation=endometriosis

- **Symptomatic**- accompanied by symptoms referable to the kidneys or urinary tract

- **Asymptomatic**- no symptoms present referable to the kidney or urinary tract
Gross Hematuria and Proteinuria

<table>
<thead>
<tr>
<th>Blood (ml/L)</th>
<th>0.5</th>
<th>1</th>
<th>4</th>
<th>5</th>
<th>7</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>Tr</td>
</tr>
</tbody>
</table>

| Blood | 3+ | 3+ | 3+ | 4+ | 4+ | 4+ |

The Urinary Sediment Examination

- Examine the second morning void after abstinence from vigorous exercise (preferably "mid-stream")
- Prepare sediment from fresh urine (within 2 hours of collection)
- Centrifuge a 10ml aliquot at 400 g for 10 minutes
- Decant (or pipette) off the supernatant, leaving 0.5ml to re-suspend sediment, by gentle to and fro aspiration of the pipette
- Transfer 50μL (0.5% of the original volume) under a 24 x 32 mm glass coverslip.

Examine sediment under a LM (preferably equipped with Phase Contrast) at 10x, 60x and 100x
**Key Features in Urinary Sediment**

- **Erythrocytes** (number per HPF, dysmorphic or normomorphic (give % of each))
- **Leukocytes** (Neutrophils, Lymphocytes, Eosinophils)
- **Casts** (erythrocyte, hyaline, fatty, "muddy" dark-brown, granular, leukocyte, waxy)
- **Renal tubular cells**
- **Crystals** (urate, Calcium oxalate, etc)

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**HEMATURIA**

**Glomerular vs Non-Glomerular**

- **Glomerular disease** is strongly associated with excretion of small (MCV<70fL), mis-shapen (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 normo-morphic), well hemoglobinized erythrocytes.

- **Glomerular disease** is strongly associated with an increase in the urinary albumin to total protein ratio (on a "spot" urine).

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**Erythrocyte Morphology in Urine**

*(Phase Contrast Microscopy)*

- **Dysmorphic**
- **Isomorphic**

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Erythrocyte Morphology in Urine
(Phase Contrast Microscopy)

- **Dysmorphic**
- **Isomorphic**

**Urinary Erythrocyte Morphology as a Diagnostic Tool**

- Distinguishes "glomerular" from "non-glomerular" causes of hematuria
- Accuracy dependent on technique and experience of the observer
- Phase-contrast microscopy or Sternheimer-Malbin supravital staining is best
- >80% "dysmorphic" erythrocytes almost always means glomerular disease

**Erythrocyte Casts**
(Phase Contrast Microscopy)

- **Low Power**
- **High Power**
HEMATURIA

Methods for Determining Erythrocyte Dysmorphism

- Bright-field light microscopy of a urine sediment (simple, inexpensive, available)
- Phase-contrast microscopy of a urine sediment (expensive, limited availability)
- Supra-vital Staining (Sternheimer-Malbin, Wright, Geimsa) of urinary sediment (simple, inexpensive, available)
- Flow-cytology (Coulter Counter) of urinary erythrocytes - (detects MCV and MCHC only, inexpensive, available).
- Electron microscopy of urinary sediment (Expensive, unavailable and tedious)

HEMATURIA

Glomerular vs Non-Glomerular
(Fogazzi, 1999)

% of patients correctly localized for the source of hematuria using the dysmorphic/isomorphic categorization by PCM:

Glomerular Disease – 345/369 = 94%
Urinary Tract Disease-240/255= 94%

Erythrocyte Dysmorphism: Sensitivity and Specificity for Detection of Glomerular Disease
(according to method used)

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>Brightfield</td>
<td>60%</td>
<td>85%</td>
</tr>
<tr>
<td>Wright/Geimsa</td>
<td>78%</td>
<td>95%</td>
</tr>
<tr>
<td>Sternheimer-Malbin</td>
<td>90%</td>
<td>80-95%</td>
</tr>
<tr>
<td><strong>Phase-Contrast</strong></td>
<td><strong>65-95%</strong></td>
<td><strong>96-100%</strong></td>
</tr>
<tr>
<td>RBC Volume (MCV &lt;70fL)</td>
<td>94%</td>
<td>91%</td>
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HEMATURIA
Acanthocytes

