Urine abnormalities

(Proteinuria & Hematuria)

Assoc. Prof. Suwannee Wisanuyotin

Proteinuria

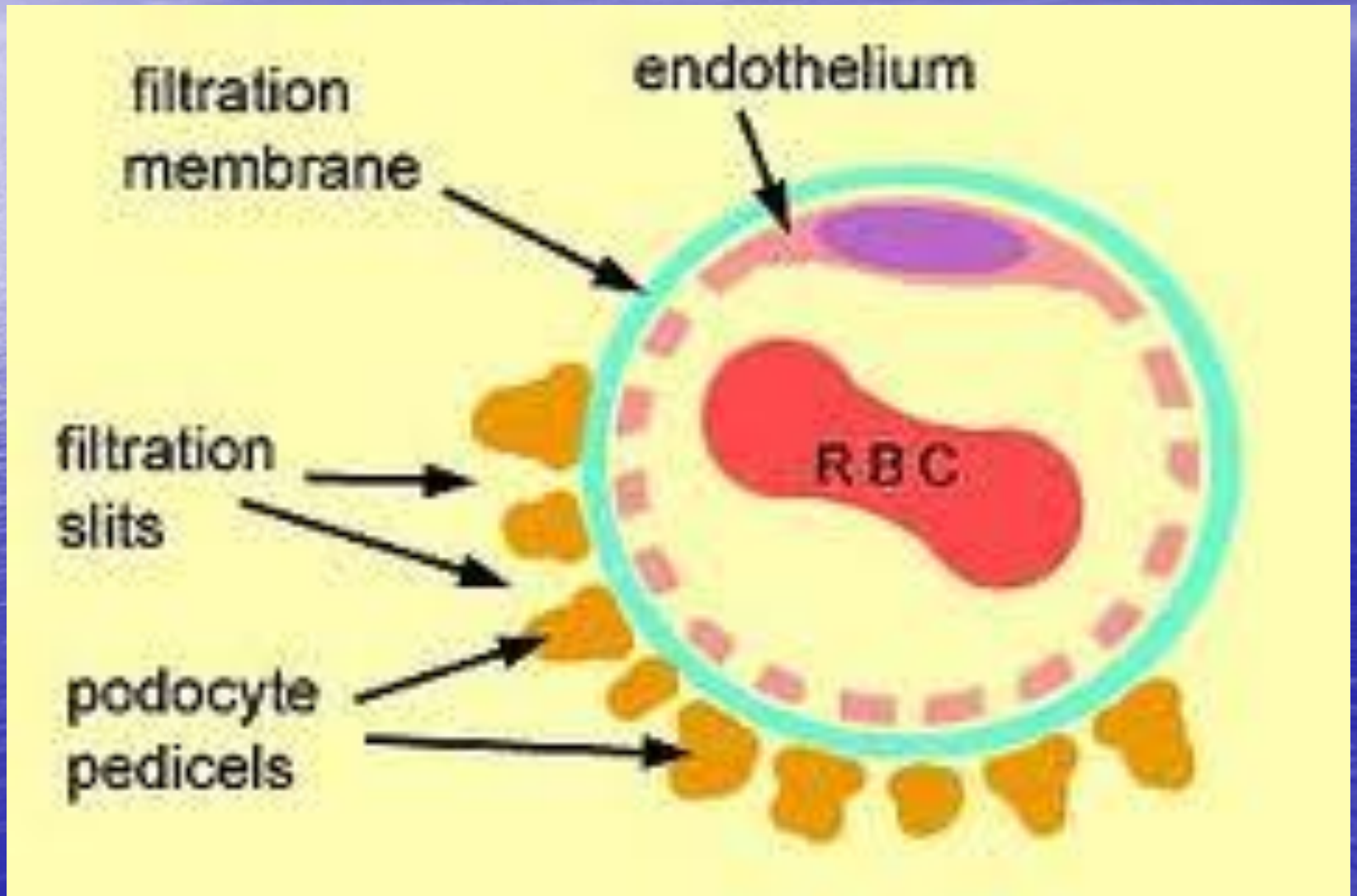
Proteinuria: Objectives

- Pathophysiology
- Type
- Epidemiology
- Method of urine collection
- Definition of significant proteinuria
- Differential diagnosis
- Evaluation

