EVALUATION OF URINALYSIS AND HEMATURIA

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OBJECTIVES

- Look at components of urinalysis
- Define microscopic hematuria
- Examine factors in the evaluation of the patient with microscopic hematuria

CASES

- Patient A , age 22yrs. an exercise enthusiast presented with generalised weakness and reddish brown coloured urine.

  Blood pressure was normal.

  What is the next step and how would you investigate the pt.

- Patient B , age 28yrs.on routine exam. was found to have Blood pressure 140/94mmHg and dipstick positive for heme. Three weeks prior, he had had an URTI.

  What is the next step and how would you investigate the pt.

URINALYSIS

Urinalysis is an informative, noninvasive, indispensable tool in the diagnosis and evaluation of Acute and Chronic kidney disease.

It consists of three parts

- Gross appearance
- Dipstick analysis
- Microscopic evaluation

GROSS APPEARANCE

Normal urine is clear, yellow (urochromes).

Turbidity may be affected by precipitated crystals, presence of infection or chyluria.

Urine Colour

- White - chyle, pus, phosphate crystals
- Deeper yellow - concentrated
- Brown/ Black - Methemoglobin, melanin, levodopa, methyldopa, alkaptonuria
- Blue/ Green - Pseudomonas, bilverdin, dyes, phenol, Vitamin B complex, propofol, amitryptiline

GROSS APPEARANCE

Urine Colour

- Yellow/Orange /Brown - Bilirubin, senna, iron compounds, nitrofurantoin,riboflavin, sulfasalazine, rifampin, phenytoin
- Red/Brown - Erythrocytes, hemoglobin, myoglobin, porphyrins, beets, senna, levodopa, methyldopa, food colorings, deferoxamine, rifampin, phenytoin, acute intermittent porphyra, iron sorbitol, urates

Urine Odour

- Sweet/fruity
- Maple syrup
- Ammoniacal

DIPSTICK ANALYSIS

The urine dipstick is a plastic strip to which paper tabs impregnated with chromogenic chemical reagents have been glued.

Parameters analysed

- pH
- Specific gravity
- Glucose
- Ketones
- Protein
- Urobilinogen
- Bilirubin
- Nitrites
- Leukocyte esterase
- Heme

DIPSTICK ANALYSIS

- pH- physiologic pH range is 4.5 – 8. Urea splitting bacteria may raise pH
- Specific gravity – ratio of its weight to the weight of an equal volume of distilled water. Sg of 1.010 denotes isosthenuria. Urine osmolality is determined by the number of particles in urine whereas Sg is determined by the number and size of the particles. Urine Sg provides an estimate of the osmolalty.
- Glucose – Glycosuria leads to the production of a peroxide which oxidises a chromogen to produce colour change, a reaction catalysed by peroxidase. Ascorbate may produce false negatives.
- Ketones – detect acetoacetate reacting with nitroprusside. False positives with levodopa, captopril(sulfhydryl group).

DIPSTICK ANALYSIS

- Protein – highly sensitive to albumin, less so, to light chains, globulins, hemoglobin. Dependent on urine concentration. 30-300mg/day albuminuria may be missed by dipstick. False positives produced by radiocontrast, penicillins, sulfonamides. Sulfosalicilic acid strips test for light chains.
- Urobilinogen – increased in nonobstructive jaundice
- Nitrite – enterobacteriaceae elaborate nitrate reductase which converts nitrate to nitrite.
- Leukocyte esterase - lysed neutrophils and macrophages produce leukocyte esterase.

  Sterile pyuria is associated with interstitial nephritis, renal tuberculosis, nephrolithiasis.

URINALYSIS

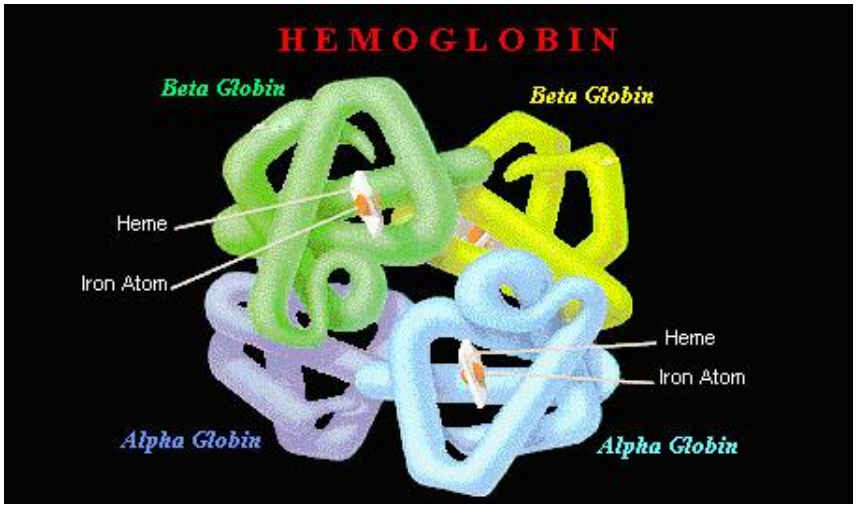
- Heme, whether from intact erythrocytes, free hemoglobin or myoglobin, acts as a peroxidase and produces a colour change when exposed to peroxide and a chromogen on the dipstick paper.
- False positives occur with other oxidants, such as semen, povidone-iodine or bacterial peroxidase. False negatives occur with ascorbate.
- **A positive dipstick does not establish the presence of RBCs in the urine and the diagnosis of hematuria requires microscopy.**

