# ANNUAL NEPHROLOGY ESSAY COMPETITION

# FOR MD/DNB MEDICINE/ PAEDIATRICS 2018

## URINALYSIS

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**Outline**

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    b. Clarity
    c. Color
    d. Specific gravity
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Word count: 3008

**Abstract:**

Urinalysis is one of the key tools to evaluate kidney and urinary tract disease. It can yield ample amount of information when done with the right clinical context. Urinalysis is most widely done using the dipstick, but there are limitations to the same. Urine sediment analysis also plays a crucial role in diagnosis of renal diseases. Urine microscopy and sediment analysis should ideally be done by the clinical personnel (eg: treating clinician) in order to not to miss out on vital details. Examination of urine is also called as uroscopy and is one of the oldest practices in medicine dating back to Babylonian era. Richard Bright, an English physician in the 18$^{th}$ century was an early proponent of routine practice of urine analysis and its application to renal disease.

Urinalysis is advantageous as it is non invasive, economical and readily available. In addition to aiding in diagnosis of renal diseases, an abnormal urinalysis findings on a routine evaluation may be the first evidence of an underlying renal disease. It can also aid in monitoring the course of an established renal disease.

In this essay a brief review about urinalysis is presented under the headings of gross, chemical and microscopic analysis.

## 1. Introduction:

Urinalysis is an essential aspect of evaluation of renal disease. Available almost immediately and most informative when done with the right clinical context. Someone has rightly said, "*What an electrocardiogram is to a cardiologist is what a urinalysis is to a nephrologist"*

A complete urinalysis consists of gross analysis, chemical analysis (usually done via dipstick) and microscopic analysis

A few instructions to be given to the patient while collecting the sample for routine urinalysis are:

- Collect specimen in a clean, dry wide mouthed, container
- Clean the genitalia with water and provide a mid stream urine for analysis
    - Midstream specimen is preferred as it avoids contamination with periurethral and periprepucial organisms
- In males, retract the prepuce and clean the glans with water. In females, labia should be separated and washed with water
- In patients with in dwelling catheter collect the sample directly from the catheter tubing and not from the urobag
- Routine examination should be performed within two hours of sample collection

## 2. Gross appearance or inspection:

### a. Odor

Ammonia is the compound responsible for imparting urine its typical odor. Ingestion of foods like asparagus can sometimes cause a change in urine odor which is similar to cooked cabbage

| Characteristic urine Odor | Condition |
|---|---|
| **Musty odor** | Phenylketonuria |
| **Sweet or fruity odor** | Diabetes, Ketosis, Maple syrup urine disease |
| **Sweaty foot or acrid odor** | Isovaleric academia, Glutaric acidemia |
| **Rancid/Fishy odor** | Hypermethionemia |
| **Swimming pool odor** | Hawkinsinuria |
| **Cat urine odor** | 3-hydroxyl 3-methyl glutaric aciduria |
| **Maple syrup** | Maple syrup urine disease |
| **Boiled cabbage** | Hypermethionemia |
| **Tomcat urine** | Multiple carboxylase deficiency |
| **Hops-like urine** | Oasthouse urine disease |
| **Rotting fish** | Trimethylaminuria |

**Table 1: Urine characteristic odors**[1,2]

Conventionally it is taught that Urinary tract infection imparts a foul or feculent odor but a few studies have shown that urine odor is often a misleading predictor of UTI in more than one third of cases[3]

**b. Clarity**

Cloudy or turbid urine is most commonly associated with urinary tract infections. It can also be caused due to other causes as below. Turbid white urine is sometimes referred to as *albinuria* [4]

| Causes of turbid urine or albinuria |
|---|
| •Chyluria<br>•Filariasis , Schistosomiasis , Postsurgery , Malignancy<br>•Hyperuricosuria<br>•Phosphaturia<br>•Hyperoxaluria<br>•Proteinuria<br>•Pyuria<br>•Lipiduria<br>•Caseous material from renal tuberculosis<br>•Congenital malformations of the lymphatic vessels |

**Figure 2: Causes of turbid urine**[4]

**c. Color**

Normal urine color varies from clear to dark yellow. Normal urine color is due to urochrome pigment.

| Characteristic urine color | Pathological cause | Food or drug causing a similar discoloration |
|---|---|---|
| **Yellow** | Concentrated urine | Carrots |
| **Orange** | Bile pigments | Phenazopyridine |
| **Red/Pink** | Hematuria<br>Hemoglobinuria<br>Myoglobinuria<br>Porphyria | Beetroot<br>Blackberry<br>Rifampicin, Phenytoin,<br>Phenolphthalein, Rhubarb |
| **Purple** | Porphyria | |
| **Black/Brown** | Melanin<br>Methemoglobin | Chloroquine<br>Levodopa<br>Nitrofurantoin<br>Fava Beans |
| **Green** | Pseudomonas infection | Triamterene |

**Table 2: Characteristic urine color** [1,2]

**Approach to red urine** [5,6]

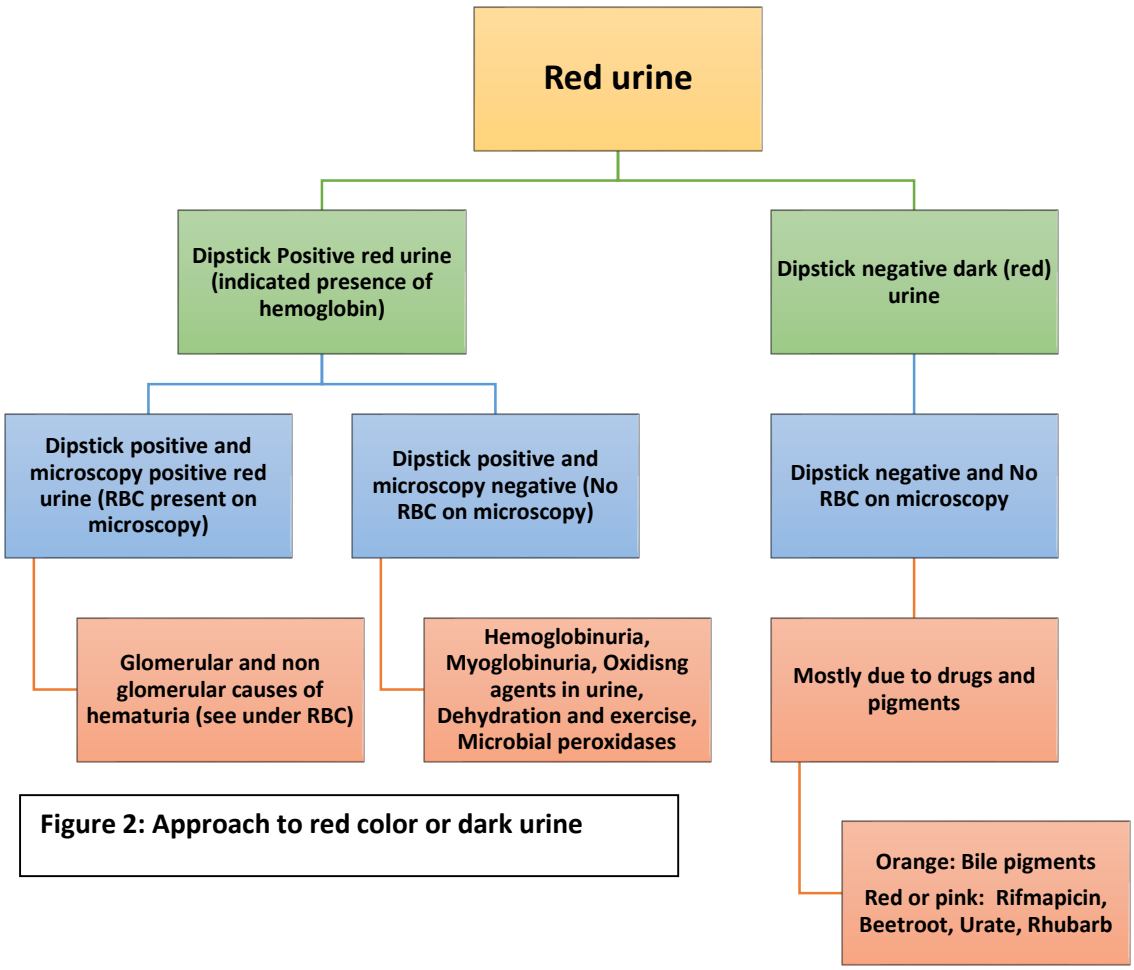



**Figure 2: Approach to red color or dark urine**

There are cases of dipstick being falsely negative despite the presence of RBC in urine when there are large amount of reducing substances (vitamin C) in urine or when the urine is very dilute.

Urine color can also be taken as a surrogate marker for total fluid intake as shown in a study. 84 % of individuals with darker urine colour who increase total fluid intake by at least 1260 mL over the course of the day will see a two-shade decrease in urine color in 24-hours[7]

**d. Specific gravity:**

Urine concentration is measured by urine specific gravity or urine osmolality Specific gravity refers to weight of volume of urine when compared with weight of same volume of distilled water. Specific gravity depends on the mass and number of dissolved particles. It is checked using a dipstick which has bromothymol blue as an indicator or by using refractometer. Values obtained with a refractometer are more accurate than dipstick because dipstick result varies depending on the urine pH (falsely high value in acidic urine) and also doesn't detect non ionic molecules like glucose, urea and heavy molecules like

protein.[8] Refractometry measures all the solutes rather than just the ionic ones. Normal urine specifc gravity ranges between 1.005 to 1.030

| Value | Indicates | Condition |
|---|---|---|
| **1.000 to 1.003** | Marked urinary dilution | Diabetes insipidus<br>Water intoxication |
| **1.010** | Isosthenuria or low fixed urine specific gravity<br>Urine specific gravity similar to plasma | In conditions where urine concentrating capacity is impaired we find this<br>Eg: Acute tubular necrosis<br>Chronic Kidney disease |
| **>1.040** | Presence of an extrinsic osmotic agent | Radiocontrast media |

**Table 3 : Variations in urine specific gravity**

Urine osmolality closely follows urine specific gravity. It is measured by freezing point depression. Normal urine osmolality ranges between 50-1200mOsm/Kg. A specific gravity of 1.010 usually represents a urine osmolality of 300 to350 mosm/kg. Urine specific gravity rises by approximately 0.001 for every 35 to 40 mosmol/kg increase in urine osmolality

