"He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all"
William Osler

Medicine

430

Haematuria

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-Red: Important notes
-Green: Team notes
-Blue: Extra information from books, websites, etc

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Normal Urine:

Urine is an aqueous solution, which consists of:

Table 1.

Components	Normal Measures
Water	95%
Urea	9.3 g/L
Chloride	1.87 g/L
Sodium	1.17 g/L
Potassium	0.750 g/L
Creatinine	0.670 g/L
Dissolved ions	--
Inorganic and organic compounds	--

Urine is **sterile** until it reaches the urethra. In the urethra the epithelial cells lining the urethra are colonized by facultatively anaerobic gram negative (-ve) rods and cocci.

Subsequent to elimination from the body, urine can acquire strong odor due to bacterial action and in particular release of Ammonia from the breakdown of urea.

❖ Characteristics of urine:

Urobilin:

Urobilin results from the breakdown of the heme of the hemoglobin during destruction of aging blood cells.

1. Color:
   - Varies, but usually pale yellow
   - Depends on the level of hydration
   - Comes primarily from the presence of Urobilin
2. Odor:
   Normally reflects what has been consumed by the person or a specific disease (e.g. Sweetened urine odor in people with Diabetes Mellitus)
3. Turbidity:
   - Normally urine is clear
   - Turbid urine may be a sign of bacterial infection, but it might also result from crystallization of salts, such as Ca^{+2} phosphate
4. pH:
   Varies between 4.6-8, but usually 7 is the normal pH
5. Volume:
   Average urine production in adult humans is about 1-2 L/day
6. Density of specific gravity:
   Normally it varies between 1.003-1.035 (g. cm^{-3})

Hematuria

❖ Definition:

Hematuria is the passage of red blood cells in the urine. Defined clinically by the presence of more than **2-3 RBC/HPF (x400)** of centrifugal freshly voided urine.

Presence of RBC in urine of Normal individuals

Normal individuals have occasional RBCs in their urine (up to 12 500 rbc/mL) [1]

❖ Investigations for detecting hematuria:

1. Urine Dipstick Test: The detection limit for dipstick testing is 15-20 000 rbc/mL, which is sufficiently sensitive to detect all significant bleeding.

However it can appear to be positive when **free hemoglobin** and **myoglobin** is present

- Other causes of red urine that might be mistaken for heamturia but result in negative dipstick test and negative on microscopy are shown in Table 2.
- True positive tests may occur in menstruation, infection or strenuous exercise, but persistent hematuria requires further investigations to exclude malignancy

When taking a urine sample from a female patient always make sure whether there's menstruation or not

Table 2. Causes of red urine resulting in negative dipstick test

Cause	Urine color
Food dyes (e.g. beetroot)	Red
Drugs: e.g.	
Phenolphthalein	Pink when alkaline
Senna/Other anthaquinones	Orange
Rifampicin	Orange
Levodopa	Darkens on standing
Porphyria	Darkens on Standing
Bilirubinuria	
e.g Obstructive Jaundice	Dark Dipstick-positive for bilirubin, negative for hemoglobin

2. Urine microscopy: It is valuable in confirming hematuria and establishing the cause of the bleeding.

❖ Initial approach to Hematuria:

1. Genuine erythrocyturia (i.e. not hemoglobinuria or myoglobinuria): presence of erythrocytes confirmed by microscopy
2. Microscopic or Macroscopic (gross)? Microscopic is invisible and cannot be detected without investigations. Macroscopic (gross) is visible and can be reported by the patient.
3. Intermittent or sustained?
4. Accompanied by proteinuria? Proteinuria is defined by the presence of >1000 mg or protein in the urine in 24 hours (>1000 mg/24 hr)
5. Associated with menstruation or catheterization?
6. Associated with infection? Infection is confirmed by pyuria or nitrates, or positive urine microscopy or culture for microorganisms

Macroscopic (gross) Hematuria:

It is more likely to be caused by tumors. It has a positive predictive value of 83% for bladder cancer (Painless hematuria) and 22% for all urothelial tumors.
Also severe infections or renal infarction can cause macroscopic hematuria, usually accompanied by pain

Hematuria accompanied by Proteinuria

If hematuria occurs with protienuria or clinical features of kidney disease, inflammatory renal disease should be considered and a renal biopsy may be indicated .

