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Urine Sediment Analysis

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Clinical Interests:

Renal transplantation, live kidney donation, CVD in CKD

Academic Interests:

CV disease in CKD & transplantation

Education and scientific research training

Transplantation immunology

Disclosures

Deputy Editor – nephSAP, American Society of Nephrology

Lexicon Pharmaceuticals – research support

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Learning Objectives:

To discuss the benefits and limitations 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

Urine sediment as a biomarker of kidney disease

Cheap, readily available, reproducible

Indicates the presence of renal injury

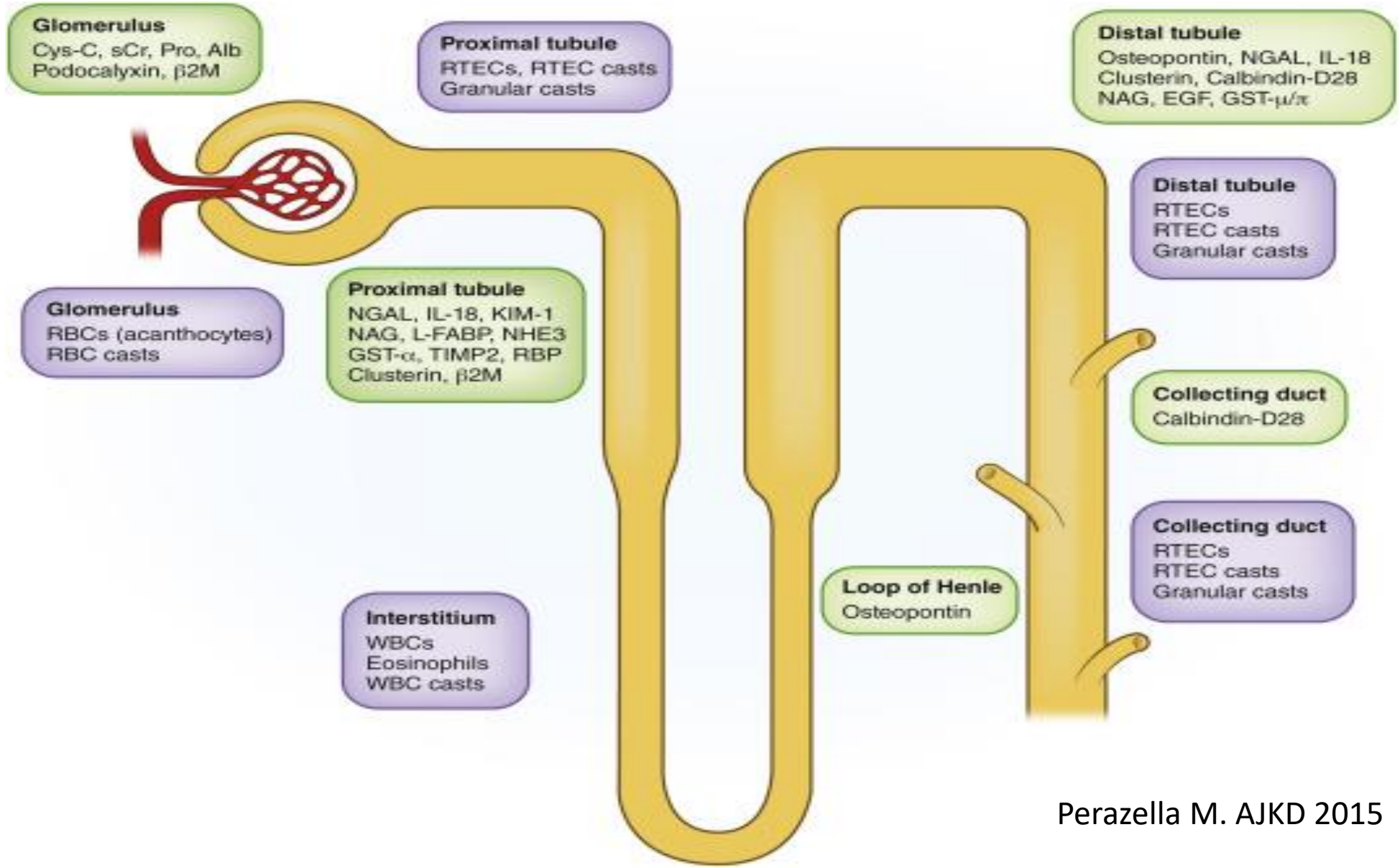
Suggests the compartment of injury

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

Aim: To assess the ability to predict worsening of AKI

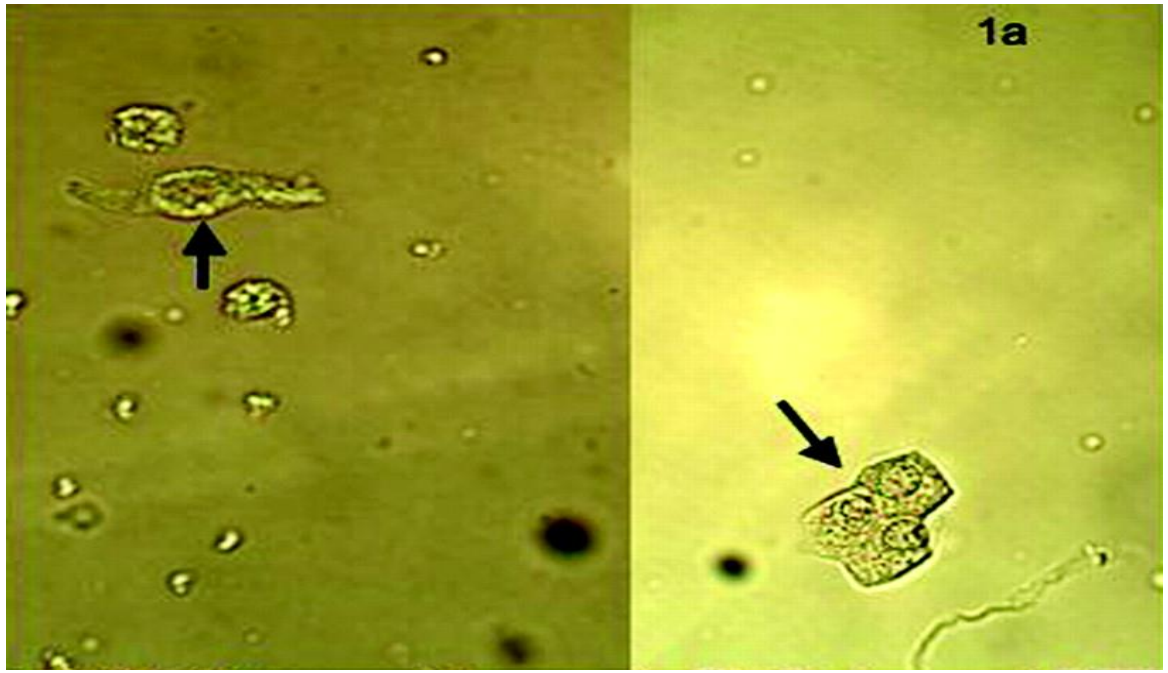
Formally trained renal consultants reviewed urine sediment