URINE MICROSCOPY

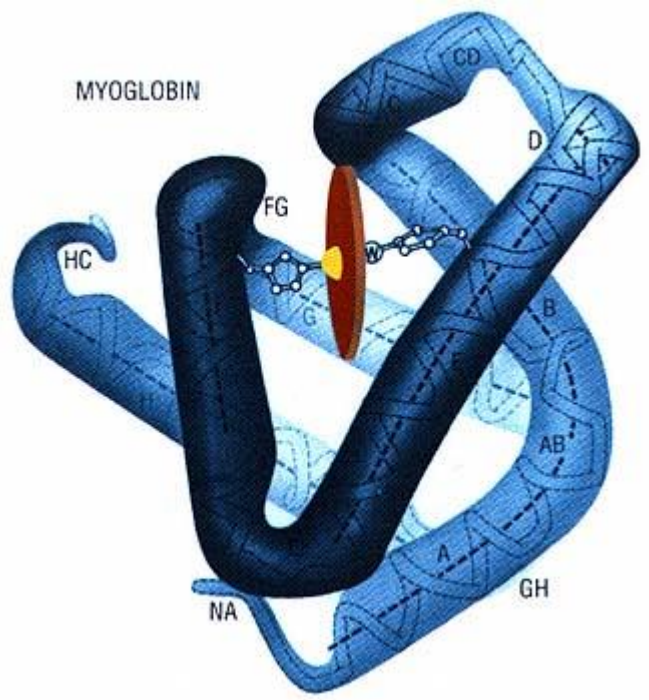
- Examination of formed constituents in urine sediment.
- 10ml of urine centrifuged for 5 mins. at 3000 rpm; 50 microL of the sediment examined microscopically using 100x and 400x magnification.
- Principal constituents include cells, crystals, microorganisms and casts.

STRUCTURE

Hemoglobin –tetramer, mol. wt 69,000, binds to haptoglobin, poorly filtered



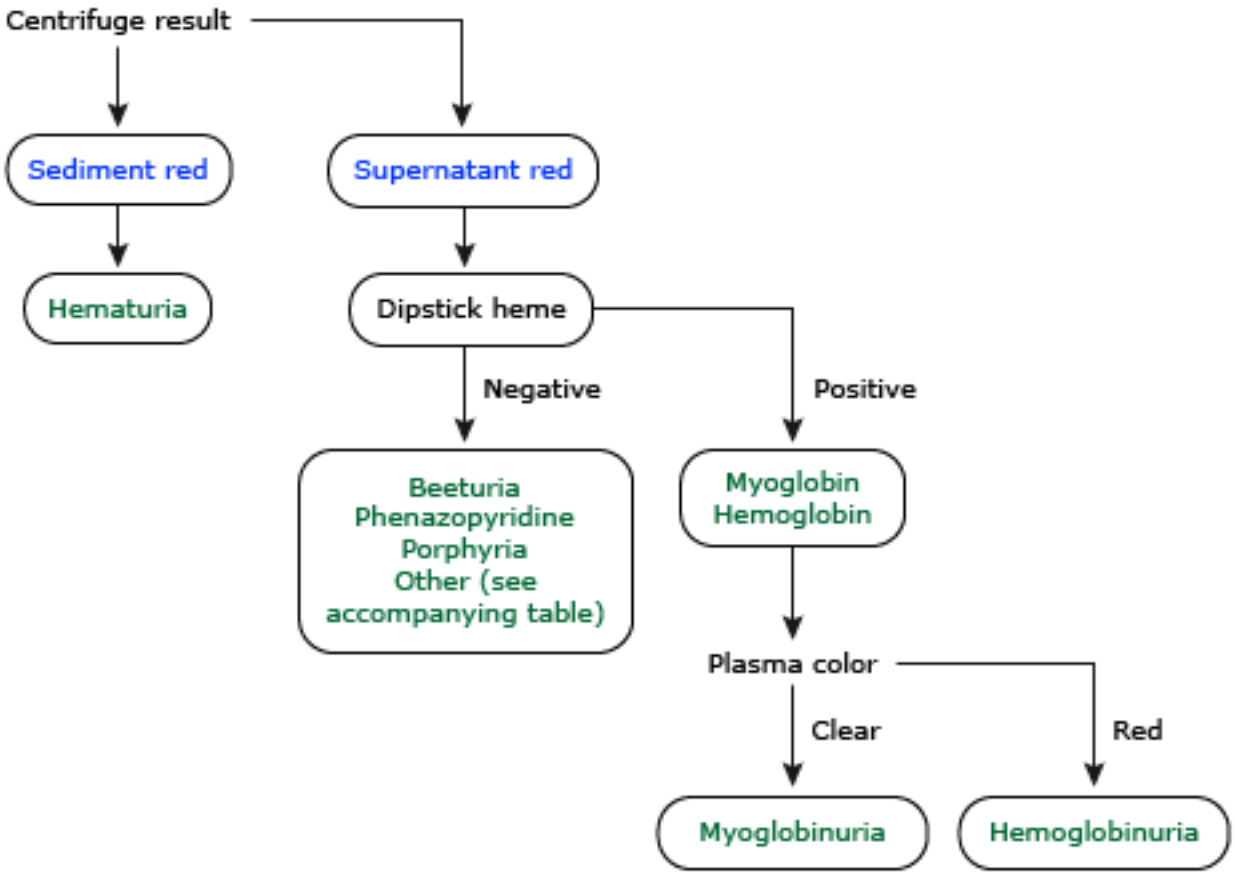
Myoglobin – monomer, mol. wt. 17,000, not protein bound, rapidly filtered