❖ Types:

Table 3. Types of hematuria and characteristics of each type

Type	Characteristics
1. Glomerular Hematuria	Microscopic or Macroscopic
	Majority of erythrocytes are dysmorphic
	Proteinuria >1000 mg/24hr
	Presence of erythrocyte casts
	Absence of symptoms, signs or other evidence of non-glomerular hematuria
2. Non-glomerular Hematuria	Microscopic or Macroscopic
	Majority of erythrocytes have normal morphology
	Proteinuria absent or <0.5 g/g (500 mg/24 hr)
	Symptoms, signs, or other evidence of nonglomerular urinary tract pathology
	Absence of erythrocyte casts
3. Intermediate Hematuria	Microscopic or macroscopic hematuria
	Presence of some dysmorphic erythrocytes
	Proteinuria present but <1000 mg/24 hr
	Absence of erythrocyte casts

❖ Causes:

Causes of hematuria can be classified into Glomerular Hematuria and Non-glomerular Hematuria

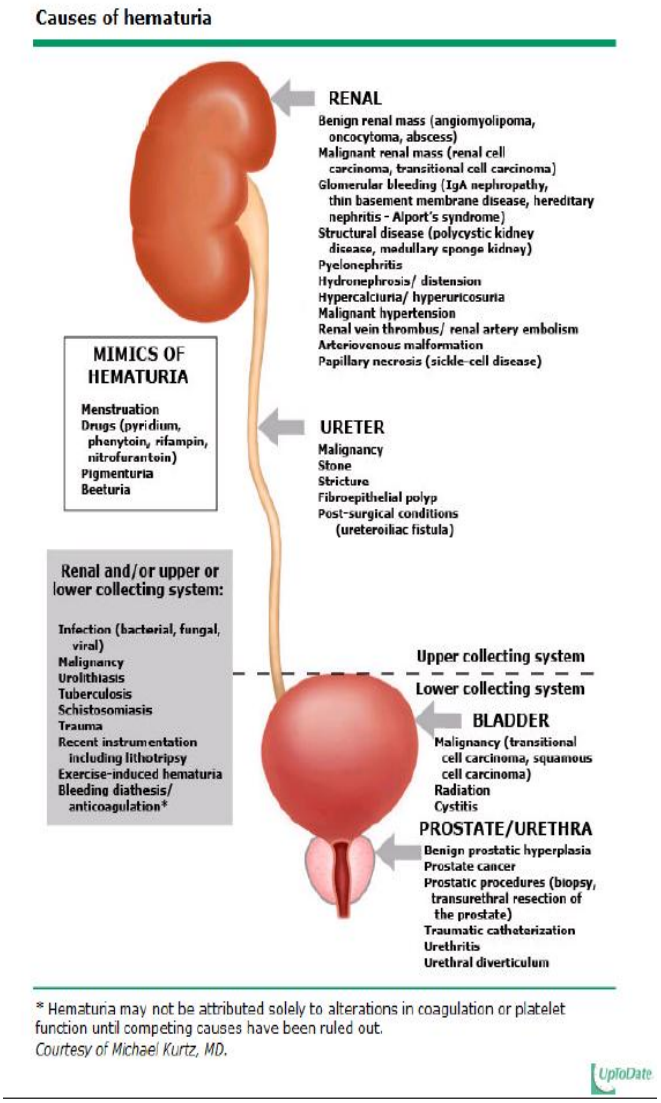
A. Glomerular Hematuria:

1. Primary Glomerulonephritis:
   - Mesangial proliferative glomerulonephritis (typically immunoglobulin A nephropathy)
   - Membranoproliferative glomerulonephritis
   - Crescentic glomerulonephritis
   - Anti–glomerular basement membrane disease
   - Focal, segmental glomerulosclerosis
   - Membranous glomerulonephritis (<30%)
   - Minimal change glomerulonephritis (<20%)
   - Fibrillary glomerulopathy
2. Multisystem Autoimmune diseases:
   - Systemic lupus erythematosus
   - Vasculitis (e.g., Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss angiitis, Henoch-Schönlein purpura)
   - Scleroderma glomerulopathy
   - Thrombotic microangiopathy (e.g., anti-phospholipid syndrome, hemolytic uremic syndrome)
3. Other:
   - Hereditary (e.g., Alport's disease, thin membrane disease, nail-patella syndrome, Fabry's disease)
   - Infection-associated glomerulonephritis (e.g., HIV nephropathy, poststreptococcal glomerulonephritis, infective endocarditis, shunt nephritis)

B. Non-glomerular Hematuria:

1. Renal Origin:
   - Tubulointerstitial disorder

- Hypersensitivity tubulointerstitial nephritis
- Tubulointerstitial nephritis with uveitis
- Sjögren's syndrome
- Vascular disorder
- Malignant hypertension
- Scleroderma renal crisis
- Polyarteritis nodosa
- Renal embolism or arterial or venous thrombosis
- Arteriovenous malformation
- Neoplasia (e.g., renal cell carcinoma, Wilms' tumor, leukemia, lymphoma, metastatic disease)
- Papillary necrosis (causes include diabetes mellitus, sickle cell anemia, analgesic abuse, and obstructive uropathy)
- Infection (e.g., pyelonephritis, tuberculosis, hantavirus, BK virus in transplants)
- Hereditary (e.g., polycystic kidney disease, medullary sponge kidney)
- Trauma
- Idiopathic renal hematuria



2. <u>Urinary tract origin:</u>
   - Neoplasia
   - Transitional cell carcinoma
   - Carcinoma of bladder, prostate, or urethra
   - Calculi (e.g., calcium oxalate/phosphate, uric acid, xanthine, cysteine, struvite, drugs)
   - Trauma or foreign body
   - Infection (e.g., periureteritis, cystitis, prostatitis, urethritis, tuberculosis, Schistosoma haematobium)
   - Malformations
   - Nevi
   - Vascular malformations
   - Hereditary hemorrhagic telangiectasia
   - Inflammatory
   - Retroperitoneal fibrosis/aortitis
   - Endometriosis
   - Diverticulitis, appendicitis, Crohn's disease
   - Hypersensitivity cystitis or urethritis
   - Vasculitis (polyarteritis nodosa and Churg-Strauss angiitis)
   - Drug and radiation-induced hematuria (e.g., by cyclophosphamide, nitrogen mustard)
   - Urinary obstruction or relief of obstruction
3. <u>Other:</u>
   - Loin-pain hematuria syndrome

- Acquired cystic disease of renal failure
- Coagulation disorder (e.g., thrombocytopenia, hemophilia, anticoagulant therapy)
- Factitious (malingering)

❖ Approach to patients with Hematuria:

➢ **History:**

- Recent Symptoms:
  - ✓ Fever
  - ✓ Rash
  - ✓ Weight loss
- Past History:
  - ✓ Hypertension
  - ✓ Diabetes Mellitus
  - ✓ Vascular diseases
  - ✓ Past history of urinary stones or surgery
  - ✓ Recurrent infections
  - ✓ Anemia
  - ✓ Malignancy
- Family History:
  Note any family members with renal diseases. The most common inherited conditions are APKD (Adult Polycystic Kidney Disease) and Alport's syndrome.
- Drug history:
  - ✓ Anti-coagulants
  - ✓ Herbal medicine
  - ✓ NSAIDs
- Social History
  - ✓ Smoking
  - ✓ Alcohol consumption
  - ✓ Dietary history (especially when suspecting renal stones)
  - ✓ Occupation