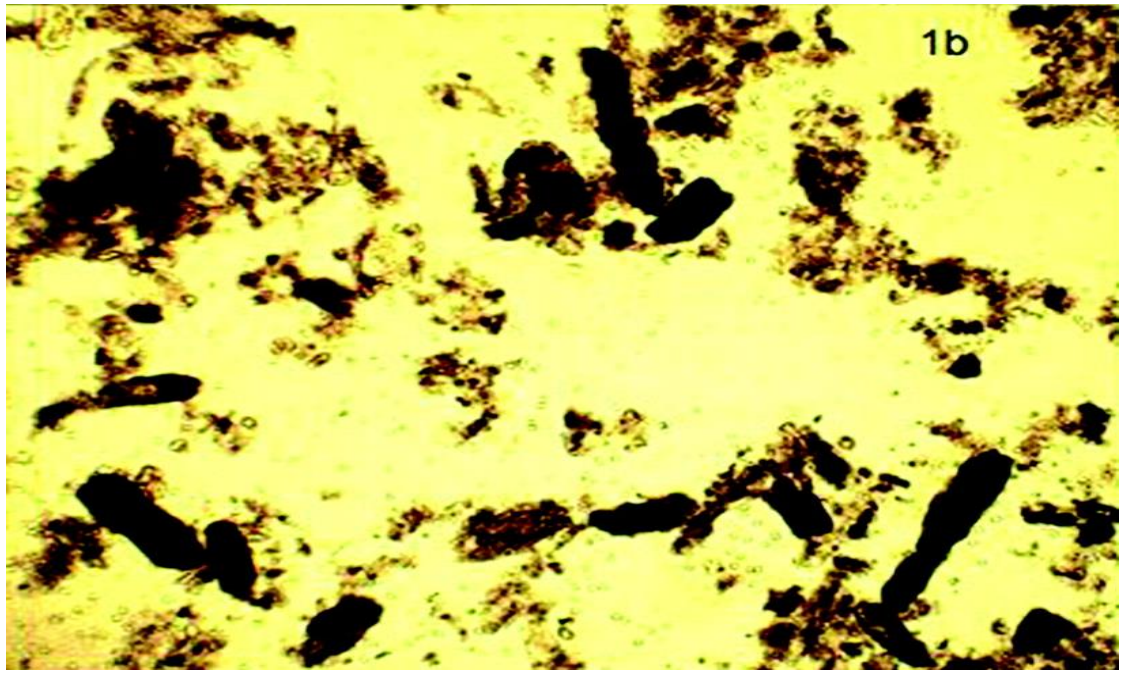
Second nephrologist performed chart review to confirm diagnosis

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

RTE Cells (per HPF)	Granular Casts (per LPF)		
	0 (0 points)	1-5 (1 point)	≥6 (2 points)
0 (0 points)	0	1	2
1-5 (1 point)	1	2	3
≥6 (2 points)	2	3	4

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

Baseline higher urinary sediment score correlated with higher AKIN stage of AKI

Urine sediment score	Worsening AKI after consultation (%)	Worsening AKI, adj. RR (95% CI)
0	9.4	ref
1	36.2	3.4 (1.3 to 6.5)
2	54.1	6.6 (3.4 to 9.1)
≥3	66.7	7.3 (3.8 to 9.6)
	p <0.001	