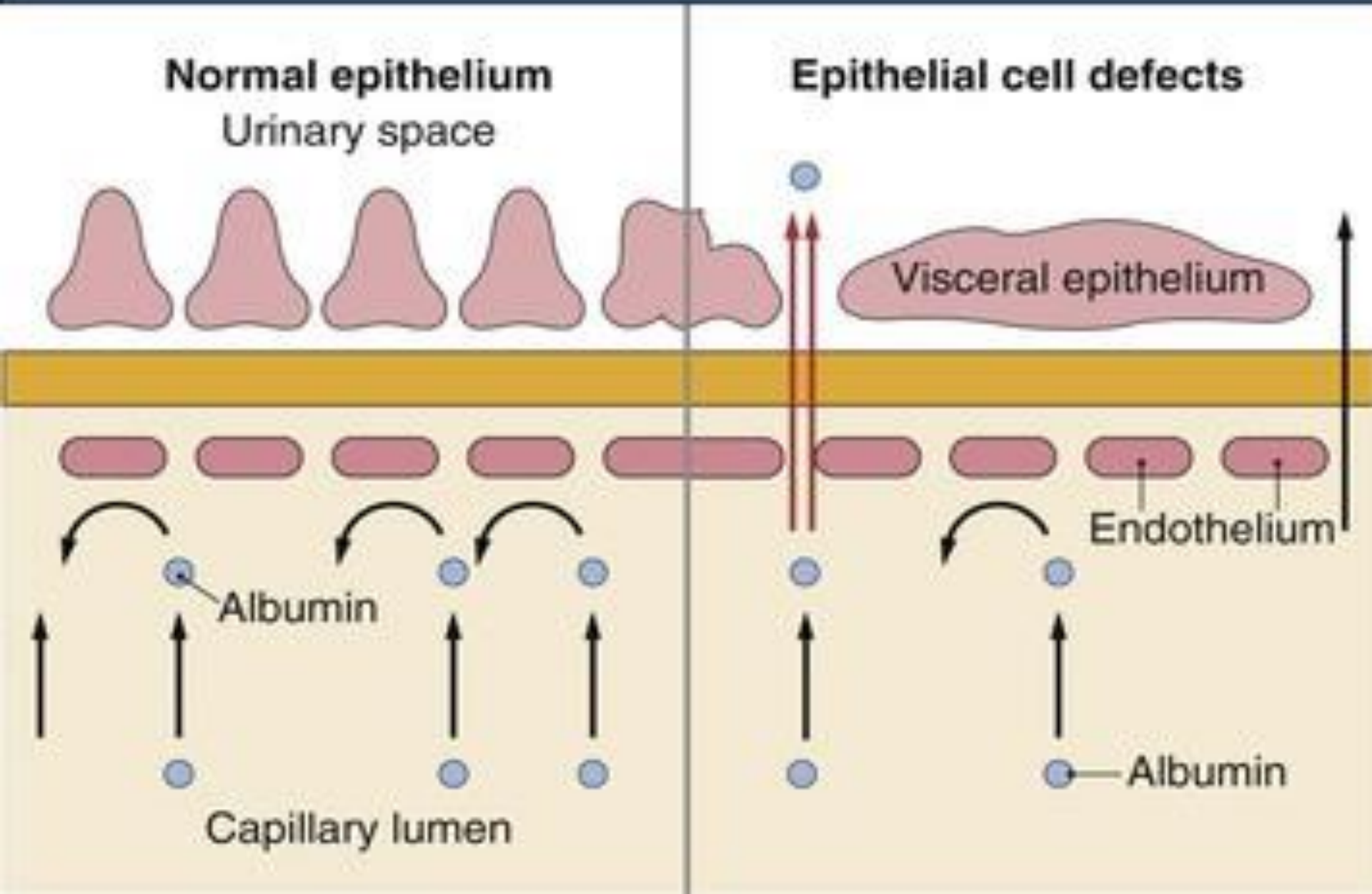
Normal urine protein

- **Type:** Tamm-Horsfall protein (uromodulin) 50%, albumin 40%, LMW protein 10%
- **Amount:** ≤4 mg/m²/hr
  ≤100 mg/m²/d
  <150 mg/d in adults