URINALYSIS

- Both hemoglobinuria and myoglobinuria produce red/ red brown or dark urine.
- Initial step in the evaluation of red urine is cetrifugation of the urine to separate sediment from supernatant.
- If the sediment is red and the supernatant is not , then the patient has hematuria.
- If the supernatant is red, it should be tested with urine dipstick for the presence of heme.
- If positive, the patient has either hematuria or myoglobinuria.
- If negative, then the patient has one of the conditions listed above that cause red urine.
- Hemoglobin and myoglobin can be distinguished on a centrifuged plasma sample by the colour of plasma and the haptoglobin concentration. With hemoglobin, the plasma is red and the haptoglobin conc. low.

Approach to the patient with red or brown urine



URINE MICROSCOPY - CELLS

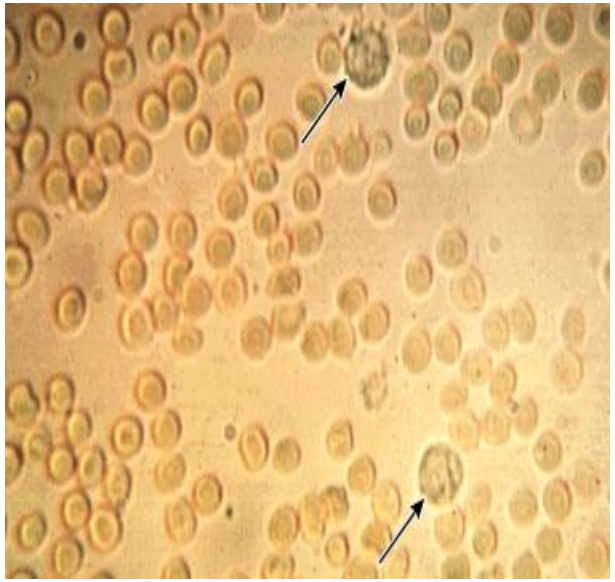
- Red blood cells – Microscopic hematuria is defined as the presence of 3 or more RBCs per hpf in a spun urine sediment. Normomorphic red cells can originate from anywhere along the urinary tract. Dysmorphic cells, with spicules, blebs folding and vesicles are usually renal parenchymal in origin ; crenated red blood cells denote hypertonic urine ; "ghost" red blood cells are seen in hypotonic urine ; **acanthocytes** (ring shaped red blood cells with vesicle shaped membrane protrusions) are glomerular in origin.

- Leukocytes – neutrophils with characteristic granules and lobes ; eosinophils – noted in allergic interstitial nephritis

