Urine Sediment Analysis
Intensive Review of Nephrology

Martina McGrath, MB, BCh, FRCPI,
Brigham & Women’s Hospital
Harvard Medical School
Medical School:
University College Cork, Ireland

Residency:
Beaumont Hospital, Dublin

Fellowship:
Brigham and Women’s/MGH

Clinical Interests:
Renal transplantation, live kidney donation, general nephrology

Academic Interests:
Transplantation immunology
CV disease in CKD & transplantation
Education and scientific research training
Disclosures

None
Learning Objectives:

• To discuss the benefits of carrying out urine sediment analysis
• To describe the utility of renal tubular epithelial cells and granular casts in AKI
• To review the causes of leukocyturia
• To review the significance and evaluation of hematuria
• To describe specific hematuria syndromes
Urine sediment as a biomarker of kidney disease

• Cheap, readily available, reproducible
• Indicates the presence of renal injury
• Suggests the compartment of injury
• Data may alter treatment plan
• Differentiation between pre-renal states and ATN
• Greater degrees of renal injury on sediment correlate with more severe AKI and need for RRT
Urine sediment as a biomarker of kidney disease

Perazella M. AJKD 2015
Urine microscopy and worsening AKI in hospitalized patients. Perazella MA, *CJASN* 2010

- Scoring system based on presence of renal tubular epithelial cells, RTE cell casts, granular casts
- Ability to predict worsening of AKI
- Formally trained renal consultants reviewed urine sediment (didactic and practical training)
- Second nephrologist performed chart review to confirm diagnosis
- 197 patients with AKIN Stage 1-3 AKI:
  - ATN (134)
  - Pre-renal AKI (63)
Urinary RTE cells and granular casts.

Mark A. Perazella et al. CJASN 2010;5:402-408
Urine microscopy and worsening AKI in hospitalized patients. Perazella MA, CJASN 2010

<table>
<thead>
<tr>
<th>RTE Cells (per HPF)</th>
<th>Granular Casts (per LPF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (0 points)</td>
<td>0 (0 points)</td>
</tr>
<tr>
<td>0 (0 points)</td>
<td>1-5 (1 point)</td>
</tr>
<tr>
<td>1-5 (1 point)</td>
<td>1</td>
</tr>
<tr>
<td>≥6 (2 points)</td>
<td>2</td>
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<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
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<td></td>
<td>≥6 (2 points)</td>
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<td>≥6 (2 points)</td>
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<td>3</td>
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<td>4</td>
</tr>
</tbody>
</table>
Baseline higher urinary sediment score correlated with higher AKIN stage of AKI

<table>
<thead>
<tr>
<th>Urine sediment score</th>
<th>Worsening AKI after consultation (%)</th>
<th>Worsening AKI, adj. RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>9.4</td>
<td>ref</td>
</tr>
<tr>
<td>1</td>
<td>36.2</td>
<td>3.4 (1.3 to 6.5)</td>
</tr>
<tr>
<td>2</td>
<td>54.1</td>
<td>6.6 (3.4 to 9.1)</td>
</tr>
<tr>
<td>≥3</td>
<td>66.7</td>
<td>7.3 (3.8 to 9.6)</td>
</tr>
<tr>
<td>( p )</td>
<td>&lt;0.001</td>
<td></td>
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</tbody>
</table>
### Table 2. Urine Sediment Examination as Biomarker for Prognosis in AKI