- Acanthocytes (or G1 cells) are highly specific for a glomerular origin for hematuria
- "Cut-offs" –

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>&gt;1%</td>
<td>89%</td>
</tr>
<tr>
<td>&gt;2%</td>
<td>80%</td>
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<td>&gt;5%</td>
<td>52-87%</td>
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<td>&gt;10%</td>
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</tbody>
</table>

Acanthocytes

- Phase Contrast
- Scanning Electron

≥5% Acanthocytes in a fresh urine sediment examined by Phase Contrast Microscopy (or possibly by Wright Stain) are virtually diagnostic of a glomerular source for the hematuria
Urinary Albumin to Total Urinary Protein Ratio (UATPR) for distinguishing Glomerular from Non-Glomerular Hematuria

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>UATPR (&gt;0.59mg/mg)</td>
<td>97%</td>
<td>100%</td>
</tr>
<tr>
<td>UACR (&gt;71mg/gm)</td>
<td>79%</td>
<td>61%</td>
</tr>
<tr>
<td>UPCR (&gt;265mg/gm)</td>
<td>68%</td>
<td>62%</td>
</tr>
<tr>
<td>Phase Contrast (&gt;80% dysmorphic rbc)</td>
<td>83%</td>
<td>75%</td>
</tr>
</tbody>
</table>

(Not useful if UTP <5mg/dL)

HEMATURIA

Glomerular vs Non-Glomerular: Summary

- **Glomerular Hematuria**
  - Over 75-80% of erythrocytes are dysmorphic
  - Red-cell casts present
  - Acanthocytes ≥ 5%
  - Proteinuria >1+ present; UATPR >0.59mg/mg

- **Non-Glomerular Hematuria**
  - Over 75% of erythrocytes are isomorphic
  - Red cell casts absent
  - No Acanthocytes present
  - Proteinuria < or = 1+ present; UATPR <0.59mg/mg

- **Indeterminate Hematuria**
  - 25 to 75% of erythrocytes are dysmorphic/isomorphic
  - Red cell casts absent
  - Less than 5% Acanthocytes
  - Proteinuria < or = 1+; UATPR <0.59mg/mg

Isolated, Asymptomatic Non-Visible (Microscopic) Hematuria is not Always Benign

- **1,203,626** asymptomatic Israeli subjects (M/F = 1.5, ages 16-25 years) were screened for isolated microscopic hematuria- **3690** (0.3%) were positive

- **22 year** (9-35 years) follow up and linkage to ESRD Registry
- Hazard Ratio for ESRD in Hematuria + vs Hematuria - = **19.5**
Isolated, Asymptomatic Microscopic Hematuria is not Always Benign
(Vivante A, et al. JAMA, 2011)

THANK YOU
(A suggested Step-wise algorithm for evaluation of Hematuria is provided in the Syllabus)

HEMURIA
Step-Wise Evaluation

☐ **Step 1** - Careful History and Physical Examination looking for clues to an etiology + Basic Laboratory values (Scr/eGFR, UACR or UPCR, Hemogram)- Repeat urinalysis in several days

☐ **Step 2** - Exclude “Pseudo-Hematuria” (if appropriate)

☐ **Step 3** - Determine Glomerular v Non-Glomerular v Indeterminate form (Phase-contrast examination of urine sediment)

☐ **Step 4** - Separate pathways depending on Step 3 (Step 4A- Glomerular; Step 4B- Non-Glomerular; Step 4C- Indeterminate)
HEMATURIA EVALUATION

Step 1

☐ Key Clues from History and Physical Examination:
  > Pattern of hematuria
  > Associated symptoms (dysuria, hesitancy, frequency, flank pain, colic)
  > Signs of systemic disease (purpura, hemoptysis, neuropathy, liver disease, arthrits)
  > Medications; toxic exposures
  > Family history of hematuria, renal failure, deafness
  > Travel to endemic areas (Schistosomiasis, TB)
  > Recent infections (URI, UTI, impetigo, TB)
  > Exercise or trauma
  > Ancestry (Black, Asian)
  > Bleeding diathesis
  > Edema, frothy urine (proteinuria)
  > Abdominal masses

HEMATURIA EVALUATION

Step 2

☐ If dipstick + for blood and urinary sediment negative for erythrocytes-then exclude hemoglobinuria or myoglobinuria (examine color of fresh plasma)

☐ If dipstick negative for blood and urine is red or red-brown- then exclude pigmenturia

HEMATURIA EVALUATION

Step 3

☐ If dipstick + for blood and urinary sediment positive for erythrocytes then evaluate for dysmorphic (glomerular) or isomorphic (non-glomerular) hematuria, unless erythrocyte casts or heavy proteinuria (2+ or greater) is present.