There is an important difference between these measures: the urine osmolality is determined by the number of particles in the urine (eg, urea, sodium, potassium), while the specific gravity is determined by both the number and size of the particles in the urine. This becomes important clinically when there are large molecules in the urine, such as glucose or radiocontrast media. In these settings, the specific gravity can exceed 1.030 ( falsely suggesting a highly concentrated urine) despite a urine osmolality that may be dilute.
In certain clinical conditions (see table), dependence upon specific gravity for determining the osmolality will result in over- or underestimation of urine concentration. In such conditions, it is recommended to always check urine osmolality and not to simply rely on specific gravity. Hence for pathological urine assessment direct measure of osmolality is preferred over specific gravity[9]

| Condition | Clinical Suggestion |
|---|---|
| Diabetes mellitus with glucosuria | Urine osmolality is overestimated by specific gravity measurements. |
| Nephrotic syndrome | Specific gravity overestimates urine osmolality. |
| Challenge with radiocontrast media | Specific gravity overestimates urine osmolality. It is not recommended to check specific gravity immediately after a dye load. |
| Saline diuresis | Urine osmolality could be slightly underestimated by specific gravity measurements. |

**Figure 3: Conditions where urine specific gravity cannot determine urine osmolality with accuracy**

## 3. Chemical analysis

### a. pH

Normal urine pH ranges from 4.5 to 9. Urine pH is measured using glass electrode (more accurate) and by dipstick method. Urine pH reflects the concentration of hydrogen ions in urine. Usually urine is acidic because of the acid load generated from dietary protein intake, but can be alkaline too in vegetarians. Urine pH should be assessed on a freshly voided sample as delay can cause urine to become alkaline due to conversion of urea to ammonia.

| Causes of low urine pH | Causes of High urine pH |
|---|---|
| **Metabolic acidosis (Acid secreted)** | Vegetarian diet (because of minimal nitrogen and acid secretion) |
| **High protein diet (increased acid and ammonia production)** | Infection with urease positive organisms (eg: proteus) : though acidification by kidneys is normal urine pH is high due to the enzyme activity in the bacteria |
| **Volume depleted state (aldosterone stimulation causes acidic urine production)** | Distal RTA (distal acidification is defective) |
| **Proximal RTA (distal acidification normal. Hence urine pH normal or low)** | |

**Table 4: Causes for change in urine pH**

Urine pH also helps to distinguish between Pre renal versus intrinsic renal AKI (cause by Acute tubular necrosis). ATN is usually associated with high urine pH due to acidification in tubules

### b. Glucose

Normally glucose is present in a very small amount in urine (<30mg/dL). Presence of detectable amounts of glucose in urine is called as glycosuria. When there is glycosuria the source of it should be determined. Glycosuria may be due to either the inability of the kidney to reabsorb filtered glucose in the proximal tubule despite normal plasma glucose concentration, or to an overflow scenario related to high plasma glucose concentrations overwhelming the capacity of the renal tubules to reabsorb glucose. In patients with normal kidney function, significant glycosuria does not generally occur until the plasma glucose concentration exceeds 180 mg/dL(Renal threshold for blood glucose)

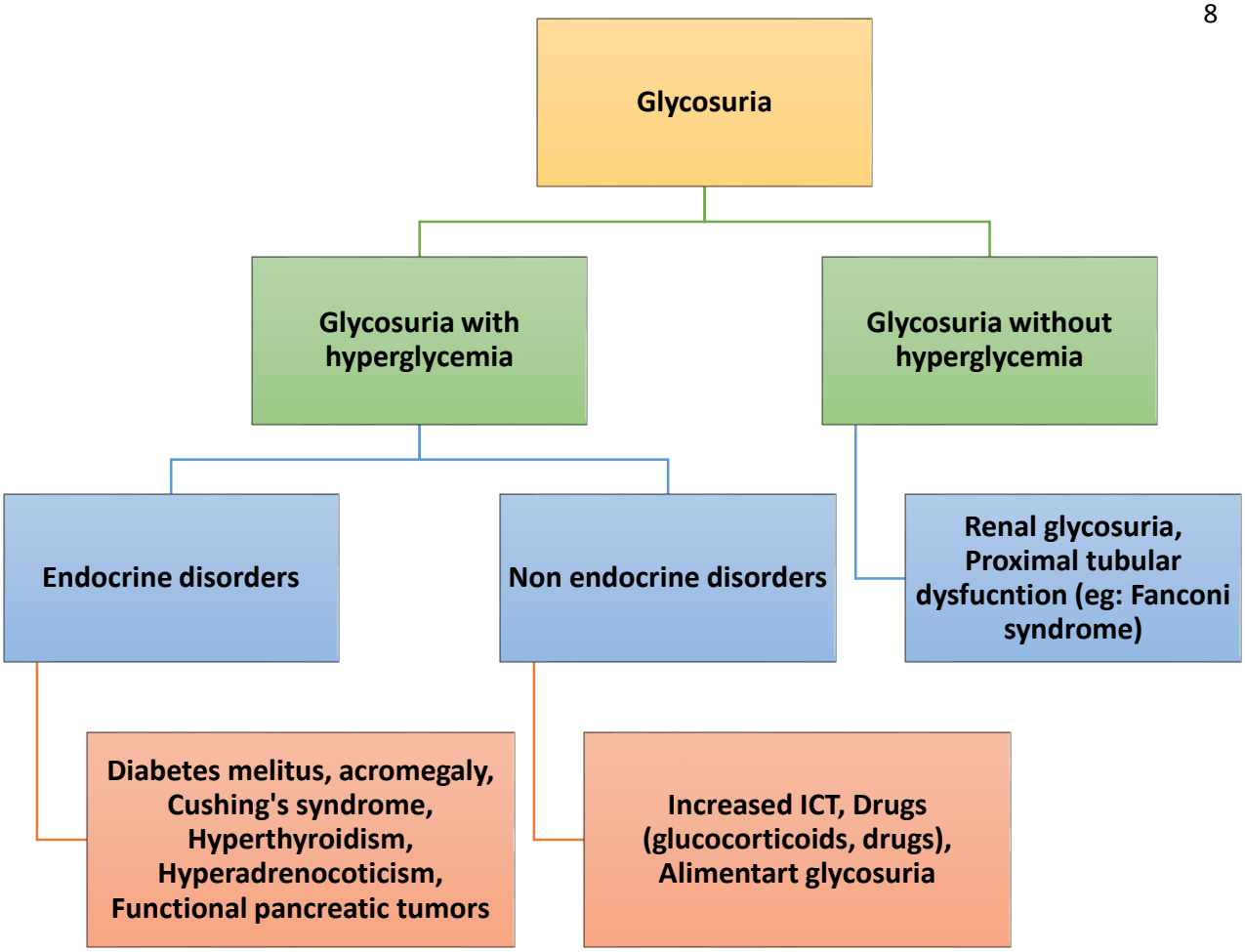



**Figure 3: Causes of glycosuria**

**Renal glycosuria**: Excretion of glucose in urine at normal blood glucose level in the absence of any signs of generalised proximal tubular dysfunction. It is inherited as an autosomal dominant disorder. It is characterised by a decreased renal threshold for glucose (<180mg/dL). Diagnosed by marble criteria[10]

| **Marble criteria for renal glycosuria** |
|---|
| Constant glycosuria with little fluctuation related to diet |
| Normal Oral glucose tolerance test |
| Identification of urinary reducing agent as glucose |
| Normal storage and utilisation of carbohydrates |

Glucose in urine was conventionally measured using Benedict's test

**Benedict test**

**Principle**: It is a semiquantitative test. The **Benedict's test** identifies reducing sugars (monosaccharides and some disaccharides), which have free ketone or aldehyde functional groups. When reducing sugars are mixed with Benedicts reagent and heated, a reduction reaction causes the Benedicts reagent to change color. The cupric (II) ions in the Benedict's solution are reduced to Cuprous (I)

ions, which causes the color change. The color varies from green to dark red (brick) or rusty-brown, depending on the amount of and type of sugar.

**Results and interpretation:**

**Yellow: 0.1-0.5 % sugar, Green: 0.5-1, Orange : 1-1.5%, Red: 1.5-2%, Brick red: >2%**

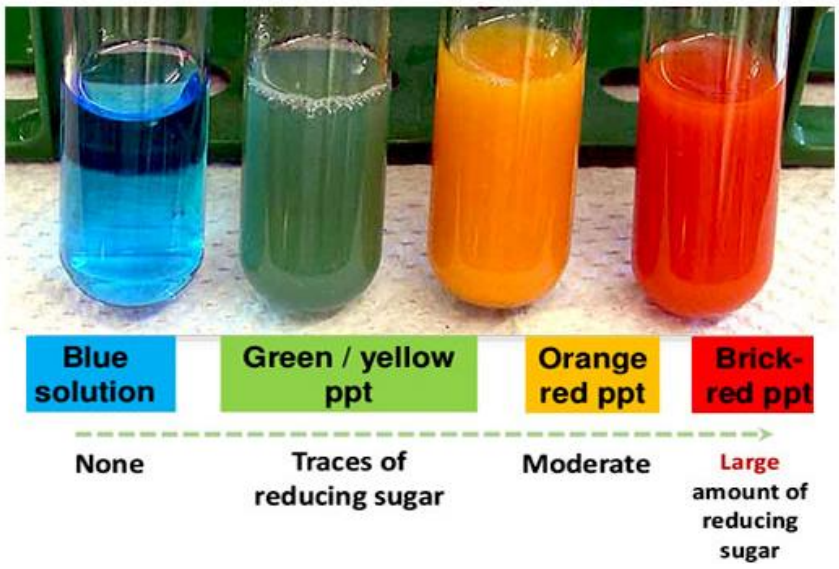



**Figure 4: Interpretation of Benedict's test**

Benedict's test is not used commonly as urine dipsticks have replaced them. Urine dipstick for glucose work on the following principle. Glucose is oxidised to gluconic acid and hydrogen peroxide with glucose oxidase. Hydrogen peroxide than reacts with reduced colorless chromogen to form a colored product. This color is charted against a concentration gradient and an approximate value of urine glucose is obtained. This test detects a concentration of 0.5 to 20g/L of glucose.