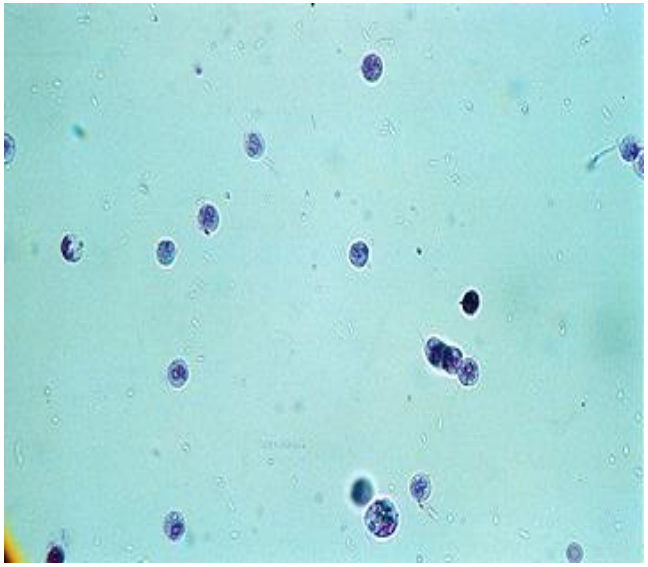
- Renal tubular epithelial cells

URINE SEDIMENT

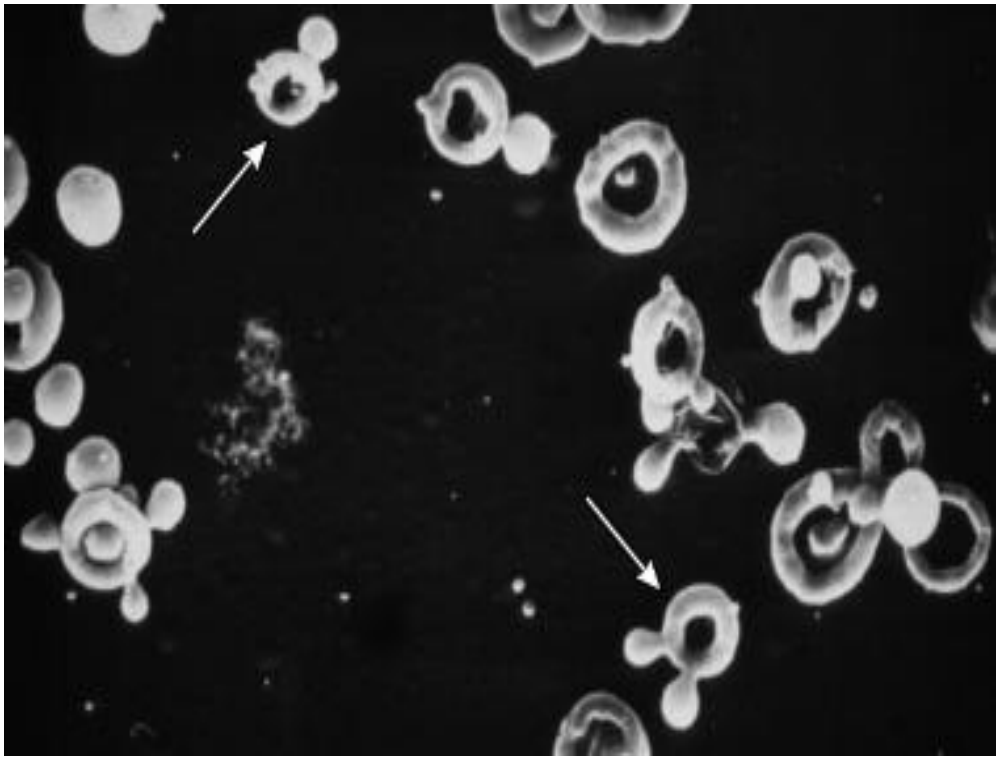
RED BLOOD CELLS



WHITE BLOOD CELLS



DYSMORPHIC RED BLOOD CELLS WITH ACANTHOCYTES



CRYSTALLURIA

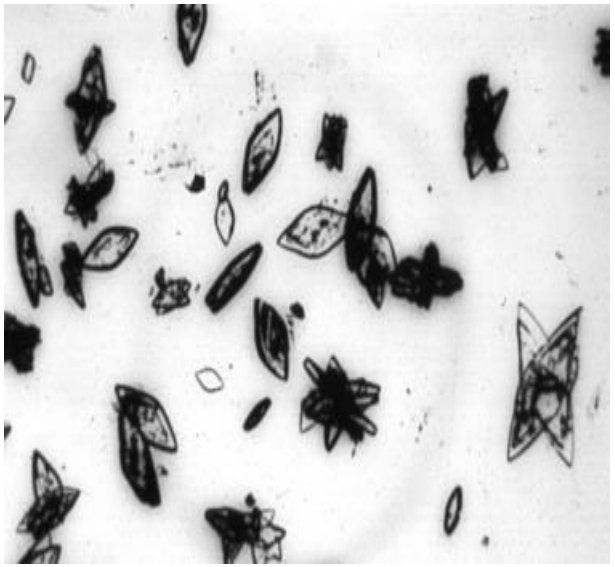
The formation of crystals depends on the concentration of the constituents, urine pH and the presence of inhibitors of crystal formation.

Common crystals include

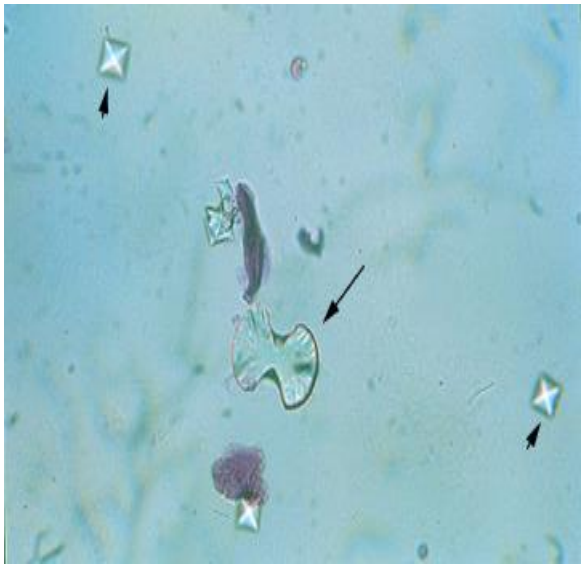
- Uric acid crystals – seen in acidic urine pH, rhomboid in shape
- Calcium oxalate or calcium phosphate crystals – phosphate crystals seen in alkaline urine
- Cystine – hexagonal in shape
- Magmesium ammonium phosphate (struvite)