Normal Glomerular Barrier



Mechanisms of Proteinuria



Pathophysiology

1. ***Glomerular filtration*** (size & charge)
   → Glomerular proteinuria
2. ***Tubular reabsorption*** (proximal convoluted tubules)
3. ***Tubular secretion***

   → Tubular proteinuria

   (Tamm-Horsfall protein)
4. ***Overflow*** (↑ plasma protein)
   → Overflow proteinuria

Type of Proteinuria

defined by:

1. Timing

- Transient
- Orthostatic
- Persistent

2. Site

- Glomerular
- Nonglomerular
  - -Tubular
  - -Overflow

Type of Proteinuria: by time

1.1 Transient Proteinuria

- Fever
- Cold stress
- Exercise
- Seizure
- CHF
- Epinephrine
- Hypovolemia

Type of Proteinuria: by time

1.2. Orthostatic Proteinuria

- Postural proteinuria
- Upright position
- Adolescent male, thin & tall
- < 1 g/d in adults
- Unknown mechanism
  (?glomerular hemodynamics)

Type of Proteinuria: by time

1.3 Persistent Proteinuria

- ≥ 2/3 positive urine protein
- Renal disease
- Severe CHF
- Significance
- Need investigations and management

Type of Proteinuria: by site

2.1 Glomerular Proteinuria

- Large molecules (albumin, Ig, etc.)
- Amount > 500 mg/d in adults
- Associated with hematuria, edema, hypoalbuminemia, hypercholesterolemia, hypertension

Type of Proteinuria: by site

2.2 Non-glomerular proteinuria

2.2.1 Tubular Proteinuria

- Small molecules (β_2 microglobulin, RBP, α_1-microglobulin, etc.)
- Amount < 1 g/d in adults

Type of Proteinuria: by site

2.2 Non-glomerular proteinuria

2.2.2 Overflow Proteinuria

- Hyperproteinemia
- Multiple myeloma

Epidemiology

- No incidence in Thailand
- 5-10% in USA
- Mostly transient
- Only 0.1% of persistent proteinuria

Urine Protein Analysis

1. **Qualitative method**
   - Dipsticks
   - 3% Sulfosalicylic acid
2. **Semiquantitative method**
   - Spot urine protein: Cr ratio
3. **Quantitative method**
   - Timed urine collection
   - Gold standard

Urine protein analysis
1.1 Qualitative method: Dipsticks

- Screening method
- Amino group + tetrabromophenol

  yellow → blue green
- Albumin
- False positive in alkaline urine, pyuria, bacteriuria, hematuria, contamination with vaginal discharge, detergents, radiocontrast agents

Urine protein analysis

1.2 Qualitative method: 3% Sulfosalicylic Acid

- Precipitation of urine protein
- Albumin & LMWP
- False positive in high level of radiocontrast media, sulfonamide, penicillin, cephalosporin in urine

Urine protein analysis

2. Semiquantitative method: Spot Urine Protein/Creatinine

- **Normal value in**
  - ♦ **6 mo – 2 yr : < 0.5**
  - ♦ **> 2 yr : < 0.2**

Urine protein analysis

3. Quantitative method: Timed Urine Collection

- Difficult in young children
- Urine creatinine in
  - ♦ 1 – 12 yr : 20 mg/kg/d
  - ♦ > 12 yr : 22-25 mg/kg/d

Significant Proteinuria

1. *Qualitative method*
   - ≥ 1^+ if sp.gr. < 1.015
   - ≥ 2^+ if sp.gr. > 1.015
2. *Semiquantitative method*
   - ≥ 0.5 if age 6 mo – 2 yr
   - ≥ 0.2 if age > 2 yr
3. *Quantitative method*

Normal	: ≤ 4 mg/m^2/hr
Abnormal	: > 4 mg/m^2/hr
Nephrotic range	: ≥ 40 mg/m^2/hr

Common causes of Persistent proteinuria

- Nephrotic syndrome
- Glomerulonephritis: APSGN, MPGN, SLE
- HSP
- Tubulointerstitial diseases