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N</th>
<th>Scoring System</th>
<th>Outcomes</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schentag(^{33}) (1979)</td>
<td>ICU patients</td>
<td>154</td>
<td>Modified Addis count</td>
<td>Increase in Scr ≥ 0.5 mg/dL within 5 d after aminoglycoside treatment</td>
<td>Urinary casts higher in nephrotic AKI (625 ± 364 vs 153 ± 196) and increased as early as 9 d before Scr increased</td>
</tr>
<tr>
<td>Chawla(^{34}) (2008)</td>
<td>AKI on renal consult service</td>
<td>18</td>
<td>Grades 1-4(^{a})</td>
<td>Renal nonrecovery</td>
<td>AUC 0.79</td>
</tr>
<tr>
<td>Perazella(^{35}) (2010)</td>
<td>AKI on renal consult service</td>
<td>197</td>
<td>Score 0 to ≥3(^{b})</td>
<td>Worsened AKI (increase in AKIN stage, RRT, or death)</td>
<td>AUC = 0.75&lt;br&gt;Score 1: RR = 3.4&lt;br&gt;Score 2: RR = 6.6&lt;br&gt;Score ≥3: RR = 7.3</td>
</tr>
<tr>
<td>Hall(^{37}) (2011)</td>
<td>≥ Stage 1 AKI</td>
<td>249</td>
<td>Score 0 to ≥3(^{b})</td>
<td>Worsened AKI (increase in AKIN stage, RRT, or death)</td>
<td>AUC = 0.66&lt;br&gt;Score 1: RR = 1.6&lt;br&gt;Score 2: RR = 2.3&lt;br&gt;Score ≥3: RR = 3.5</td>
</tr>
<tr>
<td>Bagshaw(^{36}) (2012)</td>
<td>ICU patients with AKI</td>
<td>83</td>
<td>Score 0 to ≥3(^{c})</td>
<td>Worsened AKI; RRT/death</td>
<td>AUC 0.85&lt;br&gt;Score 1-2: OR = 5.6&lt;br&gt;Score ≥3: OR = 8.0&lt;br&gt;AUC = 0.58; specificity for AKI, 91%; sensitivity, 22%</td>
</tr>
<tr>
<td>Schinstock(^{38}) (2012)</td>
<td>ED patients</td>
<td>363</td>
<td>Any RTECs or RTEC/granular casts</td>
<td>AKIN stages</td>
<td>Perazella AJKD 2015</td>
</tr>
</tbody>
</table>
Nephrologist vs. Lab urine sediment exam

• Technical differences – Volume of urine spun, speed of centrifuge, resuspension volume & volume of suspension examined

• Nephrologists use a more concentrated sample - greater yield of RTECs and dysmorphic RBCs

• Accreditation standards - Labs may have greater focus on the accuracy of WCC and RBC count

• Considerable interobserver variability (between nephrologists) in terms of both agreement and accurate identification of urine elements
Enhancing the Detection of Dysmorphic Red Blood Cells and Renal Tubular Epithelial Cells with a Modified Urinalysis Protocol Chu-Su et al. *Scientific Reports* 2017;7:40521

Isomorphic vs. dysmorphic RBCs by light and phase microscopy
Activated Neutrophil

Squamous epithelial cell

Urothelial cell

Renal tubular epithelial cell

Renal tubular epithelial cell
Leukocyturia
Leukocyturia

- Defined as > 3 WBCs/hpf on microscopy
- Most commonly related to infection
- Sterile pyuria affects up to 14% of women and 2.6% of men
- Evaluation directed by:
  - presence or absence of symptoms
  - renal dysfunction
Sterile Pyuria: Infection Related

- Current/recent antibiotic use
- Gyn infection
- Urethritis/STI (gonorrhea, chlamydia, mycoplasma, ureaplasma)
- Prostatitis/Balanitis
- GU Tuberculosis
- Parasitic infection (schistosomiasis)
- Appendicitis
## Sterile Pyuria: Non Infection Related

<table>
<thead>
<tr>
<th>Condition</th>
<th>Condition</th>
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<tbody>
<tr>
<td>Urinary catheterization</td>
<td>Interstitial nephritis</td>
</tr>
<tr>
<td>Recent instrumentation</td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Urinary fistula</td>
<td>Transplant rejection</td>
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<tr>
<td>Interstitial cystitis</td>
<td>PKD</td>
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<tr>
<td>Pelvic irradiation</td>
<td>Papillary necrosis</td>
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<tr>
<td>Neoplasia</td>
<td>Renal vein thrombosis</td>
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<tr>
<td>Renal calculi</td>
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WBC Casts

• Intra-renal inflammation

• Typically associated with interstitial inflammation

• Many types of glomerulonephritis

• Important considerations include AIN, pyelonephritis
Utility of Urine Eosinophils in the Diagnosis of Acute Interstitial Nephritis Muriithi et al, CJASN Sept 2013