Predictive value of RTE cells and casts in AKI

Table 2. Urine Sediment Examination as Biomarker for Prognosis in AKI

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

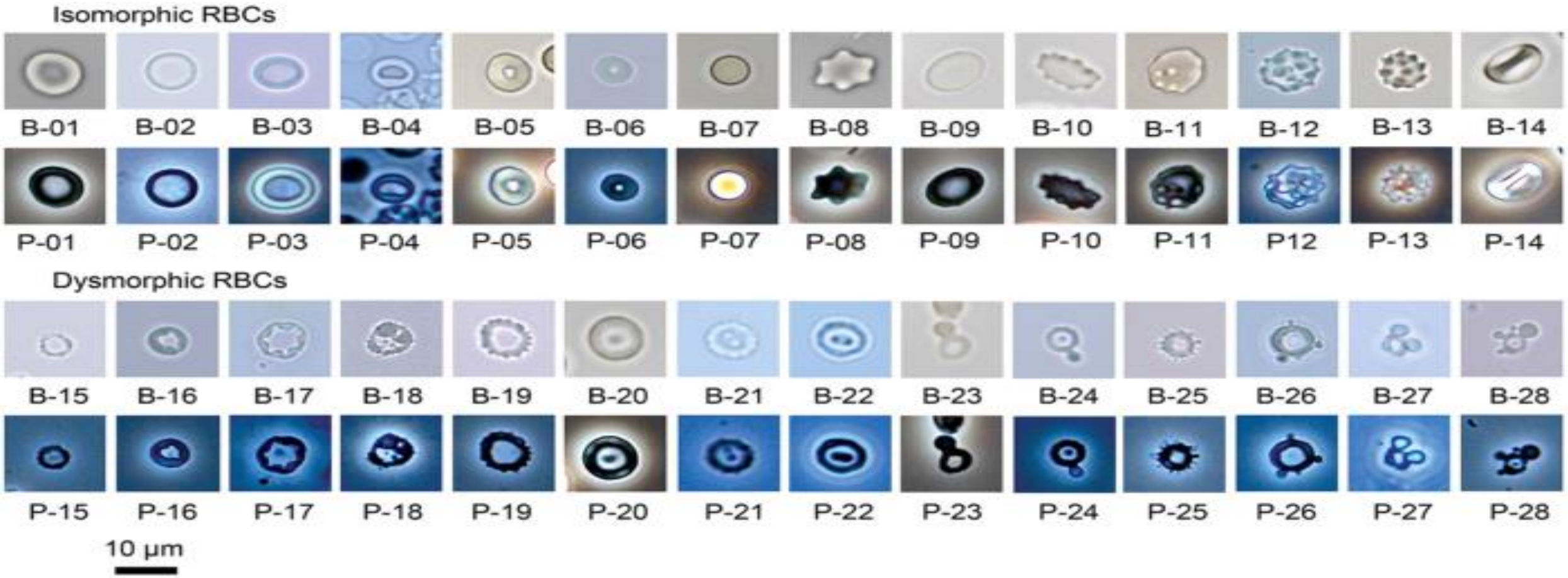
Perazella AJKD 2015

Nephrologist vs. Lab urine sediment exam

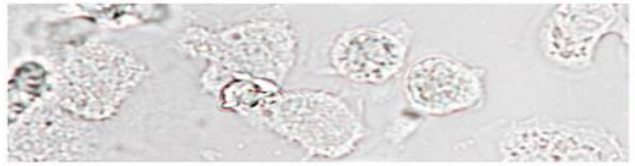
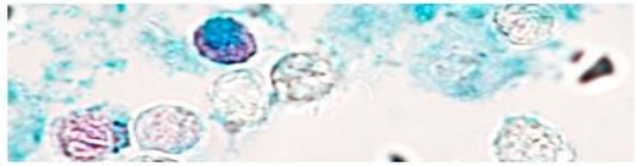
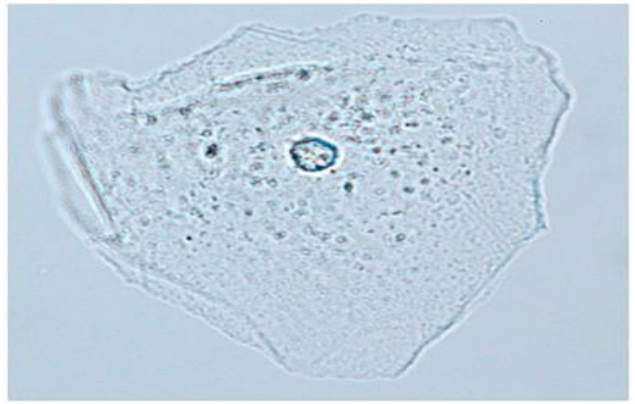
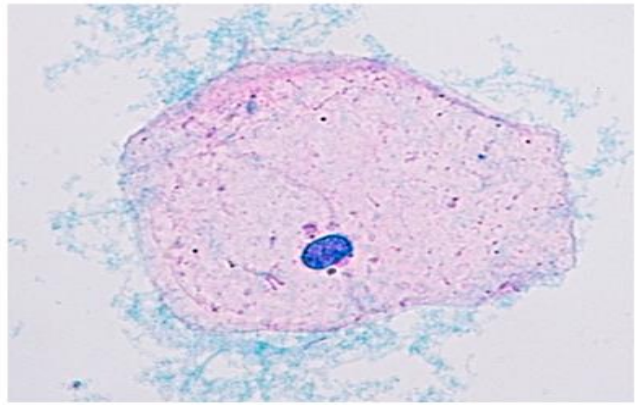
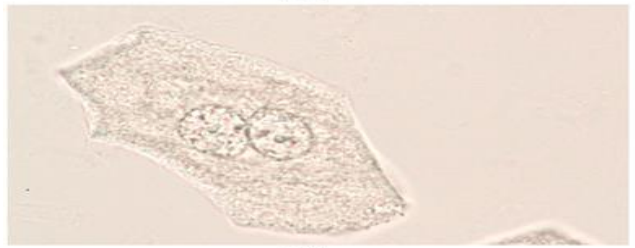
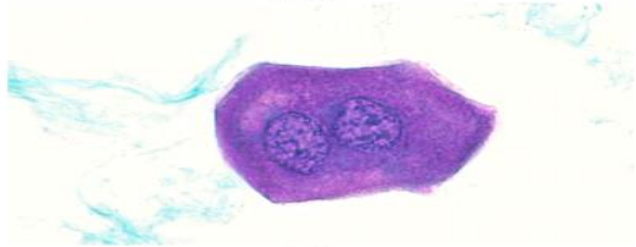
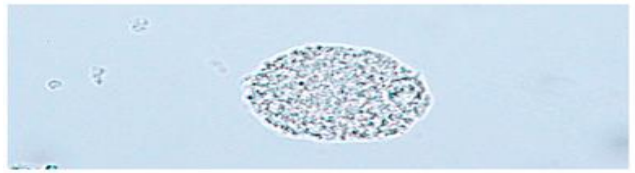
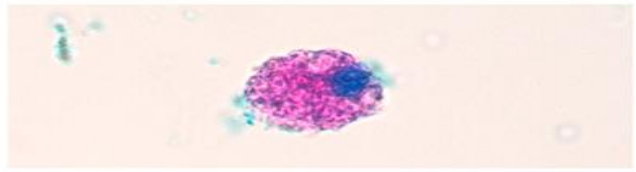
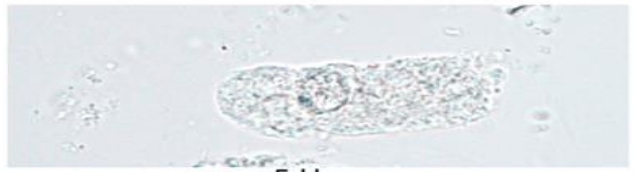
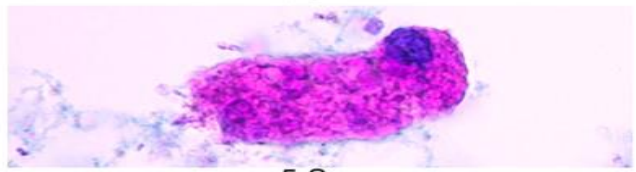
- Technical differences – Volume of urine spun, speed of centrifuge, resuspension volume & volume of suspension examined
- Nephrologists use a more concentrated sample- greater yield of RTECs and dysmorphic RBCs
- Accreditation standards - Labs may have greater focus on the accuracy of WCC and RBC count