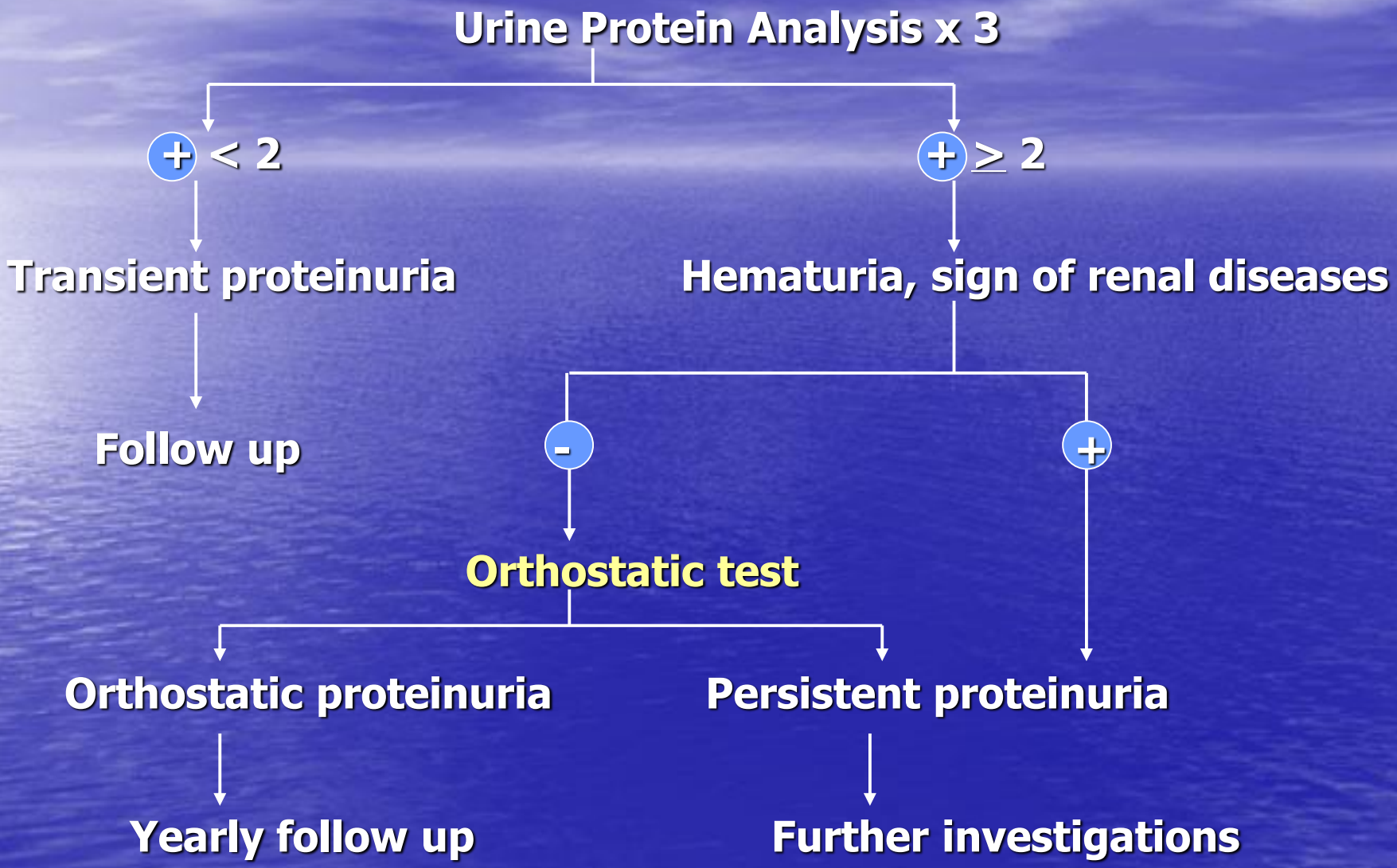
Differential Diagnosis

Dis.	Hx&PE	SCr	SAlb	C_3	UPCR	Others
Orthostatic	<10 yr	N	N	N	≤1.0	-
MCD	2-6 yr edema	N	L	N	>2.0	High cholesterol
FSGS	HTN	N,H	N,L	N	Variable	Hematuria
TI	UTI Polyuria	N,H	N,L	N	≤1.0	-