CRYSTALLURIA

URIC ACID CRYSTALS

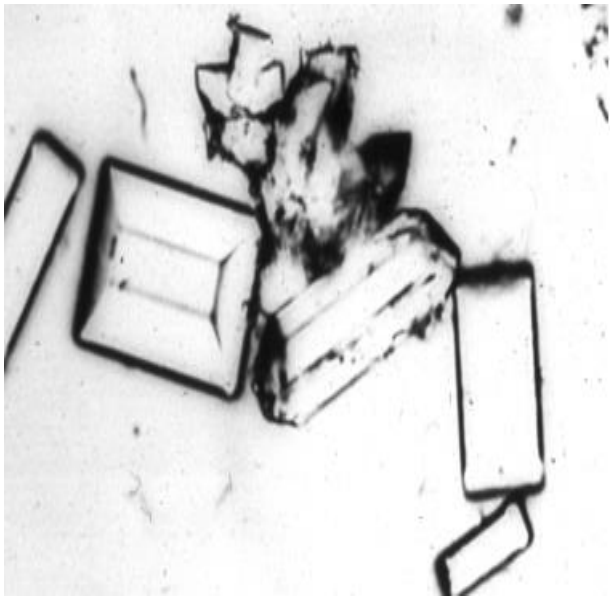


CALCIUM OXALATE CRYSTALS

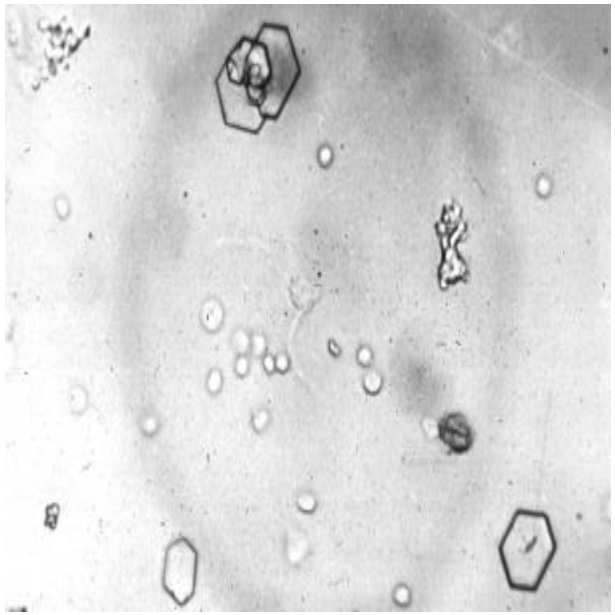


CRYSTALLURIA

STRUVITE CRYSTALS



CYSTINE CRYSTALS



CASTS

Casts are cylindrical structures formed within the tubular lumen, comprised of Tamms-Horsfall mucoprotein and named by their origin and main component.

Cast formation is favoured by stasis, low urine pH and higher urine concentration.

Hyaline casts consist of mucoprotein alone and are nonspecific.

Granular casts consist of fine or coarse grains. Fine granular casts derive from altered serum proteins. Coarse , deeply pigmented (muddy brown or heme) granular casts result from degenerated embedded cells and are usually pathologic – characteristic of ATN.

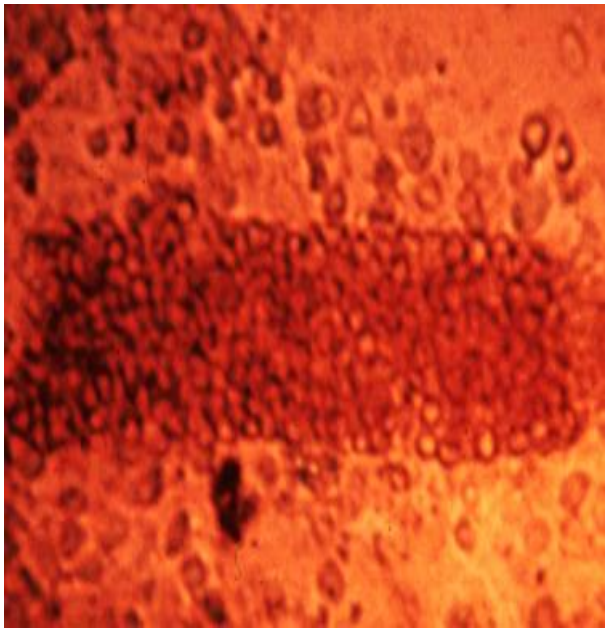
CASTS

Red blood cell casts denote glomerular hematuria and an underlying glomerulonephritis.

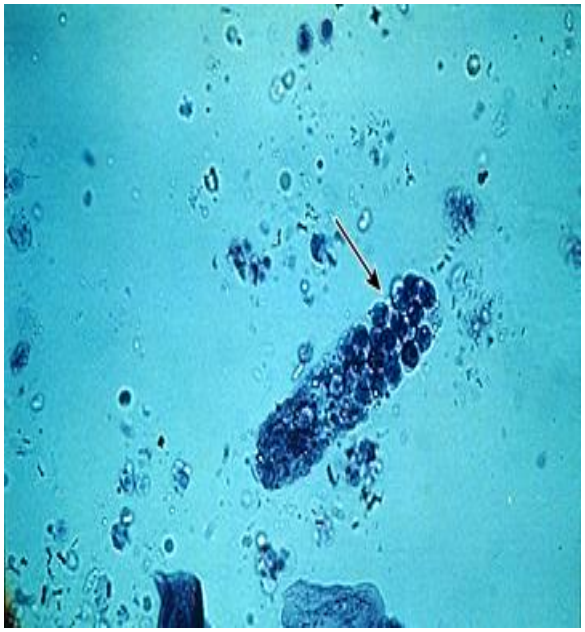
White blood cell casts denote kidney inflammation which may be infectious as in pyelonephritis or noninfectious as in interstitial nephritis.

CASTS

RED CELL CAST



WHITE CELL CAST



HEMATURIA

Defined as the excretion of abnormal quantities of erythrocytes in the urine.

May be gross or microscopic – **3 or more red blood cells per hpf in a spun urine sediment;** transient or persistent; isolated or accompanied; symptomatic or asymptomatic.

Dysmorphic erythrocyturia accompanied by proteinuria is a reliable sign of glomerular bleeding.

Lower urinary tract hematuria seldom leads to marked proteinuria.

Gross hematuria with clots almost always indicates a lower urinary tract source.