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

	Unstained	Sternheimer Stain
Activated Neutrophil	 1-U	 1-S
Squamous epithelial cell	 2-U	 2-S
Urothelial cell	 3-U	 3-S
Renal tubular epithelial cell	 4-U	 4-S
Renal tubular epithelial cell	 5-U	 5-S

50 µm

Limitations of urine sediment exam in AKI

- Unclear if serial urine sediment exams would improve prognostic ability
- Urine sediment exam has not yet been shown to alter outcomes
- Considerable interobserver variability (between nephrologists) in terms of both agreement and accurate identification of urine elements
- Paulson et al JAMA Network Open 2020
  - 14 nephrologists, reviewed images and study questions based on 10 patients undergoing biopsy
  - Agreement for casts: 59%; other elements: 69%
  - Greatest agreement in the setting of glomerular disease – 90% agreement on dysmorphic RBCs

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

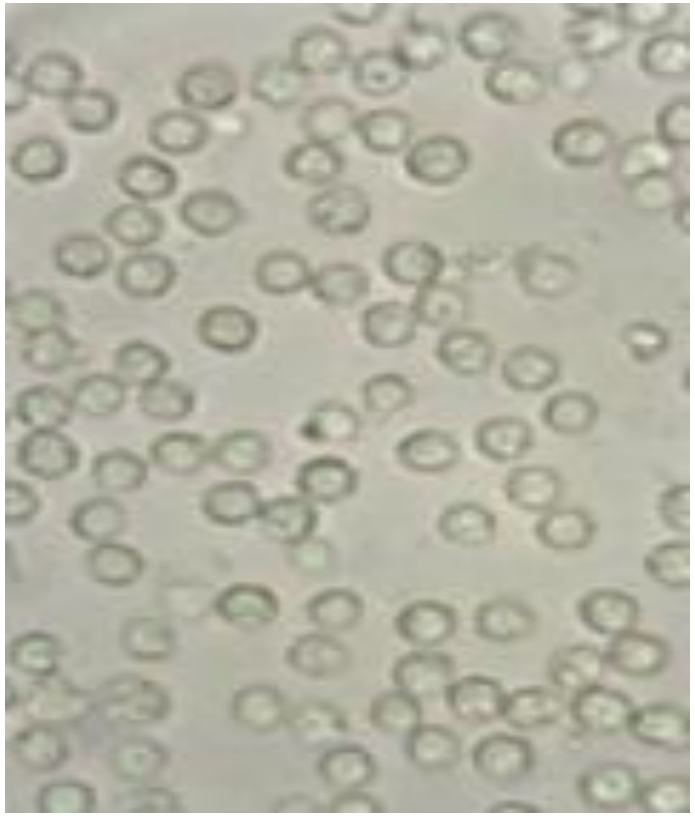
Urethritis/STI (gonorrhea, chlamydia, mycoplasma, ureaplasma)

Prostatitis/Balanitis

GU Tuberculosis

Parasitic infection (schistosomiasis)