How to Examine a patient with frank haematuria

1. Measure temperature - raised in urinary tract infection, connective tissue disease, endocarditis with renal involvement.
2. Look for bruising or purpura (coagulation disorder, Henoch-Schönlein purpura, vasculitis).
3. Examine nails for splinter haemorrhages (bacterial endocarditis with renal involvement).
4. Measure blood pressure - elevated in renovascular and chronic kidney disease.
5. Look at optic fundi for hypertensive retinopathy.
6. Examine abdomen for renal tenderness (renal or ureteric stones or other causes of obstruction, renal infection or inflammation).
7. Examine abdomen for enlarged, palpable kidneys - unilateral in renal cancer, urinary tract obstruction; bilateral in polycystic kidney disease.
8. Palpate suprapubically for palpable bladder (benign prostatic enlargement, prostate or bladder cancer).
9. Assess peripheral pulses and listen for renal artery or other bruits (renovascular disease).
10. In men, perform rectal examination to assess enlargement of prostate - irregular in prostate cancer. In women, consider a pelvic examination to assess reproductive organs

➢ **Examination:**

Check for:

1. Purpura to exclude **vasculitis**
2. Deafness to exclude **Alport syndrome**
3. Flank mass to exclude **polycystic disease**
4. Type of hematuria from urine examination

❖ Laboratory Investigation of Glomerular Hematuria

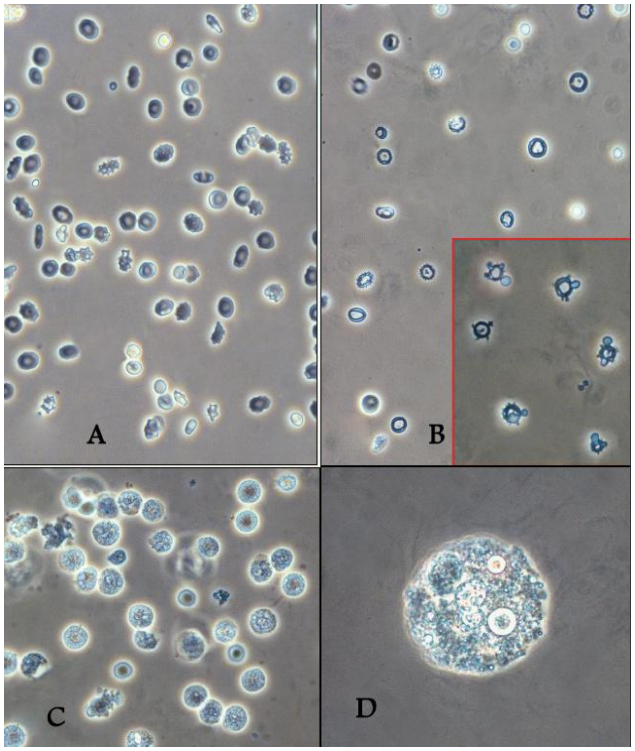
Table 4. Investigations for Glomerular Hematuria

Diagnosis	Relevant Abnormal Investigations
Membranoproliferative glomerulonephritis (MPGN)	C3/C4, C3 nephritic factor, cryoglobulins, hepatitis B/C
Anti–GBM disease	Anti-GBM antibodies, chest radiograph
Systemic lupus erythematosus	ANA, anti-dsDNA, ENAs, C3/C4, anticardiolipin
Vasculitis (Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss angii	ANCA (C-ANCA/PR3-ANCA or PANCA/ MPO-ANCA)

Thrombotic microangiopathy	Anti-cardiolipin, lupus anticoagulant
Hereditary	
Alport's disease	Audiometry
Fabry's disease	Plasma alpha-galactosidase A activity
Infection-associated glomerulonephritis	
HIV nephropathy	HIV
Poststreptococcal glomerulonephritis	ASO, anti-DNAase, C3/C4, rheumatoid factor
Infective endocarditis	Echocardiography, C3/C4, rheumatoid factor

- Urinary Sediment Cells

A. Isomorphic nonglomerular erythrocytes. The appearance of the so-called crenated erythrocytes are a frequent finding in nonglomerular hematuria.
B. Dysmorphic glomerular erythrocytes. The dysmorphism consists mainly of irregularities of the cell membrane. Inset, Acanthocytes with their typical ring-formed cell bodies with one or more blebs of different sizes and shapes.
C. Neutrophils: Note: their typical lobulated nucleus and granular cytoplasm.
D. A granular phagocytic macrophage (diameter about 60 μm).