For precise quantitative assessment of urine glucose enzymatic methods like Hexokinase methods should be used

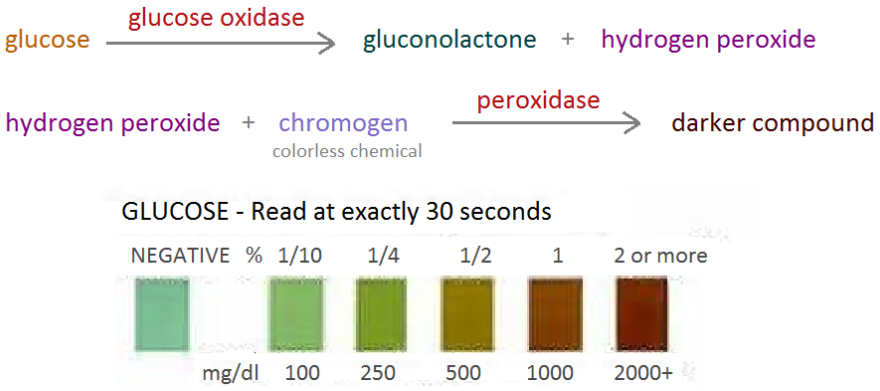



**Figure 5: Principle and results of urine dipstick for glucose**

| False Negative result (glucose present in urine but dipstick negative) | False positive result (Glucose absent in urine but dipstick positive) |
|---|---|
| **Ascorbic acid** | Presence of oxidising detergents in urine |
| **Bacteria** | |

**Table 5: Causes of false positivity and negativity for glucose on dipstick**

**c. Protein**

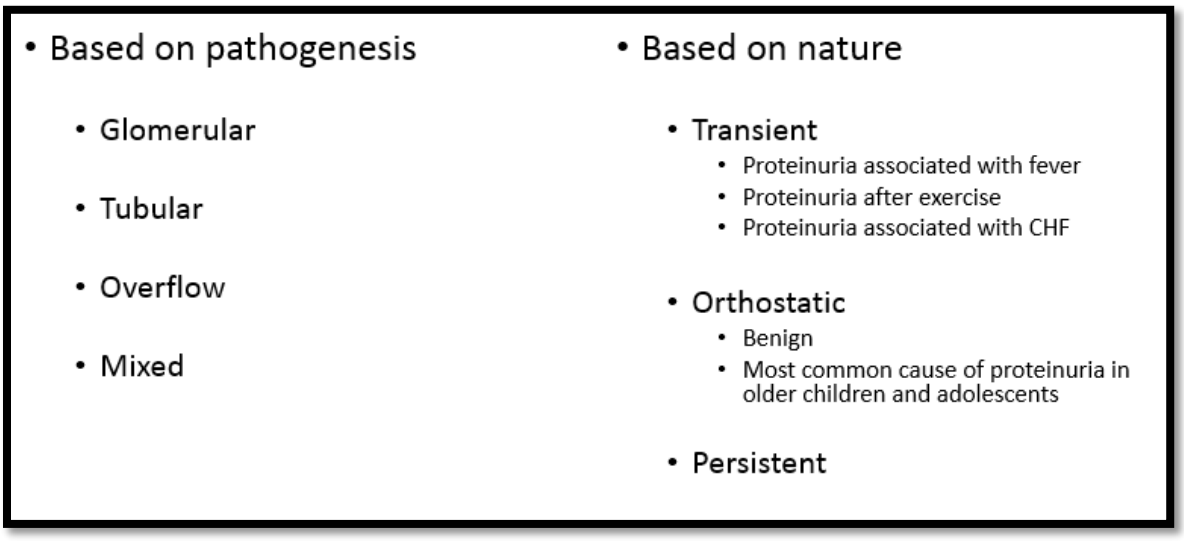
No consistent definition exists for proteinuria

Currently the following definitions are in use[11]

| Type | 24 hour urine excretion | Protein creatinine ratio (urine protein/Urine creatinine) |
|---|---|---|
| **Physiologic** | <150mg/ 24 hours<br>Or<br><4mg/$m^2$/hour | <0.5mg/mg |
| **Pathologic** | | |
| **Microalbuminuria (now called moderately increased albuminuria** | 30-300mg albumin/day | |
| **Macroalbuminuria (now called severely increased albuminuria)** | >300mg albumin/day | |
| **Non nephrotic range** | 4-40 mg/$m^2$/hour<br><3gm/24hours | <3mg/mg<br><3000mg/gm |
| **Nephrotic Range** | >40 mg/$m^2$/hour<br>>3gm/24hours | >3mg/mg or<br>>3000mg/gm |

Physiological proteinuria mainly is composed of Tomm Horsfall protein and albumin excretion is <30mg/day

**Figure 6:Types of proteinuria**



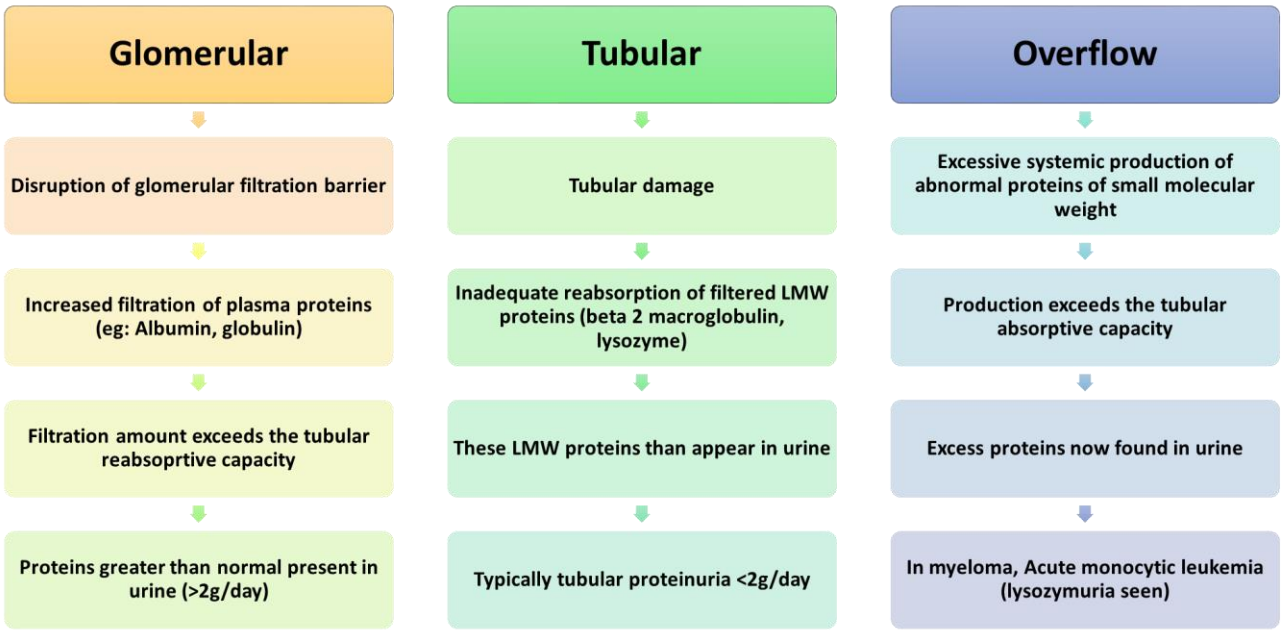



**Figure 7: Pathogenesis of proteinuria**

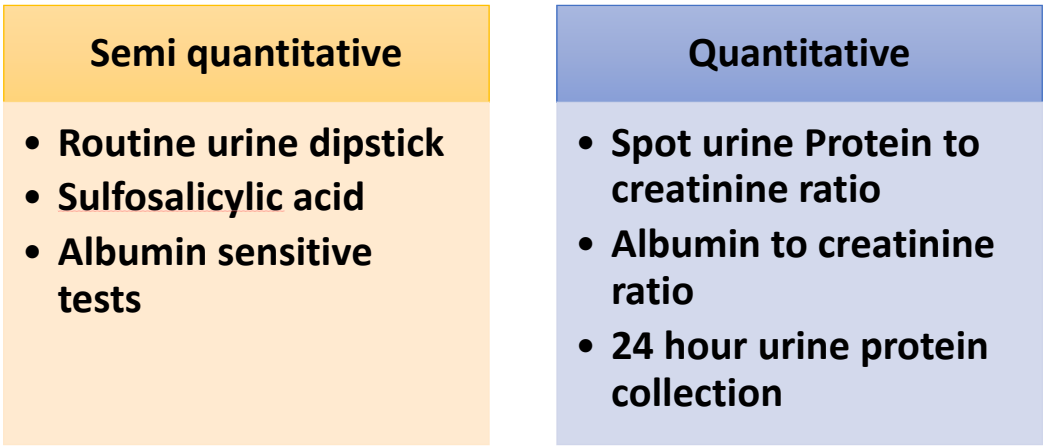



**Figure 8: Methods of testing for proteinuria**

- **Semi quantitative methods**
  - **i. Routine urine dipstick**

    Simplest and least expensive methods

    Principle: Uses tetrabromphenol blue buffered with citrate as an indicator

    Urine albumin binds to the reagent and changes the pH which results in a spectrum of color change based on degree of change of pH