Differential Diagnosis

Dis.	Hx&PE	SCr	SAlb	C_3	UPCR	Others
APSGN	Nephritis syndrome	N,H	N,L	L	≤1.0	Hematuria High ASO
MPGN	HTN	N,H	N,L	L	Variable	Hematuria
HSP	Purpura Arthralgia	N	N,L	N	Variable	Hematuria
LN	Malar rash Arthalgia Oral ulcer	N,H	N,L	L	Variable	Hematuria ANA+, Anti-dsDNA+

Evaluation


Urine Protein Analysis x 3
+ < 2
+ ≥ 2
Transient proteinuria
Hematuria, sign of renal diseases
Follow up
-
+
Orthostatic test
Orthostatic proteinuria
Persistent proteinuria
Yearly follow up
Further investigations

Hematuria

Hematuria: Objectives

- Definition
- Epidemiology
- Cause
- Evaluation
- Glomerular vs non-glomerular hematuria
- Differential diagnosis

Hematuria

Definition:

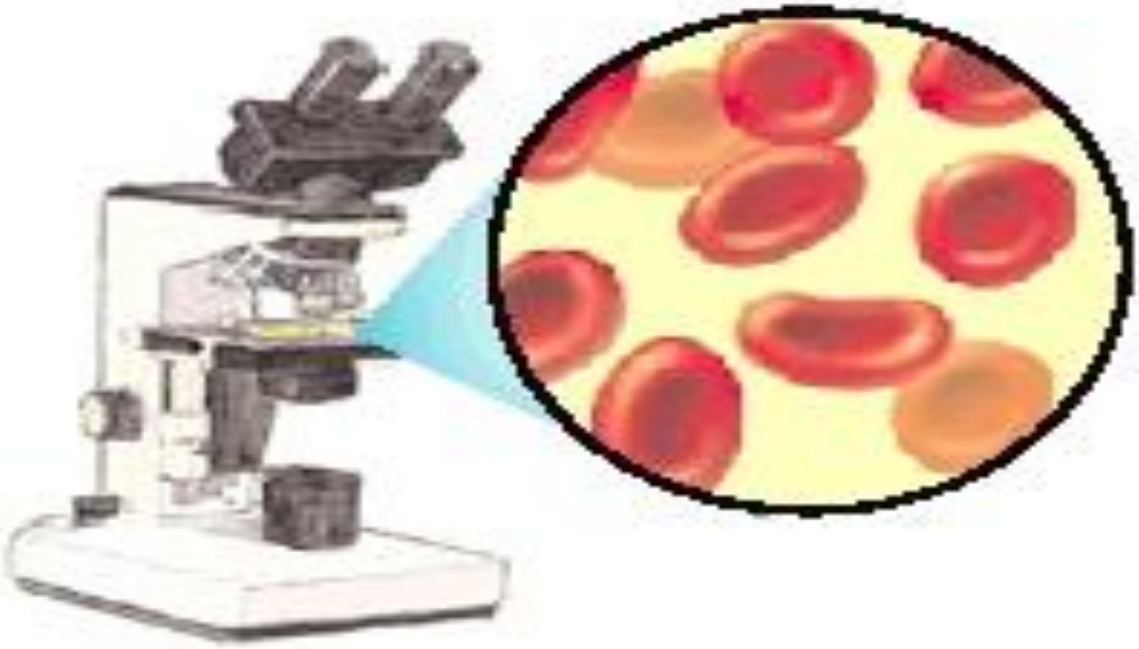
≥ 5 RBC/HPF (spun)

(Repeated)

Type of Hematuria

- **Macroscopic (gross) hematuria**
- **Microscopic hematuria**

Gross hematuria means blood can be seen in the urine.



Microscopic hematuria means blood can be seen only with a microscope.