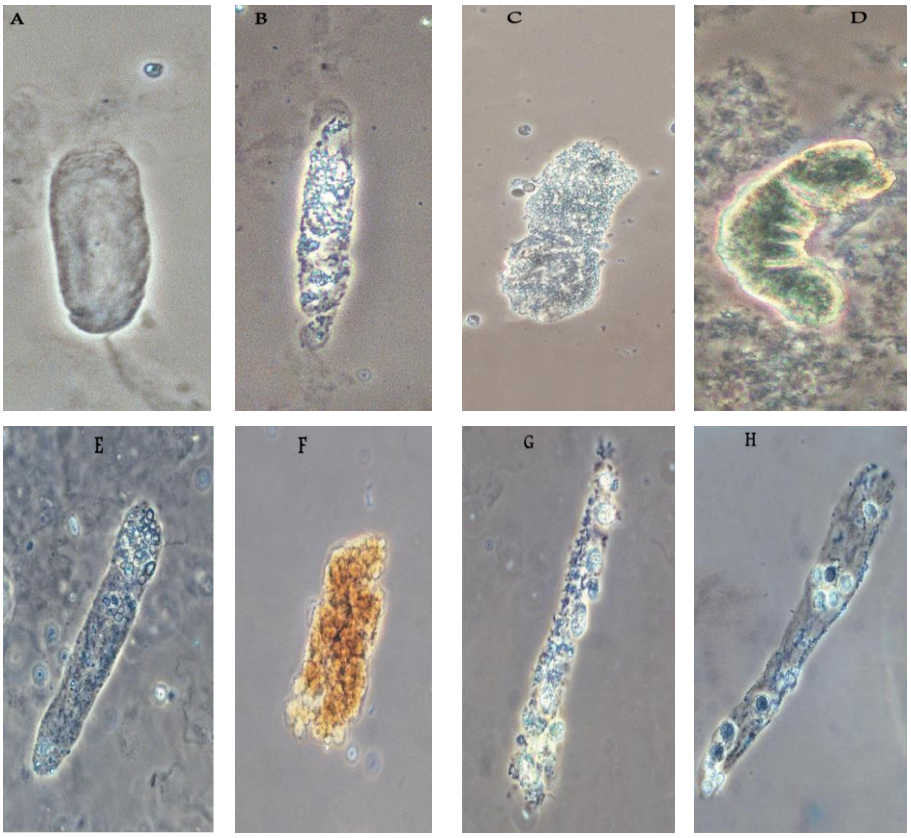


Clinical Significance of Urinary Casts

Table 5. Casts and their main clinical associations

Cast	Main Clinical Associations
Hyaline	Normal subject and renal disease
Hyaline-granular	Normal subject and renal disease
Granular	Renal disease
Waxy	Renal impairment; rapidly progressive renal disease
Fatty	Marked proteinuria; nephrotic syndrome
Erythrocyte	Glomerular hematuria; proliferative or necrotizing glomerulonephritis
Hemoglobin	The same as the erythrocyte cast; hemoglobinuria due to intravascular hemolysis
Leukocyte	Acute interstitial nephritis; acute pyelonephritis; proliferative glomerulonephritis
Renal tubular epithelial cell (epithelial casts)	Acute tubular necrosis; acute interstitial nephritis; proliferative glomerulonephritis; nephrotic syndrome
Myoglobin	Rhabdomyolysis
Bacterial, fungal	Bacterial or fungal infection in the kidney