    Lower threshold for detection : 15-20mg/dL

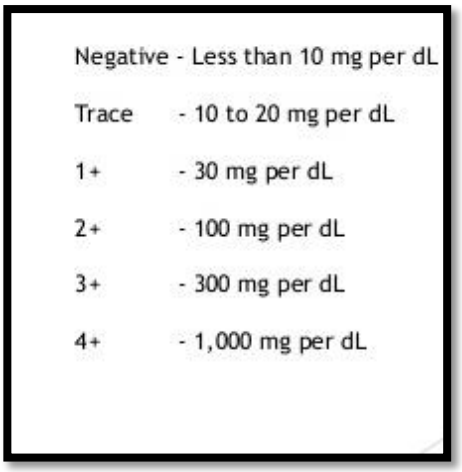



**Figure 8: Results and interpretation of urine dipstick**

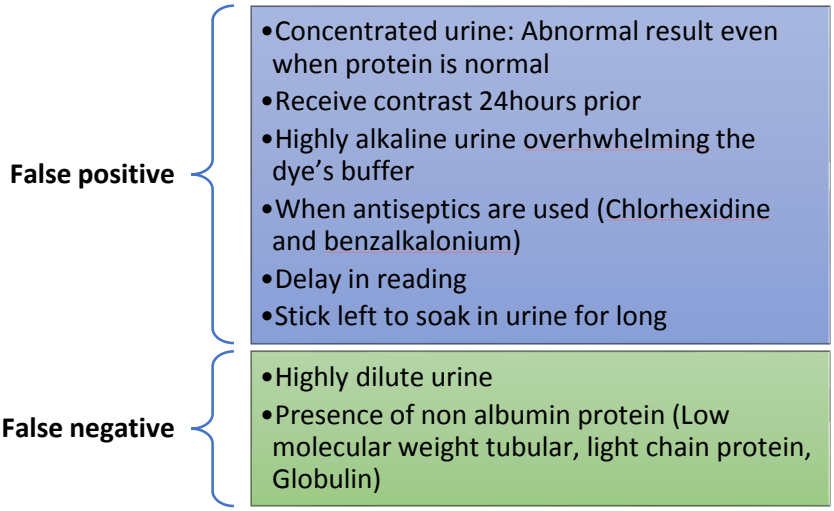



**Figure 9: False positive and false negative for protein on dipstick**

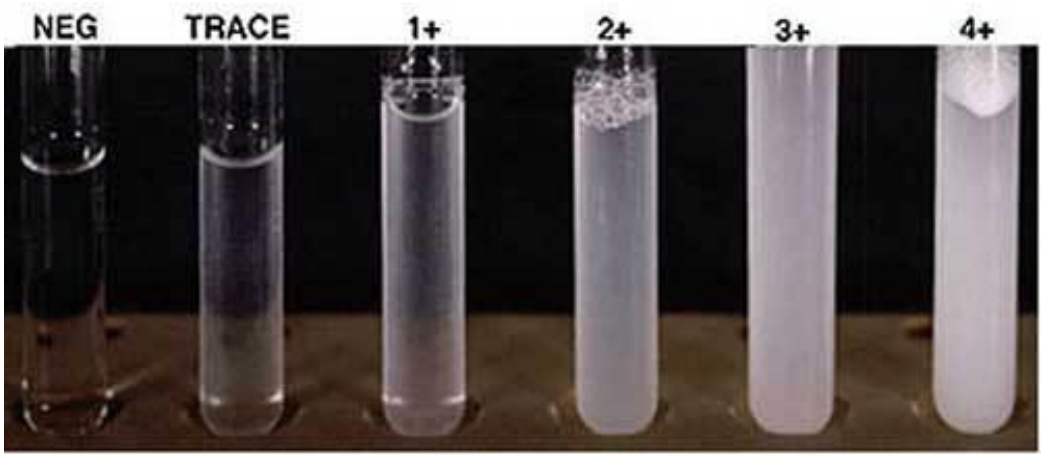
**ii. Sulfosalycilic acid (SSA) test:**

Detects all proteins in urine

Positive SSA and negative dipstick: Suspect non albumin proteins in urine

**Principle**: SSA causes precipitation of proteins

**Procedure**: Mix one part urine supernatant with 3 parts SSA




| Value | Result | Interpretation |
|---|---|---|
| 0 | No turbidity | 0 mg/dL |
| Trace | Slight turbidity | 1 to 10mg/dL |
| 1+ | Turbidity through which print can be read | 15 to 30mg/dL |
| 2+ | White cloud without precipitate through which heavy black lines on a white background can be seen | 40 to 100mg/dL |
| 3+ | White cloud with fine precipitate through which heavy black lines cannot be seen | 150-350mg/dL |
| 4+ | Flocculent precipitate | >500mg/dL |

**Figure 10: Sulfosalicylic acid test result and interpretation**

**iii. Albumin sensitive tests**

Albustix. Can detect albumin concentration as low as 30mg/day (std dipstick:300mg/day).Used to screen microalbuminuria.

- **Quantitative methods**

**i. 24 hour urine protein excretion:**

Gold standard method to quantify proteinuria. Proteinuria assessed by various methods as follows

- ✓ Chemical assay (Biuret reaction or Folin Lowry reaction)
- ✓ Turbidimetric technique (tricholoroacetic acid, ammonium chloride)
- ✓ Dye binding technique (ponceau S, Pyrogallol red)

Subject to error due to over or under collection. Simple and definitive handwritten instructions can help to reduce this error.

**ii. Spot Urine Protein To Creatinine Ratio:**

Obtained by ratio between the urine protein and creatinine excretion. Expressed as mg/mmol or mg/mg. Concentration of creatinine serves as an internal control for urine dilution. This internal control is needed as degree of urinary dilution will directly affect protein concentration.

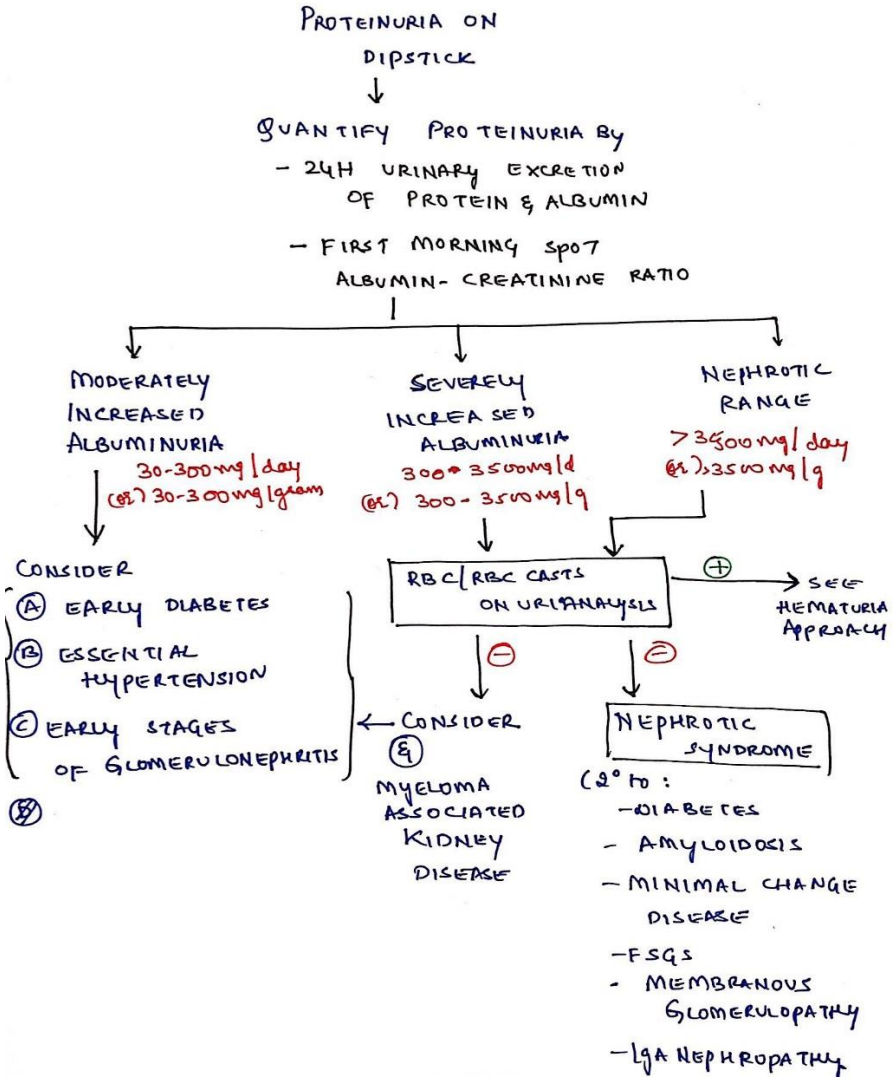
PCR hence is independent of Urine concentration Accuracy decreased in a muscular man (underestimates) or cachetic man (Overestimates). Timing of the sample also has an effect on urine protein excretion, but little effect on creatinine excretion. Best estimates obtained with morning samples but not first void [12].

Spot urine protein creatinine ratio correlates well with 24 hour urine protein values in a wide range of cases[13]. This correlation is not seen when there is high level of protein excretion[14,15] and in cases of lupus nephritis[16]

**iii. Albumin creatinine ratio**

Used to screen and monitor diabetic patients. False negative results can occur as a result of variable amounts of albumin present in urine. An elevated PCR with a negative ACR should raise the suspicion of non albumin proteinuria (Eg: Myeloma)[17]

**Figure 11: Approach to proteinuria**[18]



**b. Ketones**

Ketone dipstick tests for aceto acetic acid using the nitroprusside reaction. It does not test for beta hydorxybutyrate and acetone.

**Causes of ketonuria**:

Fasting

Vomiting

Strenuous exercise

Diabetic Ketoacidosis

Negative urine for ketones does not rule out ketosis

A study was done to check the efficacy of point of care betahydorxybutyrate capillary assay versus urinary dipstick for detection of ketoacidosis and the former was found to be more sensitive in picking up the cases of DKA[19]

**d. Bile salts and bile pigments**

Not a routinely done test after the advent of liver function test
Hay's sulphur powder test was used for bile salts
Fouchet test for bile pigments.
Ehrlich aldehyde test for urobilinogen
Unconjugated hyperbilirubinemia has increased amounts of urobilinogen and no bile salts and bile pigments in urine (Acholuric jaundice). Conjugated hyperbilirubinemia has reduced urobilinogen and increased bile salts and bile pigments in urine.

**e. Blood**

Urine dipstick detects haemoglobin by measuring the peroxidase activity. Hemoglobin catalyses the oxidation of chromogen to produce a colored product. Myoglobin also shows urine dipstick positivity. The approach to dipstick positive and negative dark urine is discussed in the section under red urine.

**f. Nitrite**

Detects the bacteria that can reduce nitrates to nitrites by nitrate reductase activity. Has low sensitivity but high specificity. Positive with most of the gram negative uropathogenic bacteria. Negative with Staphylococcus albus, Enterococcus and pseudomonas. It can be falsely positive if the diet is rich in nitrates. Urine must incubate in the urinary bladder for atleast four hours to allow adequate nitrate reduction, failing which results can be falsely negative. A study done by Weix and colleagues suggested that a negative urine nitrite test is a possible indicator that a microorganism is resistant to the first and third-generation of cephalosporins. However, Grant et al

concluded that the detection of urine nitrites should not influence the use of first-generation cephalosporins for urinary tract infections.[20]

**g. Leucocyte esterase:**

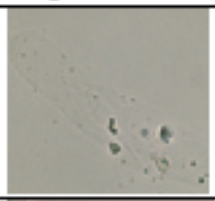
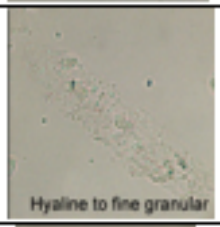
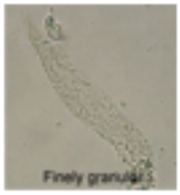
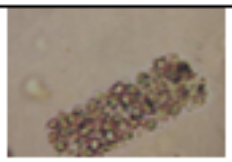
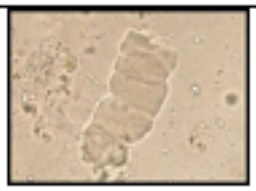
For detection of leucocyturia(25-50cells/ml of urine). Positive with neutrophils, monocytes. Eosinophils and basophils. Negative with lymphocytes. Positive test seen with UTI and interstitial nephritis.
False positive results are seen when formaldehyde used as urine preservative
False negative can be due to high glucose or high protein concentration. In the presence of antibiotics too leucocyte esterase will be falsely negative.