Appendicitis



Sterile Pyuria: Non Infection Related

Catheterization/instrumentation

Urinary fistula

Interstitial cystitis

Pelvic irradiation

Neoplasia

Renal calculi

Interstitial nephritis

Glomerulonephritis

Transplant rejection

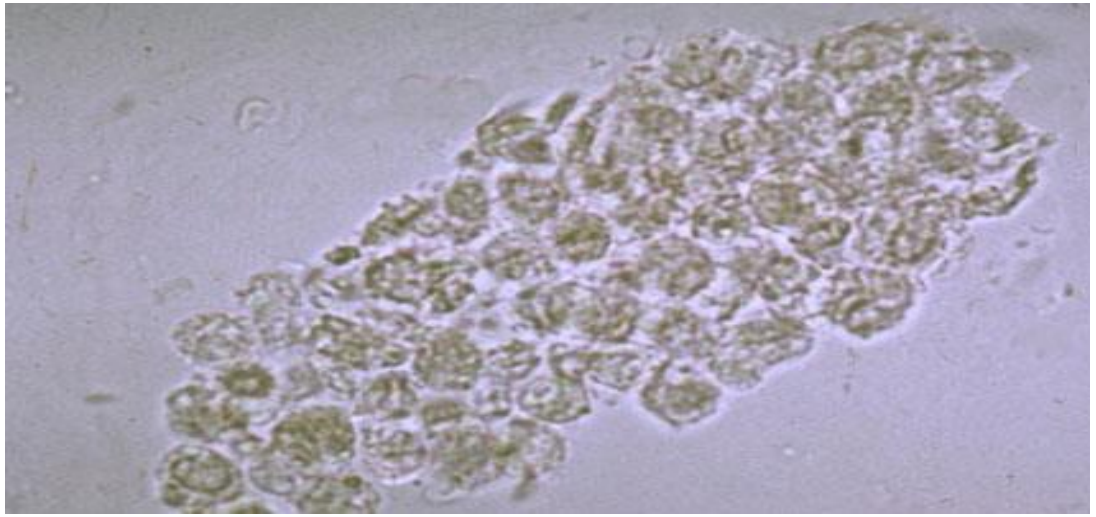
PKD

Papillary necrosis

Renal vein thrombosis

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%

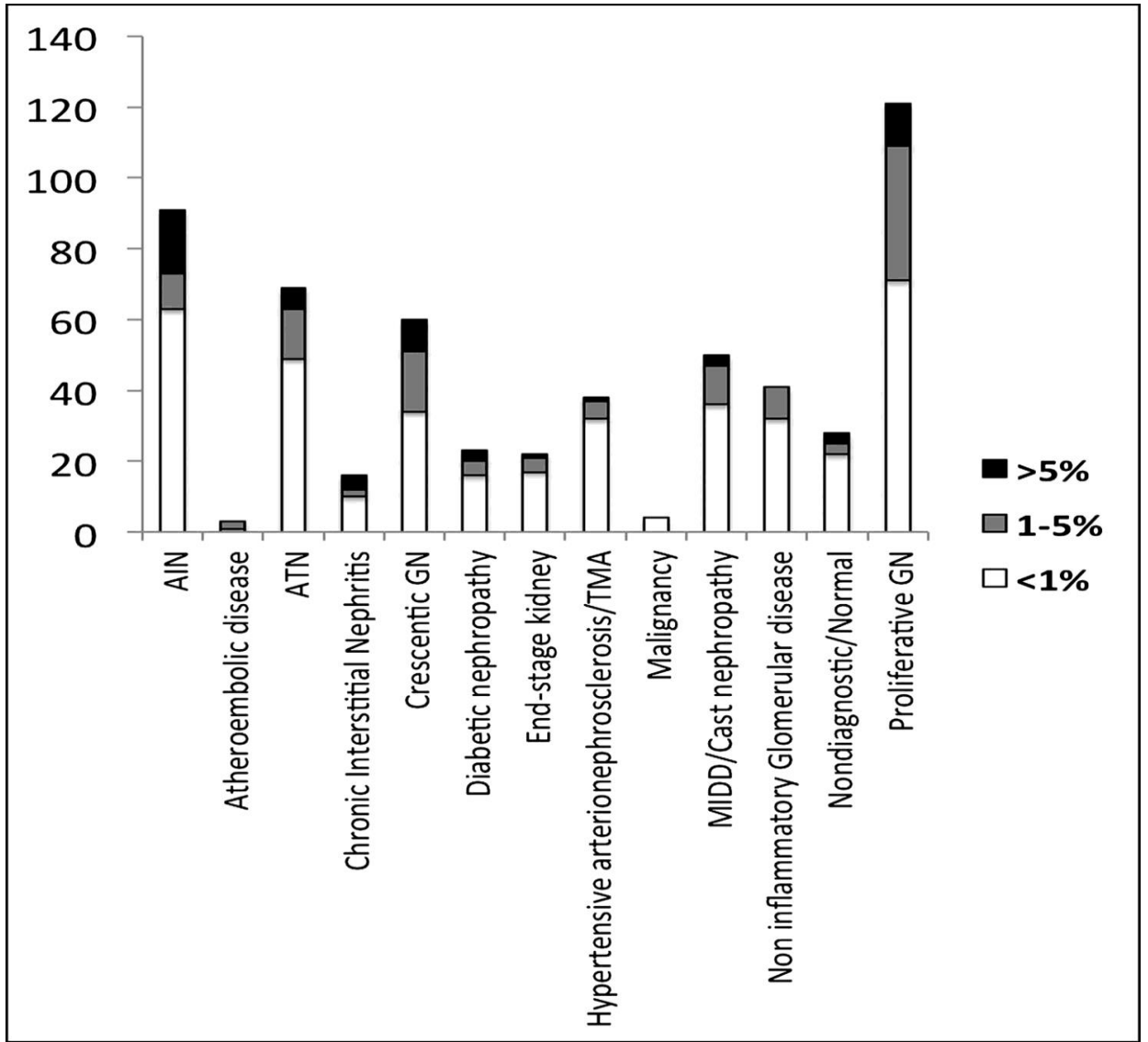
Negative predictive value: 83.7%

5% UE cutoff: Lower sensitivity, 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