☐ Phase contrast microscopy is best but bright-field unstained or stained sediment can be used (with experience)

☐ Alternatively, measure UATPR (>0.59mg/mg= glomerular disease)
HEMATURIA EVALUATION
Step 4A (Glomerular)

- If dysmorphic hematuria, erythrocyte casts, acanthocytes or proteinuria 2+ or greater are found then initiate an evaluation for primary, systemic or heredo-familial glomerular diseases (based on history and PE)—
- C3/C4, serology (FANA, ANCA, aGBM, HCV/HBV/HIV, ASLOT), CryoIg, IgA, HAA-binding, Audiogram, Slit-lamp/Retinoscopy may be indicated depending on history and PE.

HEMATURIA EVALUATION
Step 4A (Glomerular)

- **Microscopic dysmorphic hematuria:** Blood pressure, Scr and eGFR normal, Dipstick negative for proteinuria, no systemic or known hereditary disease, C3 and serology negative = "Isolated" microscopic dysmorphic hematuria (IDMH)
- Nephrology Referral and Renal Biopsy optional
- Periodic follow-up (at least annually)

Isolated Dysmorphic Microscopic Hematuria (IDMH)

- **Renal Biopsy findings:**
  - >30-40% Thin Basement Membrane Nephropathy (persistent>episodic); 50% AD inheritance; UACR-normal
  - >30-40% IgA Nephropathy (episodic>persistent); 10% familial,
  - ↑ IgA/C3 ratio (>4.0), ↑UACR, ↑HAA-binding
  - >10-20% Other specific glomerular disease or normal
Isolated Dysmorphic Microscopic Hematuria (IDMH)

- 217 Adults with IDMH underwent renal biopsy
  - IgA N= 40%
  - TBMN= 26%
  - Non-IgA N Chronic GN= 14%
  - "Normal"= 10%
- UACR and serum IgA/C3 ratio examined

<table>
<thead>
<tr>
<th>Disease</th>
<th>UACR</th>
<th>IgA/C3</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;30mg/g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgA N</td>
<td>70%</td>
<td>86%</td>
</tr>
<tr>
<td>Non-IgA GN</td>
<td>85%</td>
<td>&lt;14%</td>
</tr>
<tr>
<td>TBMN</td>
<td>4%</td>
<td>&lt;14%</td>
</tr>
<tr>
<td>Normal</td>
<td>0%</td>
<td>&lt;14%</td>
</tr>
</tbody>
</table>

IgA/C3 Ratio for detecting IgA N in subjects with IDMH

- Sensitivity 84%; Specificity= 84%
- PPV= 81%
- NPV= 88%
- When added to MA, the IgA/C3 ratio is very useful in determining which patients with IDMH should undergo renal biopsy– for diagnosis
HEMATURIA EVALUATION
Step 4A - Glomerular

- Microscopic dysmorphic hematuria + proteinuria and/or elevated Scr or reduced eGFR.

- Nephrology Referral (Urgent if Scr rising) + C3/C4, serology, search for systemic disease

- Renal biopsy very likely to be needed

HEMATURIA EVALUATION
Step 4B (Non-Glomerular)

- Helical Multi-slice CT of abdomen (or abdominal ultrasound in Pregnant women)- without contrast if calculi suspected; without and then with contrast if no calculi suspected- Referral based on lesion found- if any

  - If Helical CT negative proceed to urinary cytology- if positive proceed to cystoscopy (immediate cystoscopy if gross hematuria with clots)

  - If urinary cytology negative proceed to cystoscopy if >50 years of age and/or risk factors for bladder cancer present; if <50 years of age and no risk factors for bladder cancer evaluation may be stopped and repeated in 6 months to one year if hematuria persists or recurs.