- 556 pts with urine eosinophils (UE) & renal biopsy
- 82% had pyuria
- 133 biopsy proven AIN, 80% were drug induced

- 1% UE cutoff: 30.8% sensitivity, 68.2% specificity
- Positive predictive value: 15.6%
- Negative predictive value: 83.7%

- 5% UE cutoff: Lower sens but better specificity.
Utility of Urine Eosinophils in the Diagnosis of Acute Interstitial Nephritis *Muriithi et al, CJASN Sept 2013*

Urine eosinophils in other forms of kidney disease

Even at 5% cutoff, UE poorly distinguishes AIN from ATN or other renal disease
Hematuria
Definition & Diagnosis

- Urine dipstick: Positive in the presence of RBCs, Hb or myoglobin

- Urine microscopy: >2 RBCs per hpf

- Prevalence varies with studies 0.18-16%
Urine microscopy: Hematuria

Glomerular Bleeding:
>5% acanthocytes seen by phase contrast

Specificity 98%
Sensitivity 52%
Hematuria: false positives

- Spun urine in true hematuria: supernatant clear, pellet red

- Red supernatant with dipstick positive
  - Lysed RBCs (dilute urine)
  - Myoglobinuria
  - Hemoglobinuria

- Red supernatant with dipstick negative
  - Porphyria (acute intermittent porphyria, hereditary coproporphyria & variegate porphyria)
  - Beet ingestion
  - Phenazopyridine
Hematuria: Initial Evaluation

• Confirm (repeat sample) with microscopy
• CT urography
• Cystoscopy (esp >40yrs or risk factors)
• Urine cytology (90% sensitivity for bladder ca; poor for upper tract tumors)
<table>
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<tr>
<th>Differential Diagnosis of Isolated Hematuria</th>
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<tbody>
<tr>
<td><strong>Glomerular</strong></td>
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<tr>
<td>IgA nephropathy</td>
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<tr>
<td>Thin basement membranes</td>
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<tr>
<td>Familial nephropathies</td>
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Hematuria: Urology evaluation

>45yrs:
  20% will have abnormality on urological work up, half with malignancy

<45yrs:
  2% will have significant urological disease
American Urological Association: Evaluation of Asymptomatic Microscopic Hematuria

1. Repeat UA after treatment of other cause(s) → Release from care

2. History & Physical Assess for other potential AMH causes (e.g., infection, menstruation, recent urologic procedures)
   - Concurrent nephrologic work up if proteinuria, red cell morphology or other signs indicate nephrologic causes.
   - Renal Function Testing → Cystoscopy Imaging (CTU)
     - Treatment
     - Follow up with at least one UA/micro yearly for at least two years → Release from care
   - If unable to undergo CTU, less optimal imaging options include:
     - MR Urogram
     - Retrograde pyelograms in combination with non-contrast CT, MRI, or US
   - Follow persistent MH with annual UA. Consider nephrologic evaluation. Repeat anatomic evaluation within three to five years* or sooner, if clinically indicated.

3. Release from care

*The threshold for re-evaluation should take into account patient risk factors for urological pathological conditions such as malignancy
Glomerular Disease as a cause of isolated microscopic haematuria. *Topham et al. QJM 1994; 87:329-335*

- 165 pts: 112 microscopic, 53 macroscopic
- Age 37.5yrs (10-71)
- Normotensive, nl creatinine, no proteinuria, sterile urine, nl IVP
- 46.6% abnormal renal biopsy (77/165)
  - 29.7% IgAN, 4.3% Thin GBM, 7.3% MPGN, 3% focal proliferative GN, 2% HTN, 0.6% Interstitial nephritis, 0.6% MGN
- 6.8% abnormal cystoscopy (7/103):
  - 96 normal, 3 cystitis, 1 bladder stone, 2 blood from ureter, 1 urethral stricture
Persistent Asymptomatic Isolated Microscopic Hematuria in Israeli Adolescents & Young Adults & Risk of ESRD. 