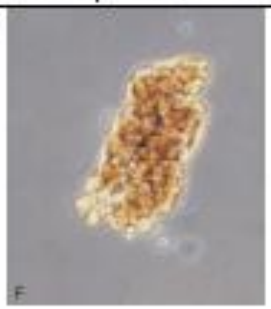
## 4. Microscopy

### a. Casts

Casts are linear tubular structures that form in the renal tubules, usually in the loop of henle, distal tubules or collecting ducts. Presence of casts in urine is called as *Cylinduria* [21]. The scaffolding for these casts is provided by the Tamm-Horsfall mucoprotein. The cells and proteins which leak into the urine get incorporated into the casts. The number of casts may predict the severity of injury

**Table 6 : The major types of casts**

| | Image | Description | Seen in |
|---|---|---|---|
| Hyaline cast |  | Colorless cast<br>Low refractive index | Normal urine (especially when concentrated)<br>Renal disease (along with other casts)<br>Congestive heart failure<br>Diuretic administration |
| Hyaline granular cast |  | Most common mixed casts<br>Variable amounts of granules in a hyaline matrix | Glomerulonephritis<br>Acute Interstitial nephritis |
| Granular cast |  <br>  | Finely granular or coarsely granular<br>Coarse granular: Partially degenerated cells<br>Fine granular: Further cellular degeneration | Markers of ATN<br>Chronic kidney disease |
| Waxy cast |  | Appearance similar to melted wax<br>Formed from disintegrated tubular cells | Renal disease (Acute/Chronic/Rapidly progressive) |
| Fatty casts |  | Contain variable amounts of lipid content<br>Polarisation reveals maltese cross | In glomerular disease associated with marked proteinuria (Eg: Nephrotic syndrome) |
| Broad cast |  | Wider than other varieties | Formed in larger collecting tubules |

| Cast | Image | Description | Seen in |
|---|---|---|---|
| **RBC Cast** |  Arrows indicate RBCs | Fresh RBC casts retain their brown color and consist of readily discernible erythrocytes in a tubular matrix Over the course of time the color is lost | Indicate intraparenchymal bleeding Hallmark of glomerulonephritis. Marker of glomerular bleeding Useful to distinguish between glomerular vs non glomerular source of haematuria |
| **WBC Cast** |  Arrows point to the WBCs | Consist of WBC in a protein matrix | Seen in pyelonephritis, interstitial nephritis, glomerulonephritis. Helpful when AIN is suspected and there is no UTI. |
| **Haemoglobin cast** |  | Brownish hue and coarsely appearing; Can also develop in hemoglobinuria | Same significance as RBC casts |
| **Epithelial cell casts** |  | Contain variable amount of renal tubular epithelial cells | Indicate damage to renal tubular epithelium Found in patients with ATN, Acute interstitial nephritis, Glomerular disease |

Other casts:

- **Myoglobin casts**: Pigmented cylinders with myoglobin providing color. Similar to haemoglobin casts. Seen in urine in patients with Rhabdomyolysis secondary with AKI.
- **Bilirubin casts**: Cylinders pigmented with bilirubin, which can stain any particle contained in the cast. Observed in patients with jaundice associated with increased direct conjugated bilirubin.
- **Mixed casts**: Contain components of different nature, such as granules, cells, and lipids.

**b. Crystals**

Crystal formation in urine depends on many factors like

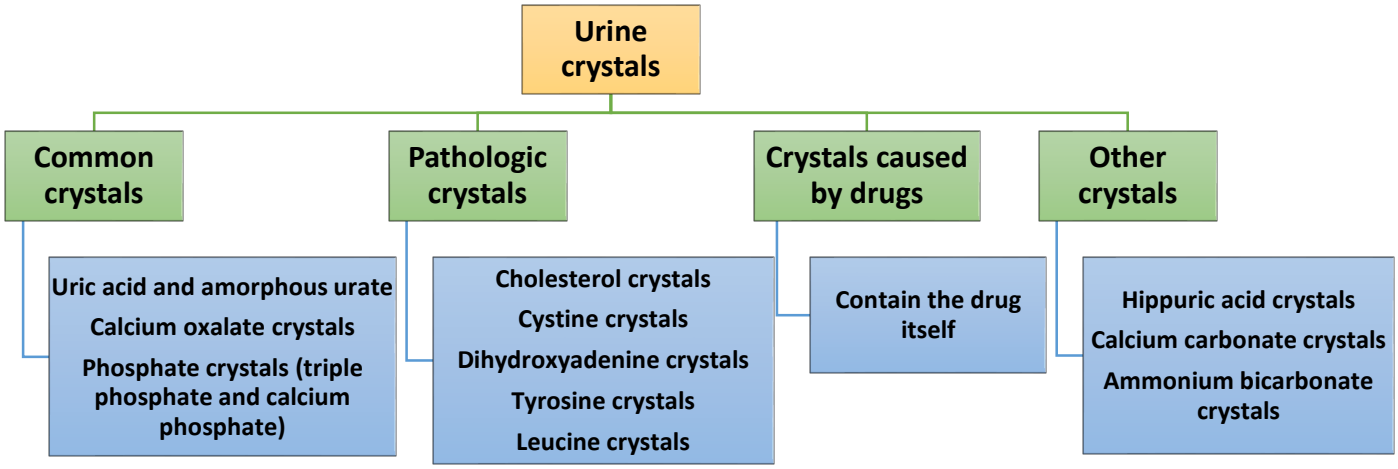
- Presence of inhibitors of crystallisation
- Urine pH: High and low urine pH promote crystallisation
- Concentration of the constituent molecules
- Temperature: Low temperature promotes crystallisation

Crystals are clinically significant when associated with renal failure, like[22]

- Calcium oxalate crystals in ethylene glycol poisoning
- Uric acid crystals in tumor lysis syndrome
- Drug crystals like acyclovir in drug associated renal failure

Examination of urine for crystalluria should be done on urine as close as 37C

Crystals found in urine can be classified as follows



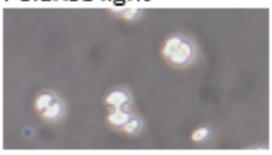
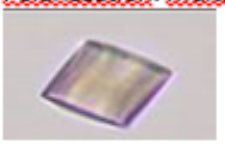
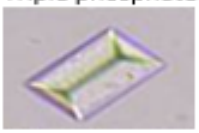

Crystals formed in

- Acidic urine: Calcium oxalate, uric acid, amorphous urate
- Alkaline urine: Calcium phosphate, triple phosphate and amorphous phosphate

❖ **Common crystals**

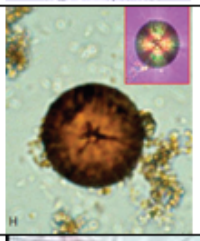
Uric acid, calcium oxalate and calcium phosphate crystals may have no clinical significance and can reflect transient urinary supersaturation. Persistence presence of these crystals requires evaluation.

**Table 7: Common urinary crystals**

| Crystal | Image | Seen in |
|---|---|---|
| **Calcium oxalate Precipitate in acidic urine** | Calcium oxalate dihydrate: Envelope shape<br>Do not polarize the light<br>  <br>Calcium oxalate monohydrate: Dumbell shape<br>Polarise light<br>  | Nephrolithiasis<br>High oxalate diet<br>Metabolic defects<br>High dose vitamin C<br>Ethylene glycol poisoning |
| **Uric acid Precipitate in acidic urine** | Flat diamond or rhomboidal<br>Wide spectrum of appearance, Rhomboid being most common<br>Polariazation: Multiocolor birefringence<br>  <br>Amorphous urates: Similar to amorphous phosphates | Nephrolithiasis<br>Hyperuricosuria<br>Tumor lysis syndrome |
| **Phosphate crystals Precipitate in alkaline urine** | Triple phosphate: Coffin lids<br>  <br>Calcium phosphate: Needles or stars<br>Also called brushite crystals<br>Pleomorphic<br>  <br>Amorphous phosphate: Fine granular clumps | |

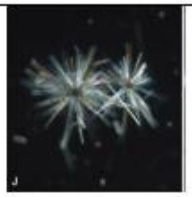
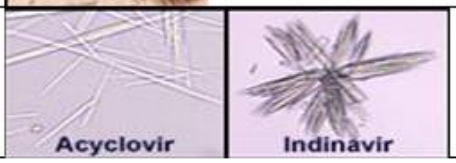
❖ **Pathological crystals**

**Table 8: Pathological crystals found in urine**

| Pathological crystal | Image |
|---|---|
| **Cholesterol crystals**<br>Thin transparent plates, often clumped together with sharp edges |  |
| **Cystine crystals**<br>Seen in cystinuria patients. Irregular and heaped on one another |  |
| **Dihydroxyadenine crystals**<br>Central umbilicus with a birefringent cross appearance under polarised light. Marker of homozygotic enzyme deficiency: Adenine phosphoribosyl transferase |  |
| **Tyrosine crystals**<br>Seen in acute liver disease and tyrosinemia |  |
| **Leucine**<br>Found in acute liver disease |  |

- **Drug induced crystals**
  Most drug induced crystalluria contain the offending drug. In a few drugs like orlistat and vitamin C cause calcium oxalate crystals. Precipitated when there is drug overdose or dehydration or hypoalbuminemia in the setting of favourable urinary pH

**Table 9: Drug induced crystals**

| Drug associated with crystal formation | Image |
|---|---|
| Amoxicillin<br>Resemble branch of broom brush<br><br>Ciprofloxacin<br>Star like crystals |  Amoxicillin  Ciprofloxacin |
| Sulfa drugs |  |
| Acyclovir and Indinavir |  Acyclovir Indinavir |

Tubular damage and obstruction by crystals may cause renal failure. Mere presence of crystals in urine is not indicative of crystal induced renal failure. To consider altering the treatment plan or removing the offending drug, if renal failure present.

**c. Cells**

- **Red blood cells**

Microscopic hematuria is defined 2-5 RBC per high power field in a centrifuged urine sample[18]. Persistent or significant hematuria is defined as <3RBC/HPF on three urinalysis, single urinalysis with >100 RBCs or gross hematuria[18].
RBCs appear as translucent biconcave discs between 4 and 7 µm. RBC in urine can be isomorphic or dysmorphic
**Isomorphic (similar to circulating RBC)**: Associated with a non glomerular hematuria from a genitourinary or external source. Urinary catheterization is also a common cause in admitted patients[23]
**Dysmorphic (showing varying degrees of anisopoikilocytosis):** RBC appear dysmorphic due to changes in urine pH, osmolality or protein concentration. Dysmorphism arises due to passage of RBC through glomerular barrier or tubules. Forms of dysmorphia associated with renal disease are anulocytes, ghost cells, Schizocytes, codocytes and knizocytes. Acanthocytes are an unique form of dysmorphic RBC characterized by round shape with one or two smaller round protrusions, vesicles or blebs attached. Acanthocyturia is particularly useful to identify non diabetic renal disease in diabtetics where hematuria is common[24] Dysmorphic RBCs are seen in hematuria due to glomerular causes[25]. Clinical application is hampered due to a lack of an uniform definition to define dysmorphism.