MICROSCOPIC HEMATURIA

The definition of microscopic hematuria is the presence of three or more red blood cells per high power magnification of urine sediment . This is usually noted in two of three properly collected urinalysis specimens.

Microscopic hematuria is not an uncommon finding.

MICROSCOPIC HEMATURIA - PREVALENCE

In population based studies, the prevalence of microscopic hematuria varied from 0.19% to as high as 39%.

In one series, the medical records of 1000 asymptomatic male air force personnel were examined retrospectively for the results of 15 yearly examinations of urine sediment. The study covered the period 1968 – 1982 with the subjects aged 18 – 33yrs. The cumulative incidence of microscopic hematuria was 38.7%.

Froom et al Br. Med. J. 1984;288(6410):20

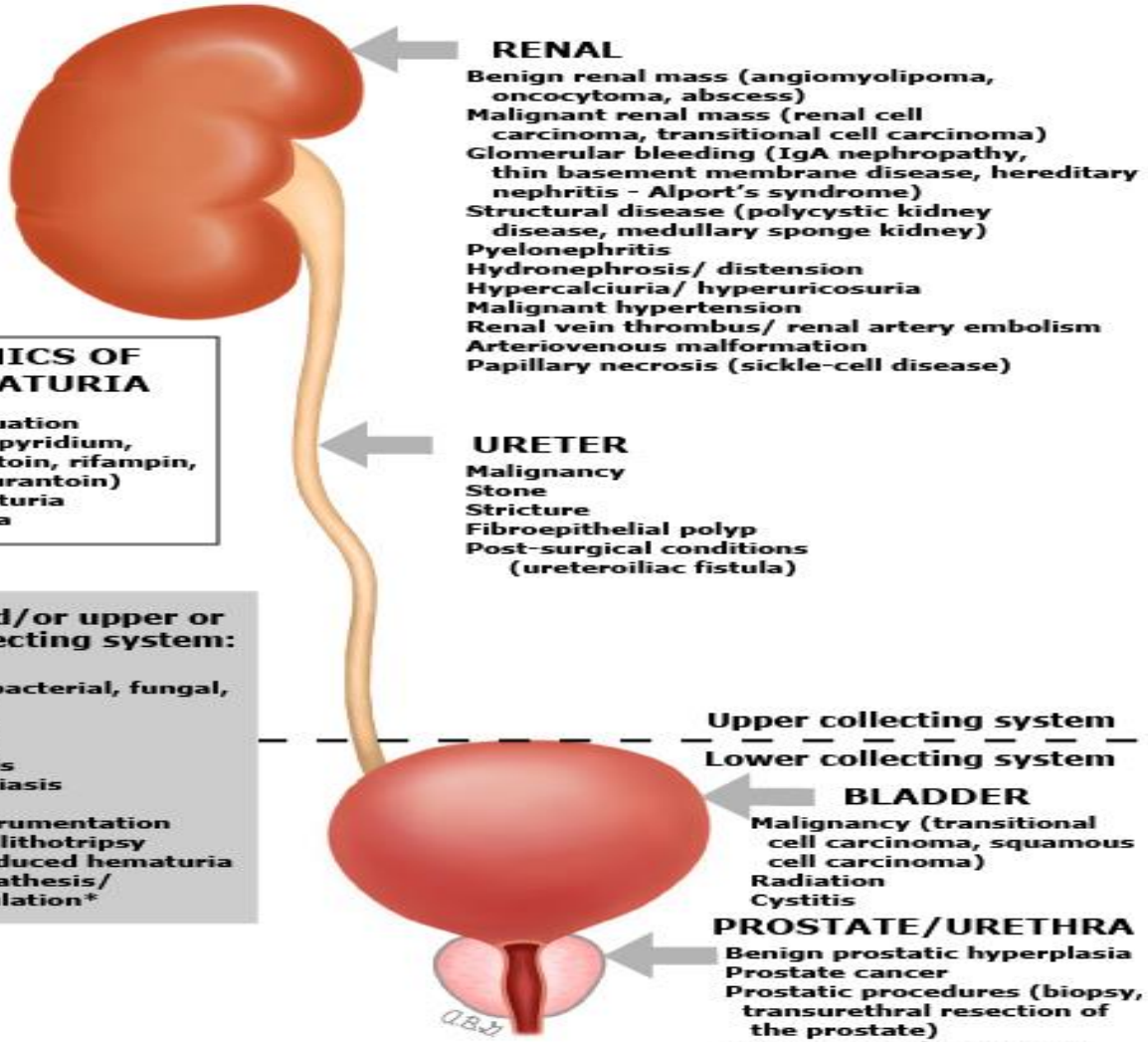
Topham, from Leicester General Hospital, U.K. in his series, found a prevalence of 22% (male and female, age range 10 – 71 yrs.)

Topham et al Q J Med. 1994.

Messing, in his series , found a prevalence of 10% in men aged 50yrs and older.