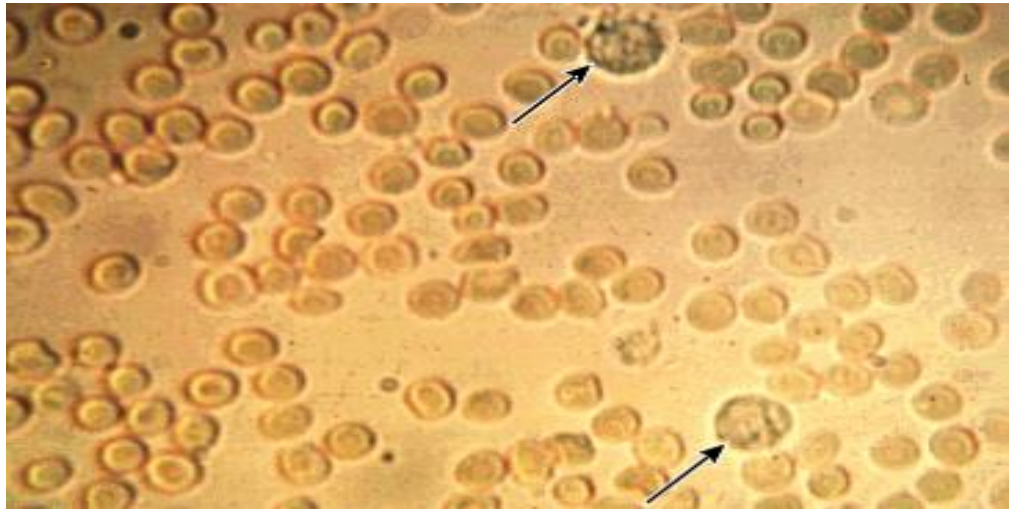
Definition & Diagnosis

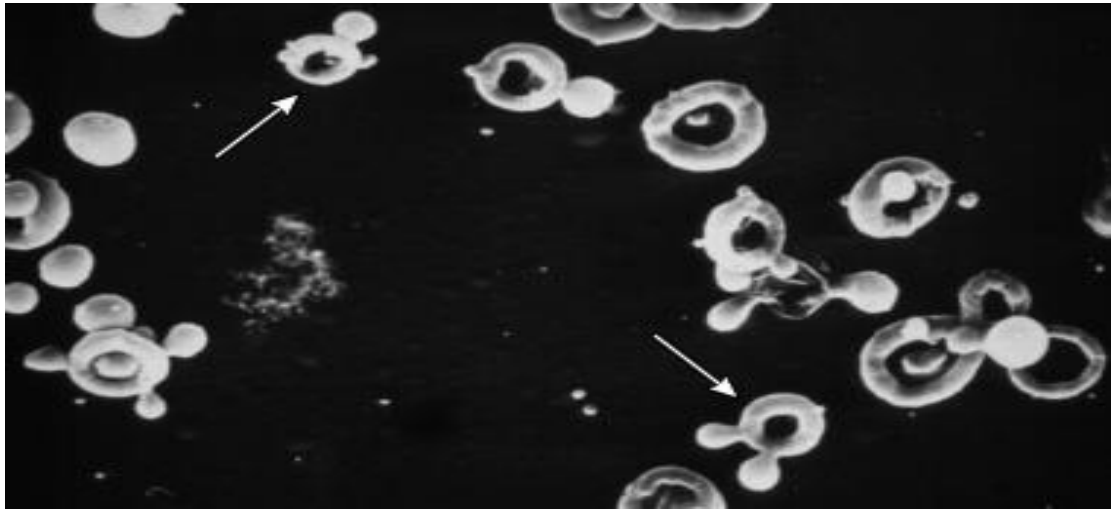
Urine dipstick: Positive in the presence of RBCs, Hb or myoglobin

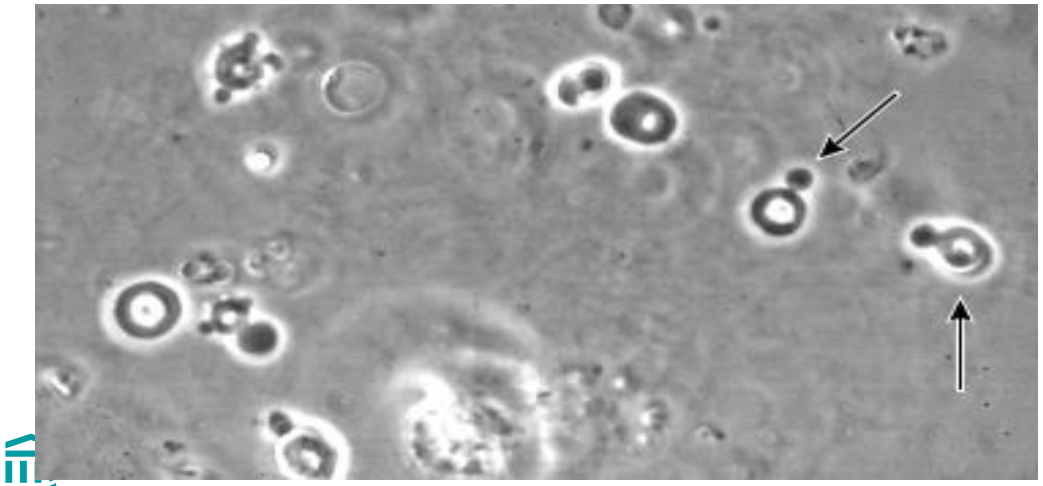
Urine microscopy: >2 RBCs per hpf

Prevalence varies with studies 0.18-16%

Urine microscopy: Hematuria







Glomerular Bleeding:
>5% acanthocytes seen by phase contrast

Specificity 98%
Sensitivity 52%

Hematuria: 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)

Differential Diagnosis of Isolated Hematuria

Glomerular

IgA nephropathy

Thin basement membranes

Familial nephropathies

Non-glomerular

Urologic malignancy (age)

Nephrolithiasis

Cystic renal disease

Papillary necrosis

Metabolic Abnormalities-

Hypercalcuria/Hyperuricosuria

Urinary tract infection

Cystitis including viral/hemorrhagic

Hematuria: Urology evaluation

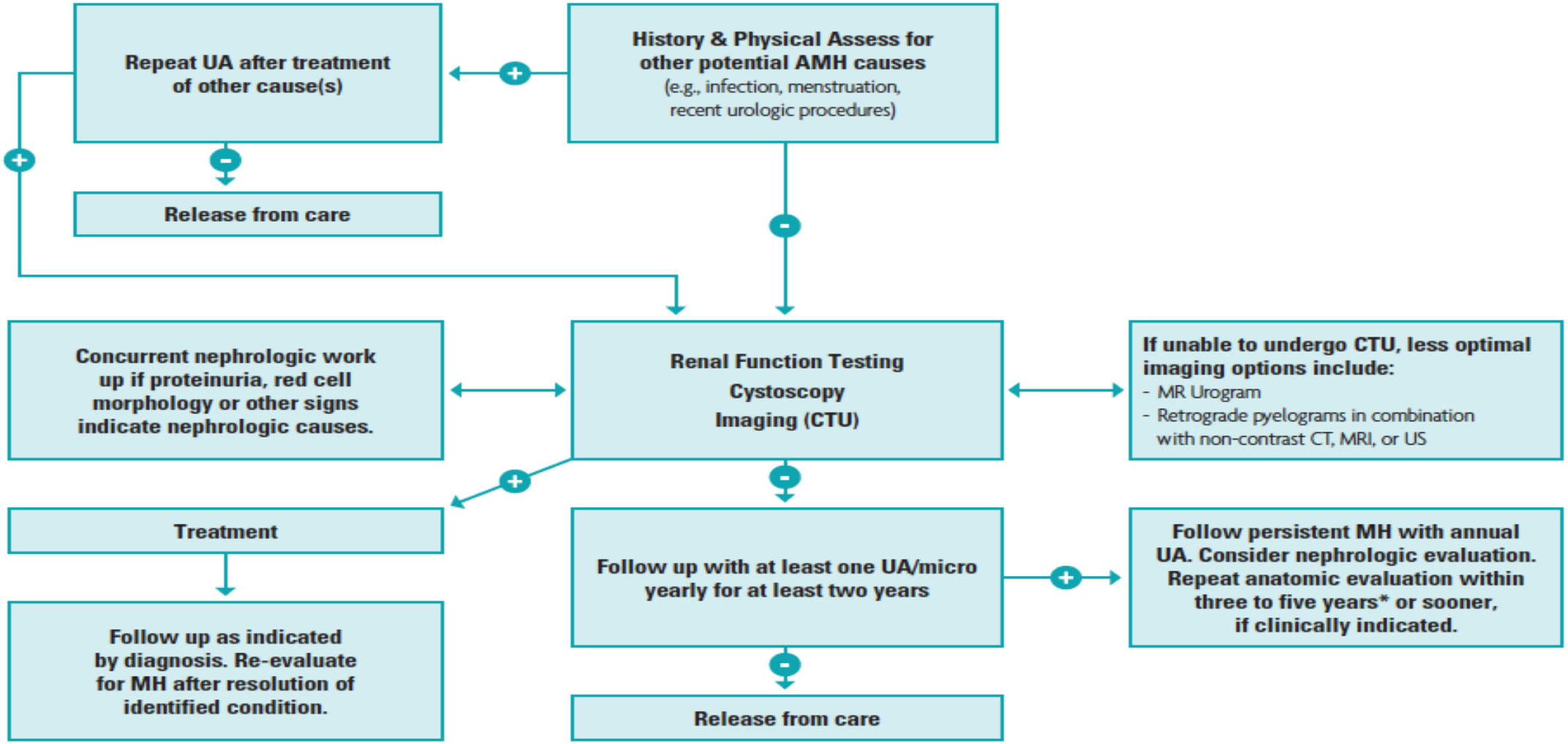
>45yrs:

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



*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, normal 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 Israeli army candidates (60% male), aged 16-25

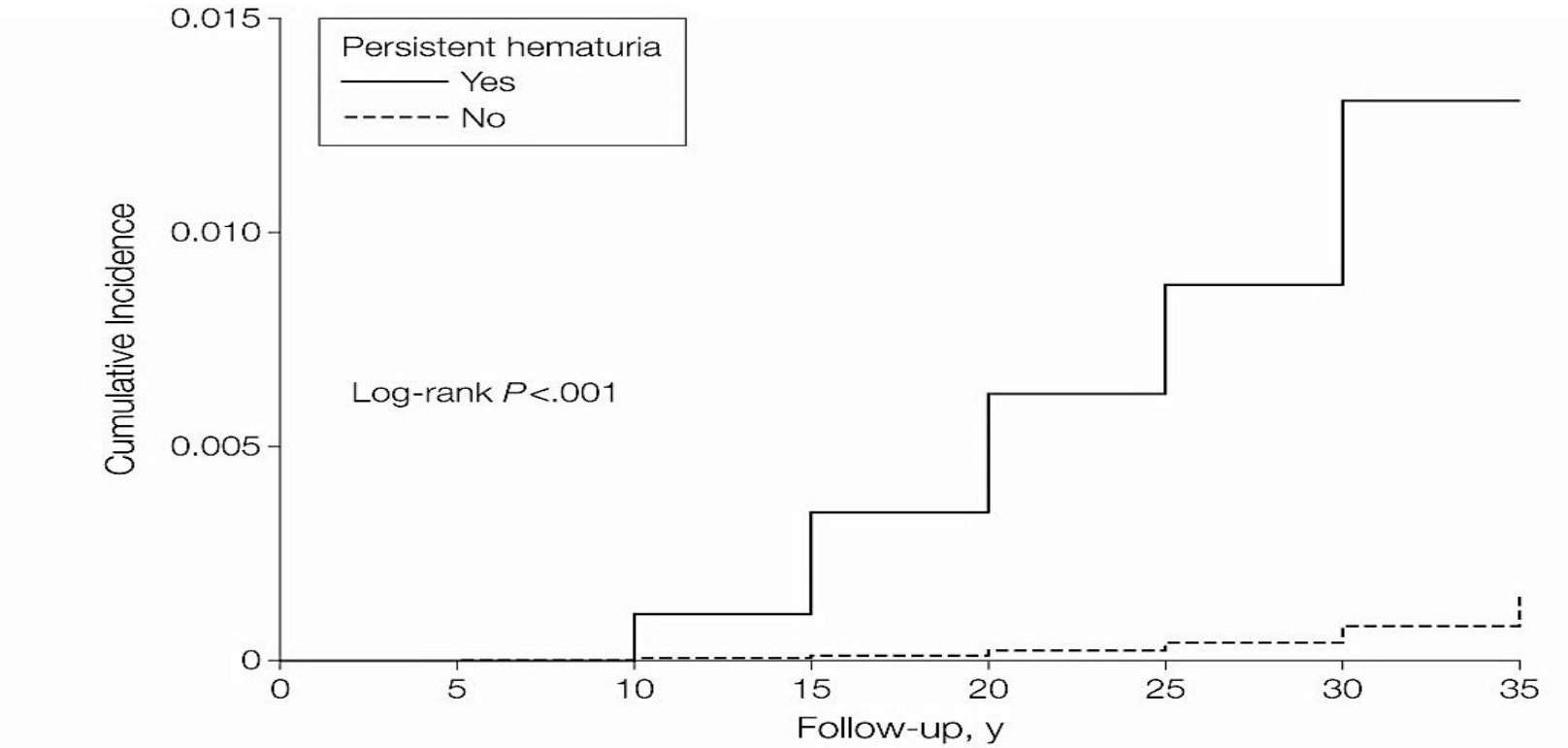
Isolated hematuria present in 0.3% of candidates

Dipstick hematuria, confirmed by microscopy

Normal GFR, no proteinuria, normal u/s.