A reasonable definition of glomerular hematuria is ≥40% dysmorphic RBCs or ≥5% acanthocytes[26]

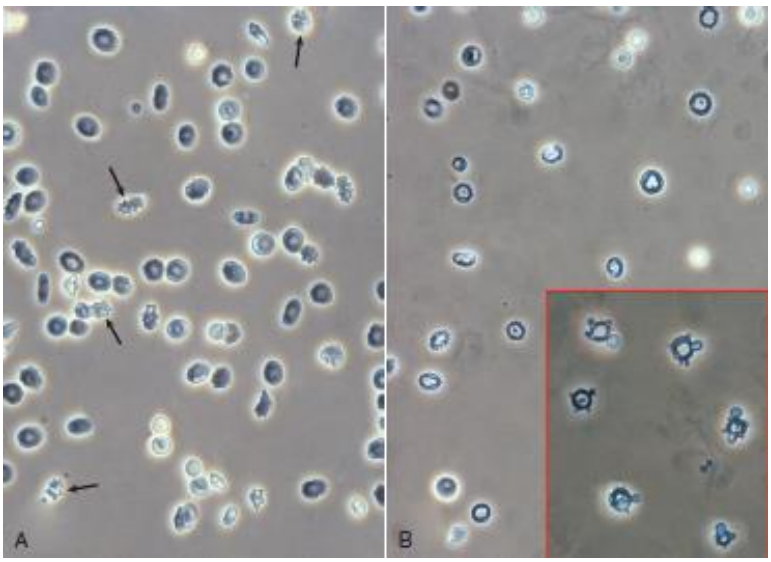



**Figure 12: A: non glomerular hematuria showing isomorphic RBC and arrow pointing to crenated RBC (numerous spiculations or spikes and don't signify any pathology) . B: Glomerular hematuria with dysmorphic RBC and inset showing acanthocytes**

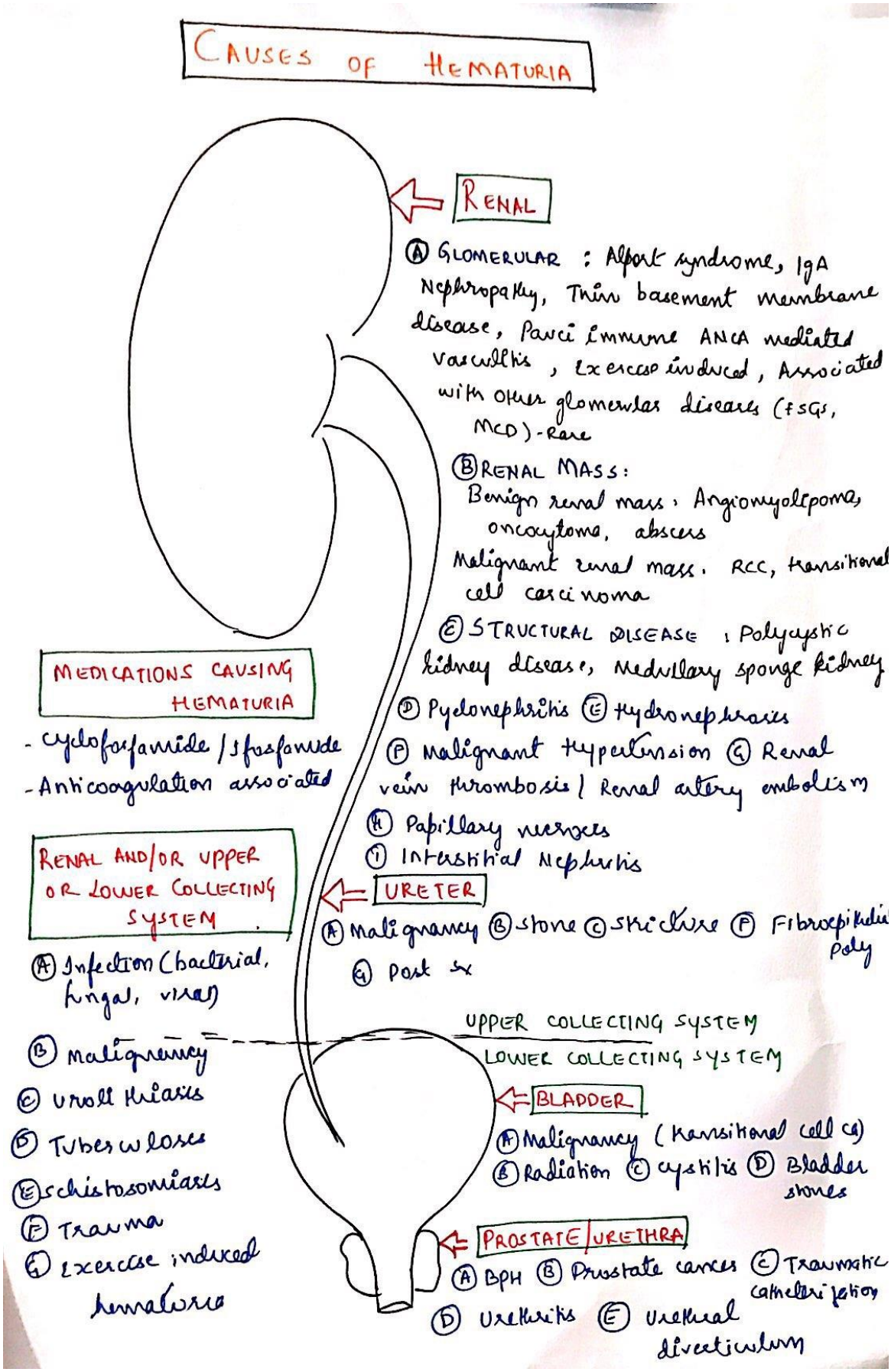
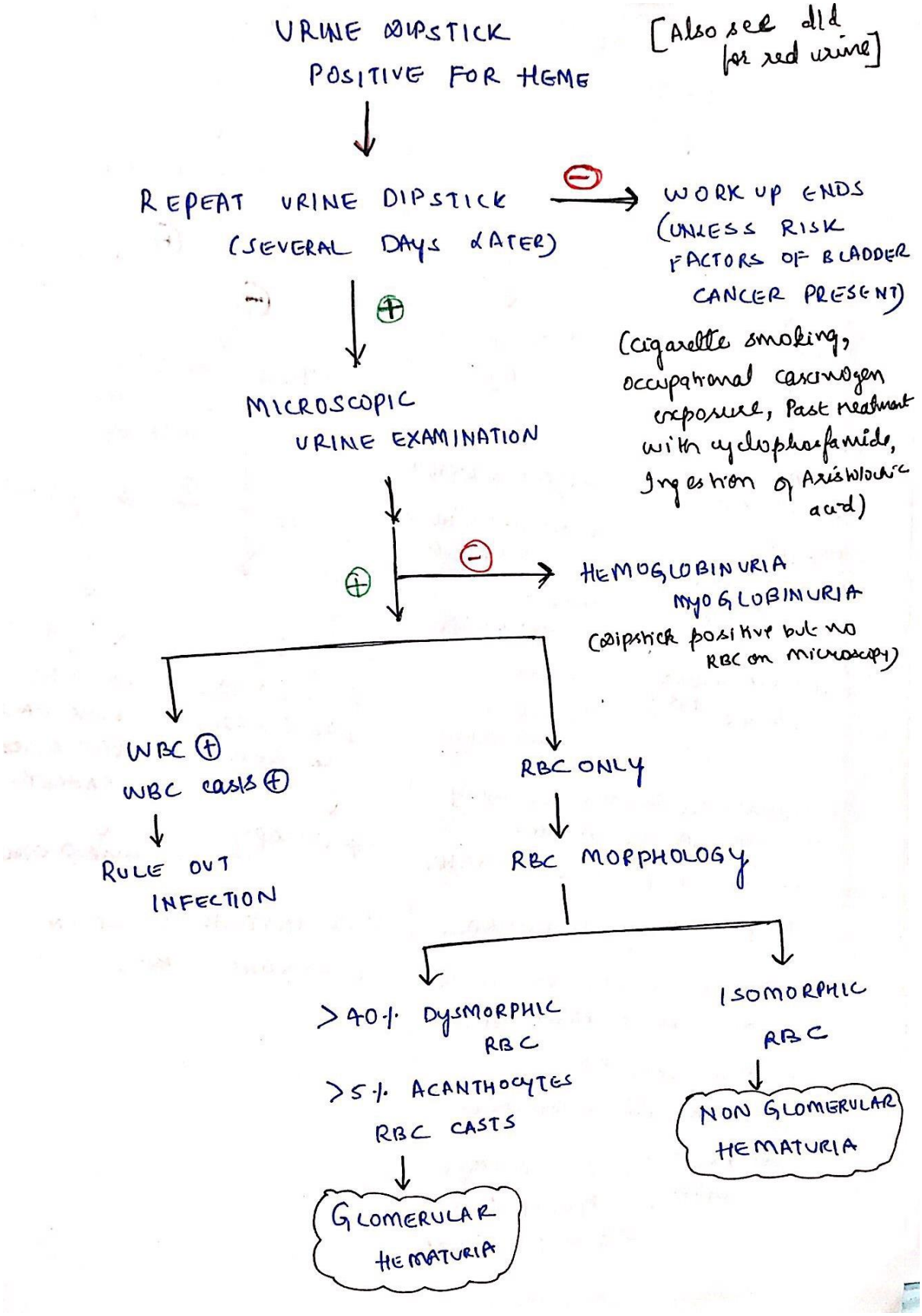