Messing et al, J Urol. 1987; 137(5)919

HEMATURIA - AETIOLOGY



RENAL
- Benign renal mass (angiomyolipoma, oncocytoma, abscess)
- Malignant renal mass (renal cell carcinoma, transitional cell carcinoma)
- Glomerular bleeding (IgA nephropathy, thin basement membrane disease, hereditary nephritis - Alport's syndrome)
- Structural disease (polycystic kidney disease, medullary sponge kidney)
- Pyelonephritis
- Hydronephrosis/ distension
- Hypercalciuria/ hyperuricosuria
- Malignant hypertension
- Renal vein thrombus/ renal artery embolism
- Arteriovenous malformation
- Papillary necrosis (sickle-cell disease)

MIMICS OF HEMATURIA
- Menstruation
- Drugs (pyridium, phenytoin, rifampin, nitrofurantoin)
- Pigmenturia
- Beeturia

URETER
- Malignancy
- Stone
- Stricture
- Fibroepithelial polyp
- Post-surgical conditions (ureteroiliac fistula)

Renal and/or upper or lower collecting system:
- Infection (bacterial, fungal, viral)
- Malignancy
- Urolithiasis
- Tuberculosis
- Schistosomiasis
- Trauma
- Recent instrumentation including lithotripsy
- Exercise-induced hematuria
- Bleeding diathesis/ anticoagulation*

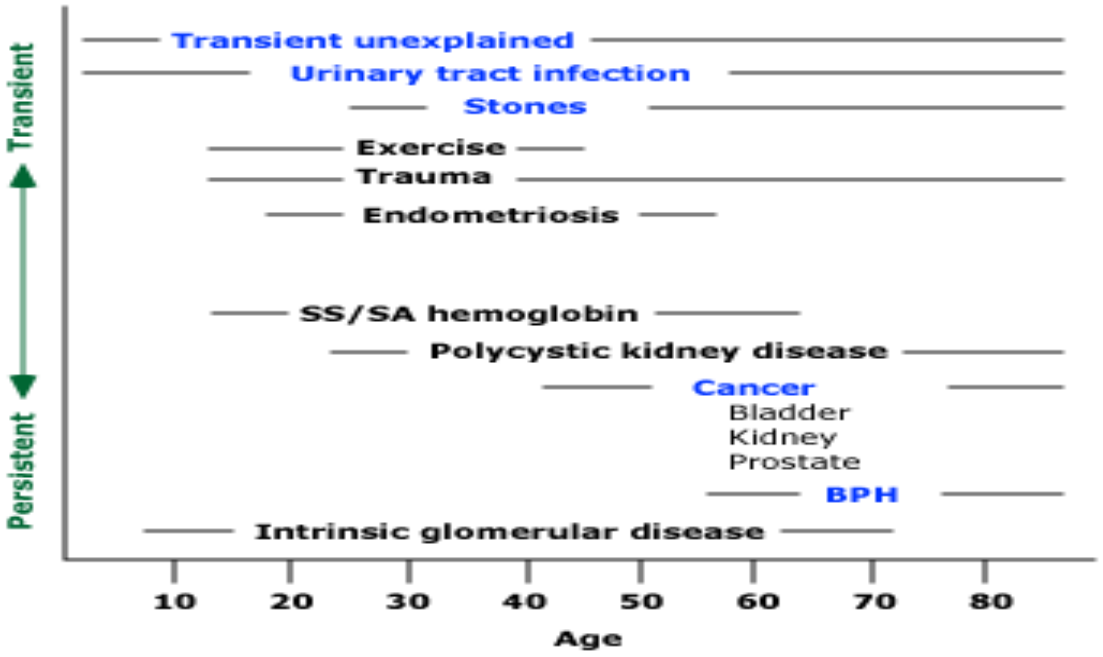
Upper collecting system

Lower collecting system

BLADDER
- Malignancy (transitional cell carcinoma, squamous cell carcinoma)
- Radiation
- Cystitis

PROSTATE/URETHRA
- Benign prostatic hyperplasia
- Prostate cancer
- Prostatic procedures (biopsy, transurethral resection of the prostate)
- Traumatic catheterization
- Urethritis
- Urethral diverticulum

HEMATURIA – AETIOLOGY BY AGE



HEMATURIA

The initial evaluation of the patient with microscopic hematuria should

- Involve thorough history, physical exam to exclude causes such as menstuation, vigorous exercise, trauma, urinary tract infections.
- Determination of risk factors for primary renal disease – significant proteinuria (>500mg/24hr.), hypertension, dysmorphic red blood cells, red cell casts elevated serum Creatinine or reduced GFR.
- Determination of risk factors for urologic disease.
- Determination of glomerular vs nonglomerular bleeding.

HEMATURIA

Glomerular hematuria may result from immune mediated injury to the glomerular capillary wall , or noninflammatory glomerulopathies.

Glomerular hematuria is likely if

- >70% of erythrocytes are dysmorphic, with acanthocytes
- Proteinuria > 500mg/24hrs or> 2+
- Presence of cellular casts, including red blood cell casts- an active urinary sediment

Non glomerular hematuria is likely if

- >70% of erythrocytes are normomorphic
- Protein excretion rate is normal or <2+
- Absence of cellular casts

HEMATURIA

The presence of red blood cell casts is virtually diagnostic of glomerular bleeding , and in particular, glomerulonephritis.

Blood clots, if present , are almost always due to nonglomerular bleeding.