Vivante et al. JAMA 2011. 306;7: 729

• 1.2 million Jewish candidates (60% male), aged 16-25
• Dipstick hematuria, confirmed by microscopy
• Normal GFR, no proteinuria, normal u/s. Asymptomatic microscopic hematuria as judged by nephrologist
• Isolated hematuria present in 0.3% of candidates
Persistent Asymptomatic Isolated Microscopic Hematuria in Israeli Adolescents & Young Adults & Risk of ESRD. *Vivante et al. JAMA 2011. 306;7: 729*

ESKD at 20 year follow up: HR 18.5 (12.4-27.6);
34.0 vs. 2.05 per 100,000 person years
ESKD due to primary glomerular disease: HR 32.4 (18.9-55.7)
Isolated microscopic hematuria: Case

A 35 year old male comes for review after dipstick hematuria was detected on an insurance medical. He is a non-smoker and has no hypertension, renal impairment or proteinuria. CT urography is unremarkable. He reports no family history of renal calculi or ESKD. His maternal grandmother has a hearing aid.

Urine sediment analysis reveals 8-10 non-dysmorphic RBC/hpf, no casts.
Isolated microscopic hematuria: Case

The most likely underlying abnormality is:

A. Defect in gene encoding \( \alpha-5 \) chain of Type IV collagen
B. Defect in gene encoding \( \alpha-3 \) chain of Type IV collagen
C. Defect in gene encoding PC-1
D. Defect in UMOD gene
E. Defect in gene encoding \( \alpha-1 \) chain of Type III collagen
Isolated microscopic hematuria: Answer

The most likely underlying abnormality is:

A. Defect in gene encoding α-5 chain of Type IV collagen
B. **Defect in gene encoding α-3 chain of Type IV collagen**
C. Defect in gene encoding PC-1
D. Defect in UMOD gene
E. Defect in gene encoding α-1 chain of Type III collagen
Isolated microscopic hematuria: Answers

- PC-1 or polycystin-1 abnormalities are caused by gene mutations of PKD-1 gene (commonest cause of ADPKD)
- UMOD gene encodes Uromodulin/Tamm Horsfall protein; abnormalities are linked to Medullary cystic kidney disease
- Ehlers-Danlos: Defects in Type III collagen
- X-linked Alport syndrome (defect in α-5 chain) is unlikely in the absence of FHx ESKD or deafness
- Thin basement membrane disease due to defective α-3 chain of Type IV collagen is the most likely diagnosis.
Thin Basement Membrane Nephropathy

- Population prevalence 5-9%; clinically seen in <1%
- 30-50% have +FHx hematuria; often dominant pattern
- No FHx hearing/visual impairment or ESKD
- Mutations in genes encoding α-3 and α-4 chains of Type IV collagen; ‘carrier state’ for recessive Alport
- Presentation: microscopic hematuria on routine u/a
- Frank hematuria, loin pain, AKI 2/2 heavy hematuria
- Dx: GBM thickness 150-225nM vs 300-400nM (nl)
- Prognosis: Generally excellent. Association with development of proteinuria & genetic forms of FSGS
Alport syndrome

• Mutations in genes encoding Type IV collagen

• $\alpha$-3, $\alpha$-4 & $\alpha$-5 chains codistributed within GBM, cochlea & eye

• 80%: X linked inheritance
  – Mutations in COL4A5 gene ($\alpha$-5 chain)
  – No father to son transmission
  – Females variably affected (lyonization)
Alport syndrome

• 15%: Autosomal recessive inheritance
  – Mutations in COL4A3 or COL4A4 genes (α-3 or 
    -4 chains)

• 5%: Autosomal dominant inheritance
  – Mutations in COL4A3 or COL4A4 genes
  – Slower progression than X-linked Alport
Alport Syndrome: Clinical manifestations

- Up to 15% have no FHx
- Hematuria: macroscopic, recurrent and temporally linked with respiratory infections in childhood
- Progressive CKD with hypertension & proteinuria
- Ocular abnormalities include anterior lenticous
- Sensorineural hearing loss – rate of progression similar to CKD
- +FHx hematuria with CKD and deafness
- ESKD by age 16-35 in X-linked or recessive forms; later in dominant (45-60 yrs)
Alport Syndrome: Diagnosis

Renal biopsy: Immunostaining reveals absence/abnormality of α-3, -4,-5 chains in GBM