Asymptomatic microscopic hematuria as judged by nephrologist

Persistent Asymptomatic Isolated Microscopic Hematuria in Israeli Adolescents & Young Adults & Risk of ESRD. *Vivante et al. JAMA 2011. 306;7: 729*



No. at risk

Persistent hematuria								
Yes	3690	3677	3665	2873	1978	1135	244	10
No	1 199 936	1 196 606	1 193 878	947 735	680 092	431 433	212 810	1608

20 year f/u: HR 18.5 for ESKD (12.4-27.6)

ESKD incidence: 34.0 vs. 2.05 per 100,000 person yrs

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. He reports no family history of renal calculi or ESKD. His maternal grandmother has a hearing aid.

CT urography is unremarkable

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 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: Case

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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

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

Type IV collagen: α-3, α-4 & α-5 chains (GBM, cochlea & eye)

80%: X linked inheritance

- Mutations in *COL4A5* gene (α-5 chain)
- Females variably affected (lyonization)

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

Alport Syndrome: Clinical manifestations

FHx hematuria with CKD and deafness (absent in 15%)

Progressive CKD:

- Macroscopic, recurrent hematuria
- Temporally linked with respiratory infections in childhood
- Hypertension & proteinuria

Ocular abnormalities

Sensorineural hearing loss – rate of progression similar to CKD

ESKD:

- 16-35yrs in X-linked or recessive forms
- 45-60 yrs dominant forms

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

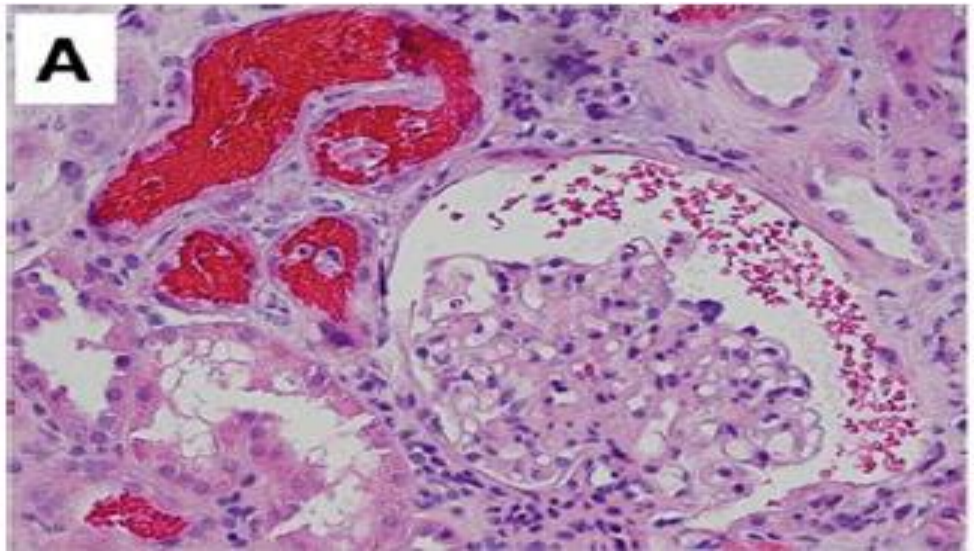
Macroscopic Hematuria: Answer

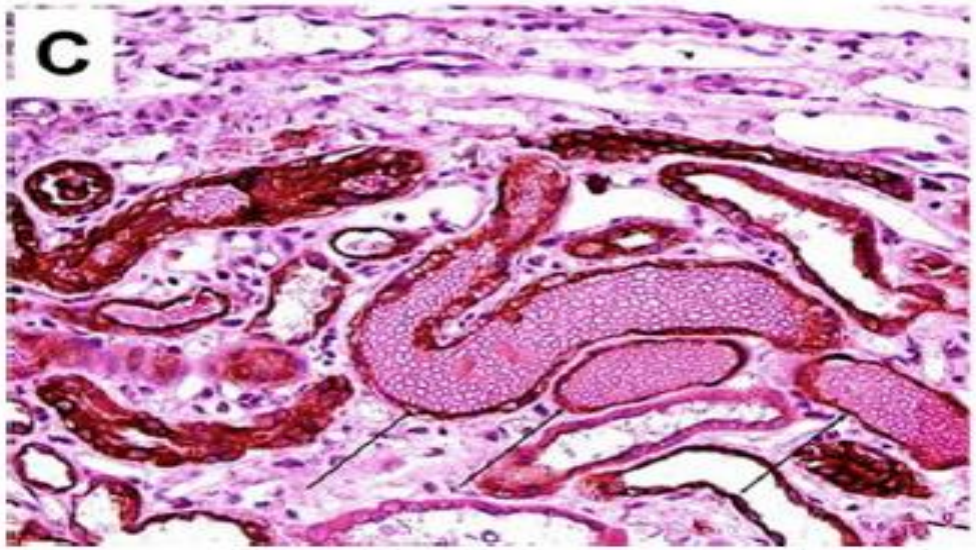
A. **This clinical presentation may relate to the treatment of his A fib – Main DDx are warfarin related nephropathy vs renal atheroemboli**
B. His prognosis for renal recovery is *poor*
C. His presentation is suggestive of *type 3* cardiorenal syndrome – (Type 1 CRS is primarily cardiac)
D. Renal atheroembolic 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
- Suggested mechanisms of AKI: Glomerular injury/hemorrhage, tubular obstruction, oxidative stress, iron injury to tubules

Anticoagulant Related Nephropathy

- Unexplained AKI within one week of an INR >3.0
- Similar presentations have been reported with DOACs

- Estimated to occur in up to 20% of CKD patients starting anti-coagulation
- Highest risk in first 8 weeks following initiation of anti-coagulation

- Associated with accelerated progression of CKD
- Up to 30% mortality within one month of diagnosis

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
- Persistent hematuria may provide prognostic information in IgA nephropathy
- 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
- Thin GBM is a carrier state of recessive Alport (defect in α-3 or α-4)
- AKI in anticoagulated patients – think anticoagulant-related nephropathy (warfarin and DOACs)

Disclosures

Deputy Editor – nephSAP, American Society of Nephrology

Lexicon Pharmaceuticals – research support

Alexion Pharmaceuticals, Vera Therapeutics, Astra Zeneca – consulting

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