**Figure 13: Causes of hematuria**

| Origin | <50 Yr of Age | ≥50 Yr of Age |
|---|---|---|
| **Glomerular** | IgA nephropathy (increased incidence in Asians) | IgA nephropathy |
| | Thin basement membrane disease (benign familial hematuria) | Hereditary nephritis (Alport's syndrome) |
| | Hereditary nephritis (Alport's syndrome) | Mild focal glomerulonephritis of other causes |
| | Mild focal glomerulonephritis of other causes | |
| **Nonglomerular** | | |
| Upper urinary tract causes | Nephrolithiasis | Nephrolithiasis |
| | Pyelonephritis | Renal-cell cancer |
| | Polycystic kidney disease | Polycystic kidney disease |
| | Medullary sponge kidney | Pyelonephritis |
| | Hypercalciuria, hyperuricosuria, or both, without documented stones | Renal-pelvis or ureteral transitional-cell cancer |
| | Renal trauma | Papillary necrosis |
| | Papillary necrosis | Renal infarction |
| | Ureteral stricture and hydronephrosis | Ureteral stricture and hydronephrosis |
| | Sickle cell trait or disease in blacks | Renal tuberculosis |
| | Renal infarction or arteriovenous malformation | |
| | Renal tuberculosis in endemic areas or in patients with HIV infection | |
| Lower urinary tract causes | Cystitis, prostatitis, and urethritis | Cystitis, prostatitis, and urethritis |
| | Benign bladder and ureteral polyps and tumors | Bladder cancer |
| | Bladder cancer | Prostate cancer |
| | Prostate cancer | Benign bladder and ureteral polyps and tumors |
| | Urethral and meatal strictures | |
| | *Schistosoma haematobium* in North Africans | |
| **Uncertain** | Exercise hematuria | Exercise hematuria |
| | "Benign hematuria" (unexplained microscopic hematuria) | Over-anticoagulation (usually with warfarin) |
| | Over-anticoagulation (usually with warfarin) | |
| | Factitious hematuria (usually presents with gross hematuria) | |

**Table 10: Causes of isolated microscopic hematuria**[27]

**Figure 14a: Approach to a patient with hematuria**



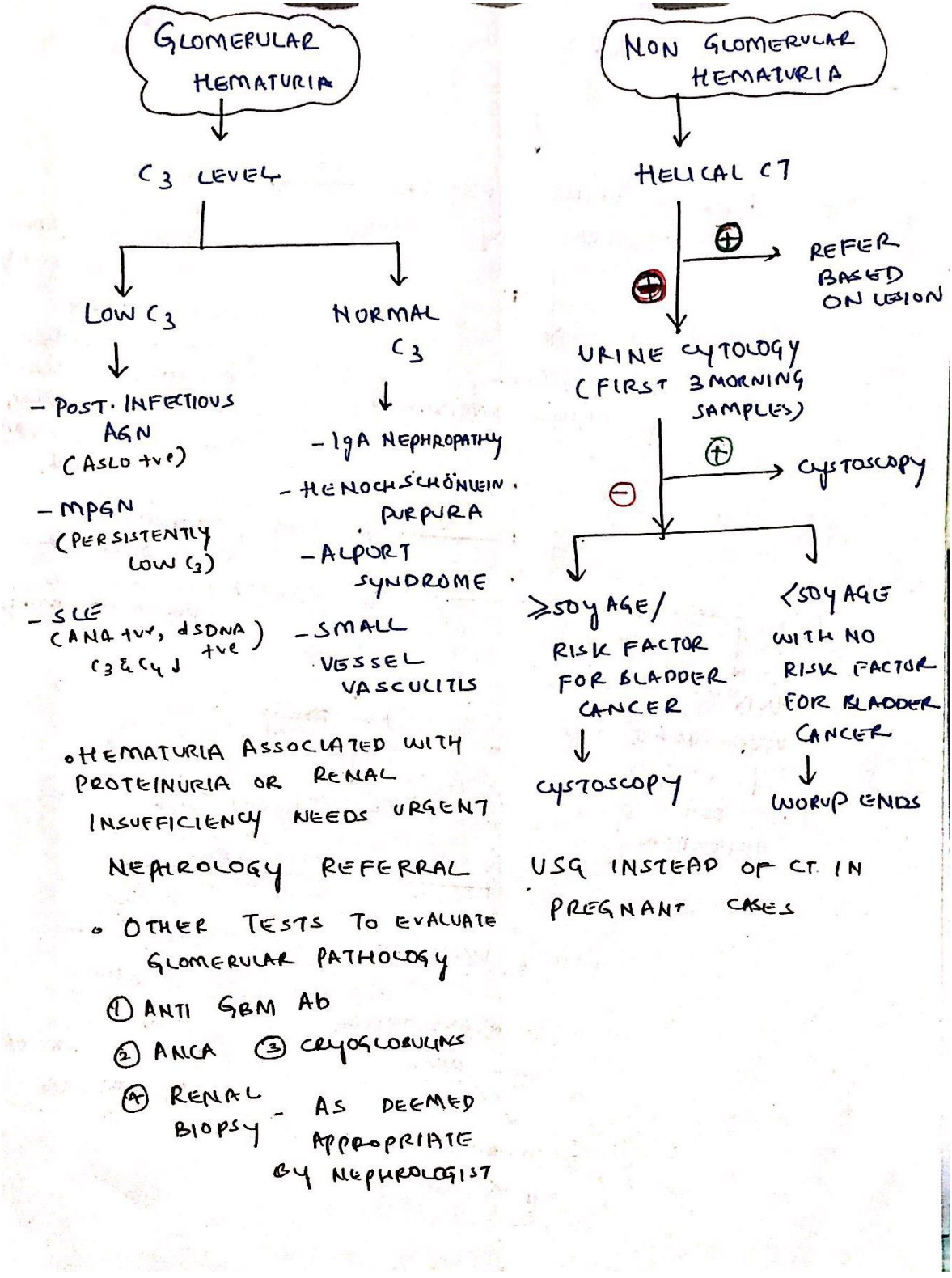



**Figure 14b: Approach to hematuria (Contd.,)**

- **White blood cells**

  Pyuria is defined as the presence of 10 or more white cells percubic millimeter in an uncentrifuged urine specimen, 3 or more white cells per high-power field of unspun urine, a positive result on Gram's staining of an unspun urine specimen, or a urinary dipstick test that is positive for leukocyte esterase[28]. Entire spectrum of WBCs can be seen in urine, but most common ones are neutrophils and eosinophils

  **Neutrophils:**

  Urinary neutrophils are commonly associated with Bacteruria. In the absence of urine culture positivity causes of sterile pyuria should be ruled out. Sterile pyuria is the persistent finding of white cells in the urine in the absence of bacteria, as determined by means of aerobic laboratory techniques (on a 5% sheepblood agar plate and MacConkey agar plate)[29].

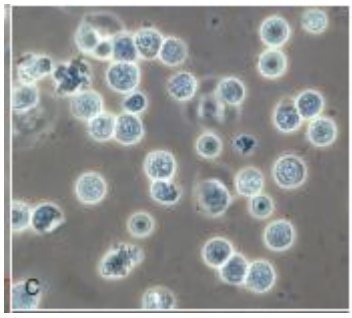
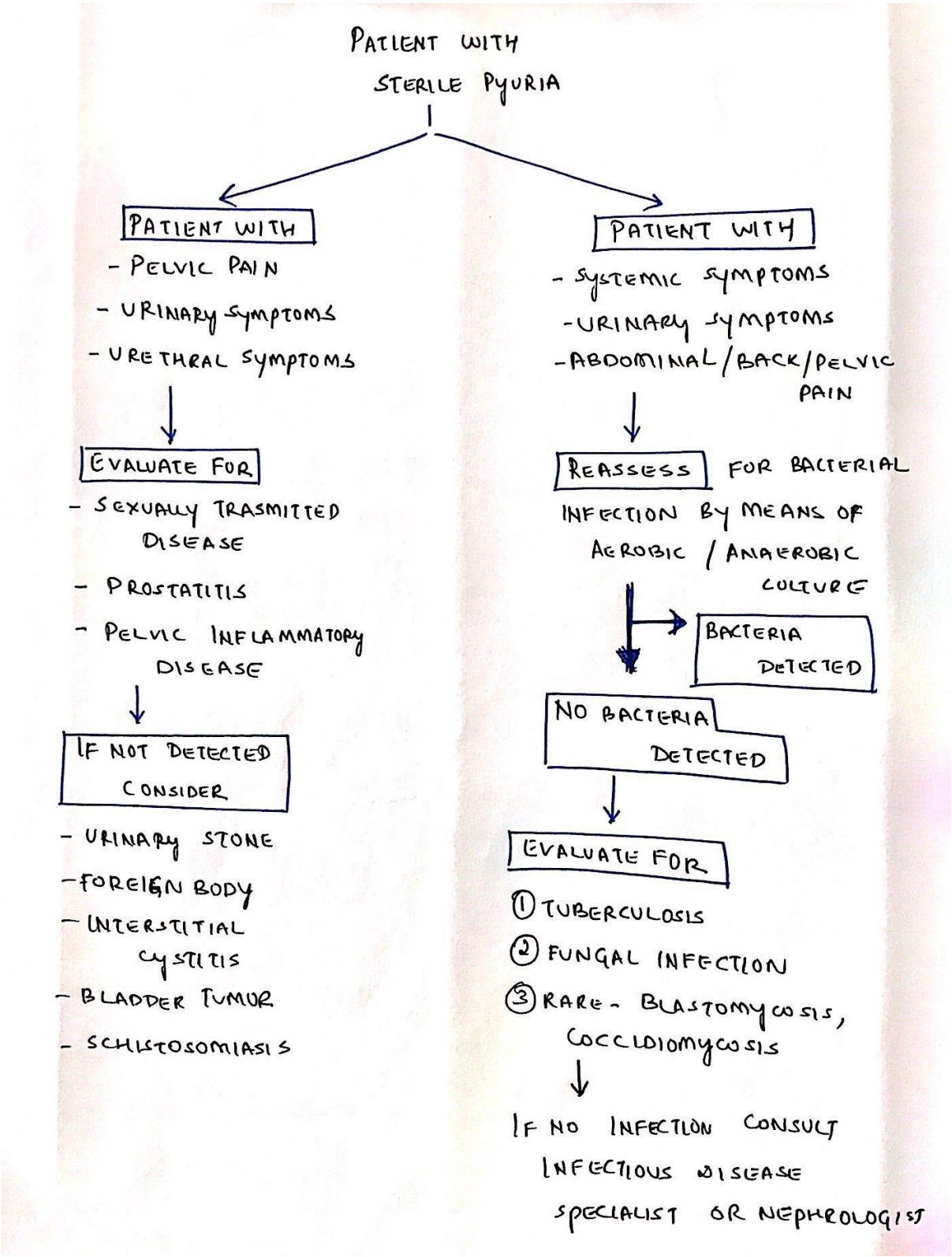


**Figure 15: Urinary neutrophil:** Intermediate size when compared to RBC and renal tubular epithelial cell. Identified by their characteristic granular cytoplasm and multilobed nuclei.

| Infectious causes | Non infectious causes |
|---|---|
| • Renal tuberculosis<br>• Urethritis<br>• Chlamydia balanitis<br>• Ureaplasma infection<br>• Viral infections | • Acute glomerulonephritis<br>• Acute tubulointerstitial nephritis<br>• Bladder tumor<br>• Foreign body<br>• Exercise<br>• Steroid and cyclophosphamide therapy |