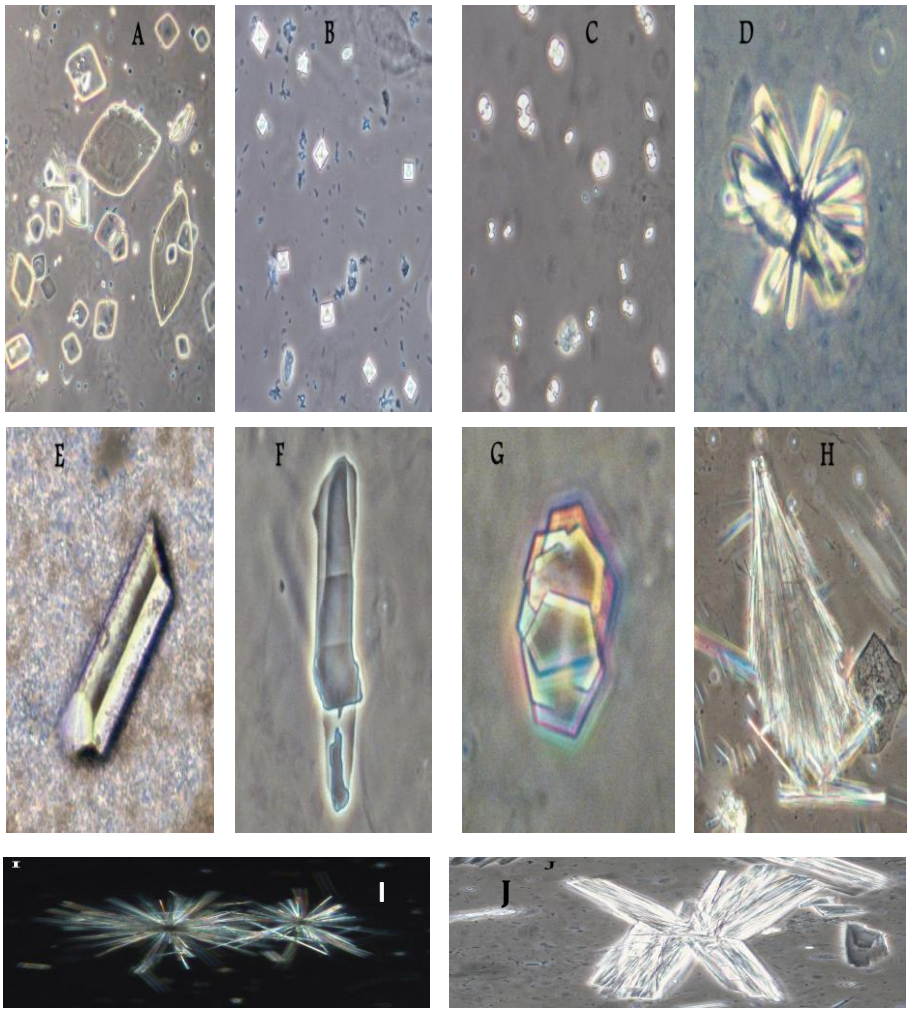
Images of Casts:



Identifications of images of Casts

A. Hyaline Cast
B. Hyaline-granular Cast
C. Finely Granular Cast
D. Waxy Cast
E. Erythrocyte Cast
F. Hemoglobin Cast (Note: typical brownish hue)
G. Leukocyte Cast (The polymorphonuclear leukocytes are identifiable by their lobulated nucleus)
H. Epithelial cells Cast (Renal tubular cells are identifiable by their large nucleus)

Images of Crystals in urine:

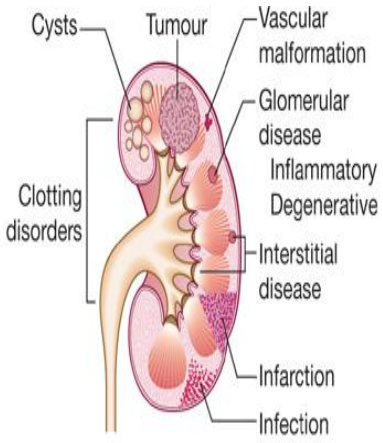


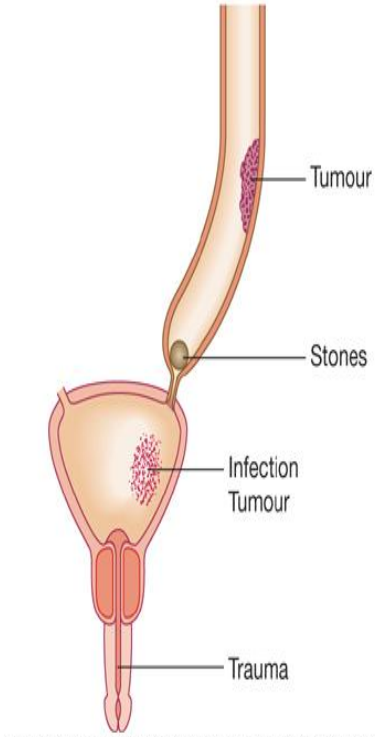
Identifications of images of Crystals:

A. Uric acid crystals. This rhomboid shape is the most frequent.
B. Bihydrated calcium oxalate crystals with their typical appearance of a "letter envelope."
C. Different types of monohydrated calcium oxalate crystals
D. A star-like calcium phosphate crystal
E. Triple phosphate crystal, on the background of a massive amount of amorphous phosphate particles
F. Cholesterol crystal
G. Cystine crystals heaped one on the other
H. Amoxicillin crystal resembling a branch of a broom bush
I. Star-like ciprofloxacin crystals as seen by polarized light
J. A large crystal of indinavir

Summary

- Hematuria is the presence of RBCs in the urine
- Urine dipstick and urine microscopy are used to detect hematuria
- Hematuria is classified into: Glomerular hematuria, non-glomerular hematuria and intermediate hematuria
- Causes of hematuria:
  - Kidney:
    - Glomerular Disease: Glomerular bleeding is characteristic of inflammatory, destructive or degenerative processes that disrupt the glomerular basement membrane (GBM) to cause microscopic or macroscopic hematuria.
    - Renal Carcinoma
    - Renal Stones
    - Trauma (including renal biopsy)
    - Less Common:
      - Polycystic kidney
      - TB
      - Embolism
      - Renal vein thrombosis
      - Vascular malformation
  - Ureter:
    - Ureter Stone
    - Tumor
  - Bladder:
    - Carcinoma
    - Inflammation (e.g. cystitis, TB)
    - Stones
    - Trauma
  - Prostate
    - Benign Prostatic Hypertrophy
    - Carcinoma
  - Urethra:
    - Trauma
    - Stone
    - Urethritis
    - Neoplasm





Colledge et al: Davidson's Principles and Practice of Medicine, 21st Edition

- Patient's full history and examination are very important.
- In examination check for Purpura (to exclude vasculitis), deafness (to exclude Alport's syndrome) and Flank masses (to exclude polycystic disease)
- Casts have clinical significance, for if cast is found, depending on its type, it might indicate for a specific disease.

References

- Nicki R. Colledge, Brian R. Walker, Stuart H. Ralston – Davidson's Principles & Practice of Medicine, 21st edition – Churchill Livingstone
- Parveen Kumar, Michael Clark – Kumar & Clark's Clinical Medicine, 7th edition – Saunders
- Akram Askar, consultant of nephrology at King Saud University's College of Medicine and King Khaled University Hospital – Hematuria; 2012
- Andrew T Raftery, Eric Lim, Andrew J K Oster – Differential Diagnosis, 3rd edition – Churchill Livingstone
- Graham Douglas, Fiona Nicol, Colin Robertson – Macleod's Clinical Examination, 12th edition – Churchill Livingstone