Skin biopsy: Immunostaining for α-5 chain
Alport Syndrome: Management

Treatment:
- ACEi: Delays progression to ESKD in proteinuric pts with normal GFR (European Alport Registry)
- Cyclosporine: Conflicting data

Renal Transplantation:
- Excellent outcomes
- 3% incidence of anti-GBM disease, M>>F
- Diagnosis: IF of allograft biopsy essential
- Serological testing for anti-GBM may be negative (Ab against Goodpasture antigen vs α-5 chain)
Macroscopic Hematuria: Case

A 78 yr old male presents with dyspnoea, increasing peripheral edema and is found to have AKI. He reports dark urine with decreased output for the last 3 days.

Recently diagnosed with A fib and started on warfarin. One week ago, his INR was 4.8; INR today is 1.5.

Creatinine 3.5mg/dL (baseline 1.7mg/dL). Urine sediment shows large numbers of non-dysmorphic RBCs, and no casts.
Macroscopic Hematuria: Case

Which of the following is correct regarding his presentation?

A. This clinical presentation may relate to the treatment of his A fib
B. His prognosis for renal recovery is excellent
C. His presentation is suggestive of Type I cardiorenal syndrome
D. Complement C3 levels would be increased with this presentation
Macroscopic Hematuria: Answer

Which of the following is correct regarding his presentation?

A. This clinical presentation may relate to the treatment of his A fib
B. His prognosis for renal recovery is excellent
C. His presentation is suggestive of Type I cardiorenal syndrome
D. Complement C3 levels would be increased with this presentation
Macrosopic Hematuria: Answer

A. This clinical presentation may relate to the treatment of his A fib – **Main DDx are warfarin related nephropathy vs renal atheroemboli**

B. His prognosis for renal recovery is *poor*

C. His presentation is suggestive of type 3 cardiorenal syndrome – (Type 1 CRS is primarily cardiac)

D. Renal atheroembolic disease is associated with complement *consumption* and decreased C3.
Warfarin Related Nephropathy (WRN)
Brodsky et al AJKD 2009, 54:1121

- 9 patients with unexplained AKI on warfarin therapy.
- Histological characteristics:
  - Occlusive RBCs casts in distal nephron
  - RBCs within Bowman’s space
  - Dysmorphic RBCs on EM
Warfarin Related Nephropathy (WRN)

Brodsky et al AJKD 2009, 54:1121

- All patients had underlying CKD (biopsy)
- 6/9 failed to recover, 4 remained in ESKD

Epidemiologic studies:
- Presumptive Dx: Unexplained AKI within one week of an INR >3.0, in a warfarinized patient without overt evidence of hemorrhage
Anticoagulant Related Nephropathy

• True incidence is unknown due to lack of biopsies
• Estimated to occur in up to 20% of CKD patients
• Highest risk in first 8 weeks following initiation of anti-coagulation
• Generally observed when INR >4
• Associated with accelerated progression of CKD
• Up to 30% mortality within one month of diagnosis
• Similar presentations have been reported with novel oral anticoagulants
Urine sediment Analysis: Take Home Points I

• It is worth examining the urine yourself!
• Urine sediment has many of the expected characteristics of a biomarker
• There are reasons why your interpretation and the lab read vary
Urine sediment Analysis: Take Home Points II

• Leukocyturia – if unexplained, consider infectious causes associated with negative cultures
• Urine eosinophils have little utility in the diagnosis of AIN
• Asymptomatic hematuria is commonly urological in origin in patients >40 years and repeat screening may be necessary
Urine sediment Analysis: Take Home Points III

• Isolated asymptomatic hematuria is associated with increased risk of ESKD in long term follow up
• Alport syndrome is a defect in α-3, α-4 or α-5 chains of Type IV collagen in GBM
• Thin GBM is a carrier state of recessive Alport (defect in α-3 or α-4)
• AKI in anticoagulated patients – think warfarin-related nephropathy (also seen with NOACs)
Disclosures

• None
Selected References:

1. Diagnosis, Evaluation and Follow-Up of Asymptomatic Microhematuria (AMH) in Adults: AUA Guideline (2012)