**Figure 16: Causes of sterile pyuria**

**Figure 17: Approach to sterile pyuria**[29]



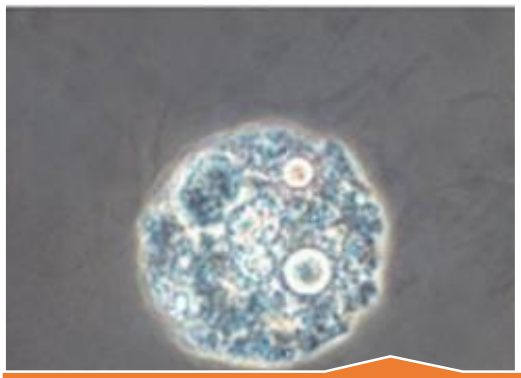
**Eosinophils:**

Detected by Wright's or Hansel stain to urine sediment. Presence of eosinophils in urine is called eosinophiluria, the causes of which are enlisted below[30]

| Causes of eosinophiluria |
| --- |
| • Acute interstitial nephritis<br>• Transplant rejection<br>• Pyelonephritis<br>• Prostatitis and cystitis<br>• Atheroembolic disease<br>• Rapidly progressive glomerulonephritis |

**Figure 18: Causes of eosinophiluria**

**Other WBCs seen in urine**

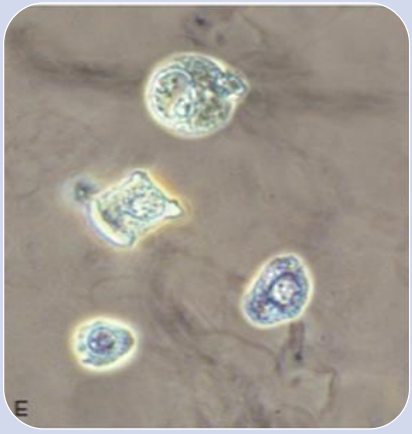


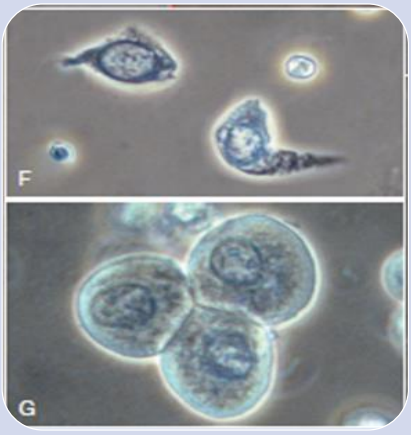
Urinary macrophage:

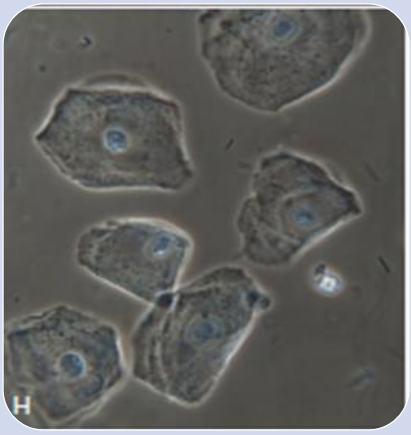
- Large cells ; 15 to >100µm diameter, seen in glomerular diseases or as oval fat bodies containing phagocytosed lipids

Lymphocytes are also seen in urine in a few cases of transplant rejection

**Figure 18: Other cells that can be seen in urine:**




**Renal tubular epithelial cell (RTE)**

11-15µm in diameter

Round or rectangular with a large nucleus

Seen in :

ATN, AIN, Glomerulonephritis

**Urothelial cell**

From the urinary tract lining of the bladder, ureter or renal perlvis

Figure Above: Deep urothelial cell which tend to be smaller with a granular cytoplasm

Figure below: Superficial layer cell which are larger with a clear cytoplasm

Urothelial cells are strongly associated with urologic diseases like Stones, cancer and hydronephrosis

**Squamous epithelial cell**

Large flat cell with a single flat nucleus.

May come from bladder trigone, urethra or genital skin

When observed with bacteria and white cells suspect gential contaminationof the urine

**d. Microrganisms**

Bacteria are a common finding in urine secondary to either non sterile collection techniques or delayed examination. Suspect urine infection only if bacteria seen in non contaminated freshly voided midstream urine sample. Gential contaminants include: Candida, enterobius, Trichomonas.

## 5. Bibiliography


1. Jhonson Richrd J, Feehally John FJ. Comprehensive Clinical Nephrology. 5th ed. Elsevier; 2015. 39-51 p.
2. Ross DG. Urinalysis. Imaging Technol Urol Princ Clin Appl. 2012;9781447124:127–30.
3. Struthers S, Scanlon J, Parker K, Goddard J, Hallett R. Parental reporting of smelly urine and urinary tract infection. Arch Dis Child. 2003;88(3):250–2.
4. Vera M, Molano A, Rodríguez P. Turbid white urine. NDT Plus. 2010;3(1):45–7.
5. LB B. When the urine is red. JAMA [Internet]. 1977 Jun 20;237(25):2753–4. Available from: http://dx.doi.org/10.1001/jama.1977.03270520063032
6. Turner neil, Lameire Robert, Goldsmith David J, Winearls Christopher G. Oxford textbook of clinical nephrology. 4th ed. Oxford university press; 2016. 36-43 p.
7. Perrier ET, Johnson EC, McKenzie AL, Ellis LA, Armstrong LE. Urine colour change as an indicator of change in daily water intake: a quantitative analysis. Eur J Nutr. 2016;55(5):1943–9.
8. De Buys Roessingh AS, Drukker A, Guignard JP. Dipstick measurements of urine specific gravity are unreliable. Arch Dis Child. 2001;85(2):155–7.
9. Voinescu GC, Shoemaker M, Moore H, Khanna R, Nolph KD. The relationship between urine osmolality and specific gravity. Am J Med Sci [Internet]. 2002;323(1):39–42. Available from: http://dx.doi.org/10.1097/00000441-200201000-00007
10. WD D, RF F, GASTON J. Diabetes mellitus and preexisting renal glucosuria. Arch Intern Med [Internet]. 1962 Aug 1;110(2):199–204. Available from: http://dx.doi.org/10.1001/archinte.1962.03620200059011
11. Turner neil, Lameire Robert, Goldsmith David J WCG. Oxford textbook of clinical nephrology. Oxford university press; 2016. 478-483 p.
12. Is W, Evidence THE. Testing for proteinuria. Diabetes Care [Internet]. 2004;9(January 2003):3–7. Available from: http://www3.interscience.wiley.com/cgi-bin/abstract/118802806/ABSTRACT
13. McIntyre NJ, Taal MW. How to measure proteinuria? Curr Opin Nephrol Hypertens. 2008;17(6):600–3.
14. LANE C, BROWN M, DUNSMUIR W, KELLY J, MANGOS G. Can spot urine protein/creatinine ratio replace 24 h urine protein in usual clinical nephrology? Nephrology [Internet]. 2006;11(3):245–9. Available from: https://doi.org/10.1111/j.1440-1797.2006.00564.x
15. Wahbeh A, Ewais M, Elsharif M. Comparison of 24-hour urinary protein and protein-to-creatinine ratio in the assessment of proteinuria. Saudi J Kidney Dis Transplant [Internet]. 2009;20(3):443–7. Available from: http://www.sjkdt.org/article.asp?issn=1319-2442;year=2009;volume=20;issue=3;spage=443;epage=447;aulast=Wahbeh

16. Birmingham DJ, Rovin BH, Shidham G, Nagaraja HN, Zou X, Bissell M, et al. Spot urine protein/creatinine ratios are unreliable estimates of 24 h proteinuria in most systemic lupus erythematosus nephritis flares. Kidney Int. 2007;72(7):865–70.

17. Atkins RC, Briganti EM, Zimmet PZ, Chadban SJ. Association between albuminuria and proteinuria in the general population: The AsuDiab study. Nephrol Dial Transplant. 2003;18(10):2170–4.

18. Jameson JL, Kasper DL, Fauci AS HS. Harrison's Principle of Internal medicine. 20th ed. 2018. 294 p.

19. Arora S, Henderson SO, Long T, Menchine M. Diagnostic accuracy of point-of-care testing for diabetic ketoacidosis at emergency-department triage: β-hydroxybutyrate versus the urine dipstick. Diabetes Care. 2011;34(4):852–4.

20. Medows M, Nijres BM, Elbakoush F, Alali A, Patel R, Mohammad S. Can urinary nitrites or other urinalysis findings be a predictor of bacterial resistance of uncomplicated urinary tract infections? Int J Pediatr Adolesc Med [Internet]. 2016;3(1):12–7. Available from: http://www.sciencedirect.com/science/article/pii/S2352646716000065%5Cnhttp://linkinghub.elsevier.com/retrieve/pii/S2352646716000065

21. Caleffi A, Lippi G. Cylindruria. Clin Chem Lab Med. 2015;53:S1471–7.

22. Frochot V, Daudon M. Clinical value of crystalluria and quantitative morphoconstitutional analysis of urinary calculi. Int J Surg. 2016;36(PD):624–32.

23. Hockberger RS, Schwartz B, Connor J. Hematuria induced by urethral catheterization. Ann Emerg Med [Internet]. 1987 May 1;16(5):550–2.

24. Kohler H, Wandel E, Brunck B. Acanthocyturia - A characteristic marker for glomerular bleeding. Kidney Int. 1991;40(1):115–20.

25. Birch DF, Fairley KF, Whitworth JA, Forbes I, Fairley JK, Cheshire GR, et al. Urinary erythrocyte morphology in the diagnosis of glomerular hematuria. Clin Nephrol [Internet]. 1983 Aug;20(2):78—84.

26. Fogazzi GB, Edefonti A, Garigali G, Giani M, Zolin A, Raimondi S, et al. Urine erythrocyte morphology in patients with microscopic haematuria caused by a glomerulopathy. Pediatr Nephrol. 2008;23(7):1093–100.

27. Parmar M. Microscopic Hematuria - Correspondence. N Engl J Med. 2003;349(13):1292–3.

28. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care–associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control [Internet]. 2008 Jun 1;36(5):309–32.

29. Moore T. Sterile Pyuria. J R Soc Med. 1940;33(9):593–9.

30. Corwin HL, Haber MH. Special Report: The Clinical Significance of Eosinophiluria [Internet]. Vol. 88, American Journal of Clinical Pathology. 1987. 520-522 p.