RENAL PARENCHYMAL DISEASES CAUSING HEMATURIA

May be Glomerular or Vascular and Tubulointerstitial

<u>Glomerular</u>

- Primary – IgA Nephropathy, Thin Basement Membrane nephropathy, mesangial proliferative GN, Membranoproliferative GN
- Multisystem – S.L.E., HUS, TTP, Goodpasture's, Microscopic Polyangiitis, Wegener's granulomatosis, Henoch-Schonlein purpura
- Infection – Post strep GN, Infective endo, acute bacterial pyelonephritis
- Hereditary disease – Alport syndrome, Fabry's disease

RENAL PARENCHYMAL DISEASES CAUSING HEMATURIA

Vascular and Tubulointerstitial

- Hypersensitivity – Acute interstitial nephritis
- Neoplastic – Renal cell carcinoma, Wilm's tumor
- Hereditary – Polycystic kidney disease, medullary sponge kidney
- Vascular – Malignant Hypertension, AV malformations, renal artery emboli or thromboses
- Papillary necrosis – analgesic nephropathy, sickle cell trait, ankylosing spondilytis
- ATN

HEMATURIA

The presence of red blood cell casts is virtually diagnostic of glomerular bleeding , and in particular, glomerulonephritis.

Acute and rapidly progressive glomerulonephritis often present with the aute onset of manifestations of nephritis – azotemia, oliguria, Hypertension, proteinuria and hematuria with an active urine sediment containing red blood cell casts, pigmented casts and cellular debris.

CLINICAL MANIFESTIONS OF GLOMERULAR DISEASES

- **Asymptomatic proteinuria**
- **Nephrotic Syndrome** – Minimal change, Membranous GN, FSGS, Mesangioprolif.GN, Diabetic Nephropathy, Amyloidosis, Light Chain
- **Asymptomatic Microscopic Hematuria** – TBM nephropathy, IgA, Alport's syndrome, Mesangioprolif. GN
- **Acute Nephritis** – Diffuse Prolif. GN, Focal prolif. GN, Membranoprolif.GN
- **Rapidly Progressive GN** – Anti GBM GN, Immune complex GN, ANCA GN
- Pulmonary –Renal Vasculitides – Immune complex vasculitides, ANCA vasculitides, Goodpasture's syndrome
- **Chronic Renal failure**
- **Chronic sclreosing GN**

ROLE OF KIDNEY BIOPSY

The main indication for performing a kidney biopsy in a patient with glomerular hematuria is the presence of risk factors for the progression of kidney disease, i.e. proteinuria and/or elevation of serum Creatinine, an elevated Blood pressure and the presence of symptoms of systemic disease.

ROLE OF KIDNEY BIOPSY

Kidney biopsy is not usually performed for isolated microscopic glomerular hematuria (no proteinuria, normal renal function, normotensive, no systemic illness) as the management of these patients is not altered by the results.

In one series, at the Queen Elizabeth Hospital in Birmingham, England, Richards et al conducted a prospective study looking at 276 native renal biopsies in 1991 to assess the effect of the knowledge of renal histology on clinical management. The results of the biopsies in patients with isolated glomerular hematuria altered the management in only 3% of the patients.

Richards et al Nephrol Dial Transp 1994;9(9)

ROLE OF KIDNEY BIOPSY

The most common findings on histology when biopsies are done for isolated microscopic hematuria are

- no pathologic abnormality
- IgA nephropathy
- Thin basement membrane nephropathy
- Mesangioproliferative GN

McGregor, in his series at Christchurch hospital in New Zealand, had figures of

- no pathologic abnormality 28%
- IgA 23%
- Thin basement membrane nephropathy 36%
- MPGN 13%

McGregor et al Clin Neph 1998;49(6):345

University of North Carolina Nephropathology division published figures of

- No abnormalities 30%
- IgA 28%
- TMN 26%
- MPGN 16%

Lab Inves 62 :15A 1990

IMAGING , CYSTOSCOPY, CYTOLOGY

Kidney biopsy is not indicated in patients with persistent non glomerular hematuria. These patients require thorough urologic evaluation with imaging and/or cystoscopy.

CT Urography – unexplained persistent hematuria(without infection, glomerular hematuria, obvious source of bleeding)

- transient hematuria in patients with risk factors for malignancy

Cystoscopy - all patients with gross hematuria unless there is presence of active UTI, nephrolithiasis, known glomerular hematuria; glomerular hematuria and clots; persistent unexplained microscopic hematuria with risk factors for malignancy

Cytology - voided urine cytology recommended for patients with gross hematuria ; microscopic hematuria with risk factors for urothelial malignancy or carcinoma in situ

IgA NEPHROPATHY

IgA is an antibody mediated glomerulonephritis, diagnosed by kidney biopsy : commonest form of glomerulonephritis worldwide; patients present in one of three ways

- Asymptomatic microscopic hematuria with mild proteinuria
- Macroscopic hematuria following URTI and intermittent microscopic hematuria
- Nephrotic syndrome or RPGN with renal insufficiency

THIN BAESMENT MEMBRANE NEPHROPATY, ALPORT'S

Thin basement membrane nephropathy is also called benign familial hematuria; in addition to the family history, patients present with microscopic hematuria +/- gross hematuria +/- AKI.

Alport's syndrome is a hereditary progressive form of glomerular disease often associated with sensorineural hearing loss adn ocular abnormalities.

SUMMARY

- Urinalysis has three components.
- Red urine is not synonymous with hematuria.
- Microscopic hematuria is defined as the presence of at least 3 red blood cells in the centrifuged urine sediment.
- Evaluation must include if the bleeding is glomerular or non glomerular as well as risk factors for renal disease or urologic disease.
- Renal causes are varied.
- Algorithms exist for investigations.


THANK YOU