HEMATURIA EVALUATION
Step 4B (Non-Glomerular)

- Urine cytology- Sensitivity too low (50-70%) to exclude Bladder Cancer, but very high Specificity (>95%)

- Urine Tumor Markers- Not yet proven to be useful, but great potential- probably will eliminate cytology

- Cystoscopy and CT are required for proper evaluation of all cases
HEMATURIA EVALUATION

**Step 4B (Non-Glomerular)**

- Abdominal Ultrasound first - if negative then CT or
- Abdominal Multi-Detector (Spiral) CT first (without Ultrasound) are of approximately equal cost-effectiveness but
- Studies of exact sequencing of tests and which tests to use (IVU, US, CT) are inconclusive

BLADDER CANCER

**Risk Factors**

- Age >50 years (Males > Females)
- Cigarette smoking; coal tar chewing
- Exposure to chemicals (analine dyes, leather/dye/rubber manufacturing)
- Heavy phenacitin use (Analgesic Abuse Nephropathy)
- Use of “Herbal Medicins” containing/contaminated with Aristolochic Acid
- Prior treatment with cyclophosphamide

HEMATURIA EVALUATION

**Step 4B**

- If *macroscopic* (non-glomerular) *hematuria* present or patient is at high risk for Bladder cancer may proceed directly to *immediate flexible (office-based)* Cystoscopy (without Urinary Cytology, US or abdominal CT)
Macroscopic Isomorphic Hematuria

- Strongly associated with Renal Cancer, Bladder Cancer and ADPCKD
- 25% will have Bladder Cancer
- “Fast-track” (same day) Hematuria Clinic Evaluation is very effective
- CT urogram and flexible (office-based) cystoscopy
- CT Urogram alone is 93% sensitive and 98% specific for detecting Bladder Cancer

**Algorithm >40 years old**

```
Macroscopic Isomorphic Hematuria

Immediate CT Urogram

Negative  Positive

Flexible Cystoscopy  Rigid Cystoscopy and Biopsy
```

HEMATURIA EVALUATION

**Step 4C - Indeterminate**

- Abdominal Ultrasound or Helical CT Scan of abdomen (without contrast) or abdominal MRI- consider Cystoscopy if normal or patient >50 years of age
- Repeat UACR or UPCR, Scr and Urinalysis (quantitate dysmorphic erythrocyte content of urine in dysmorphic cells/mL of urine)
- Re-evaluate History and Physical Exam
- If >10^7 dysmorphic erythrocytes/mL of urine then proceed as in Step 4A (irregardless of the % of dysmorphic erythrocytes in urine)
GROSS HEMATURIA

"Three Glass Test"

- For evaluation of Gross Hematuria the "three glass test" may be sometimes be useful. During spontaneous voiding first 10-15 ml in one glass, next entire volume until "almost empty" feeling of bladder in second glass, last 10-15 ml in third glass
  - Blood in first glass only = Urethral bleeding
  - Blood in the last glass only = Bladder bleeding (Cancer or S. Haematobium)
  - Blood in all three glasses = Upper tract bleeding

Exercise-Induced Hematuria

- 10-25% of apparently normal subjects develop dipstick positive hematuria after strenuous exercise (marathon races, endurance swimming, rowing, "iron-man" contests)
- 70% of such subjects have an increase in erythrocytes/ml of urine (to as high as 10^6 per mL)
- In almost all the hematuria disappears after 7 days
- Some studies indicated bladder trauma and isomorphic erythrocytes, others suggest dysmorphic erythrocytes and a glomerular source
- **No evaluation needed unless hematuria persists for over one week**

HEMATURIA EVALUATION

Special Circumstances

- African, African-American and Mixed Races should have a Sickle Cell Hemoglobin measured
- Recent travel to areas endemic for S. Haematobium should have a urine for Ova and Parasites
- If a clear cut Family History of hematuria is present, evaluate for IgA N (variable patterns of inheritance), Thin Basement Membrane Nephropathy (AD), Alport Syndrome (XL, AD, AR), Fabry’s Disease (XL), ADPKD, ARPKD
- If hematuria occurs during anti-coagulation evaluate as for Stage 4A,B,C
- Children or young adults with "isolated" microscopic hematuria should have Uca and Uric acid measured
- Adults with Loin-Pain Hematuria Syndrome should have Uca and Uox measured
- Urine TB culture if pulmonary TB present or suspected