Epidemiology

- USA:
- Gross hematuria 0.13%
  - most common: cystitis
- Asymptomatic microscopic hematuria : 1%
  - mostly transient
  - if repeated UA: <0.5%

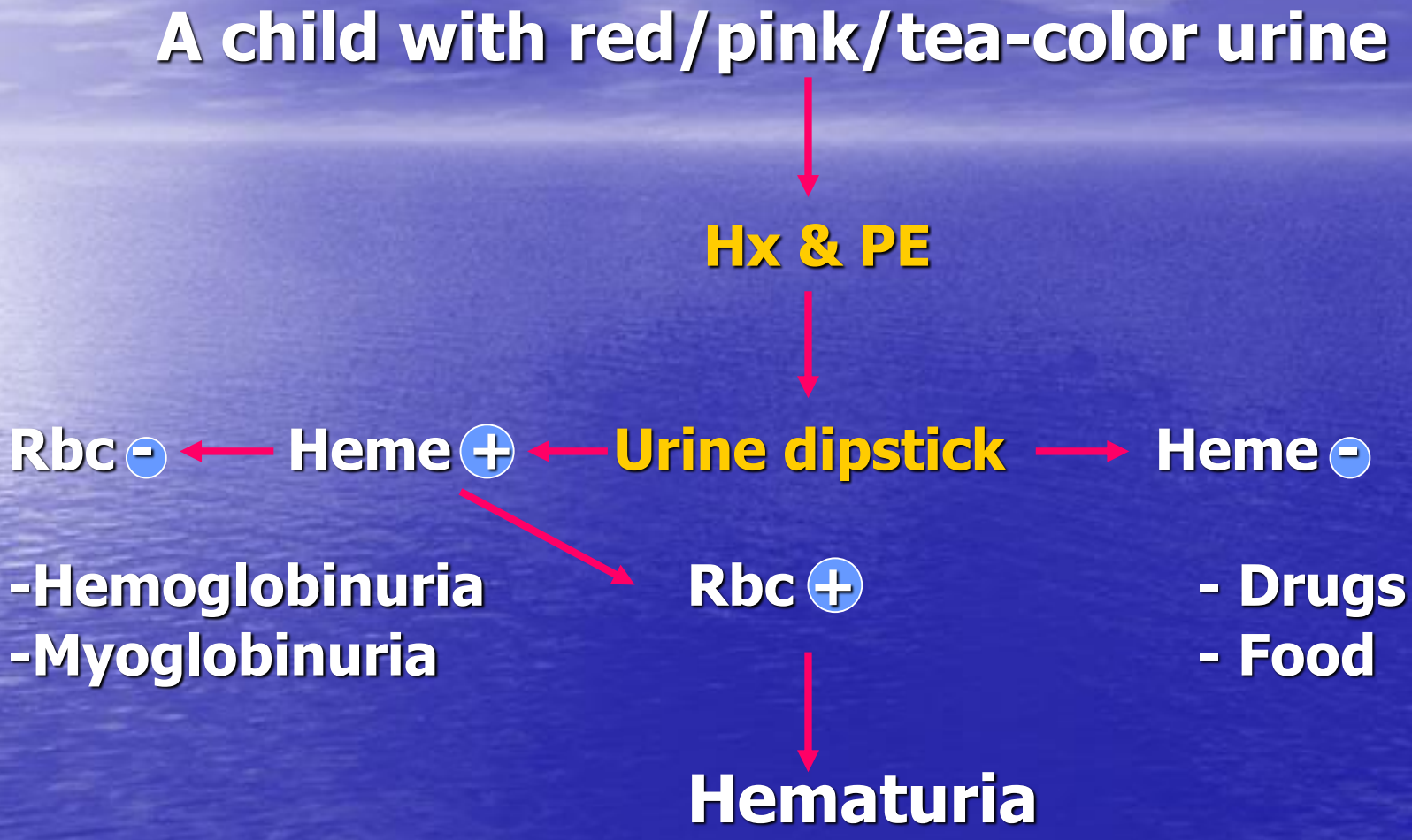
Cause

- Glomerular diseases
- Infection
- Hematologic conditions
- Urolithiasis and hypercalciuria
- Anatomic abnormalities
- Exercise
- Drugs

How to Approach a Child with Urine Discoloration

A child with red/pink/tea-color urine

What should we do ?


A child with red/pink/tea-color urine
Hx & PE
Urine dipstick
Rbc -
Heme +
Heme -
-Hemoglobinuria
-Myoglobinuria
Rbc +
- Drugs
- Food
Hematuria

Urine dipsticks for heme

- **Hydrogen peroxide + Hb or myoglobin + tetramethylbenzidine → blue-green color**
- **False + : alkaline urine (pH>9), contaminate with oxidizing agent**
- **False - : formalin, high concentration of Vit C**

Drugs & Food Caused Urine Discoloration

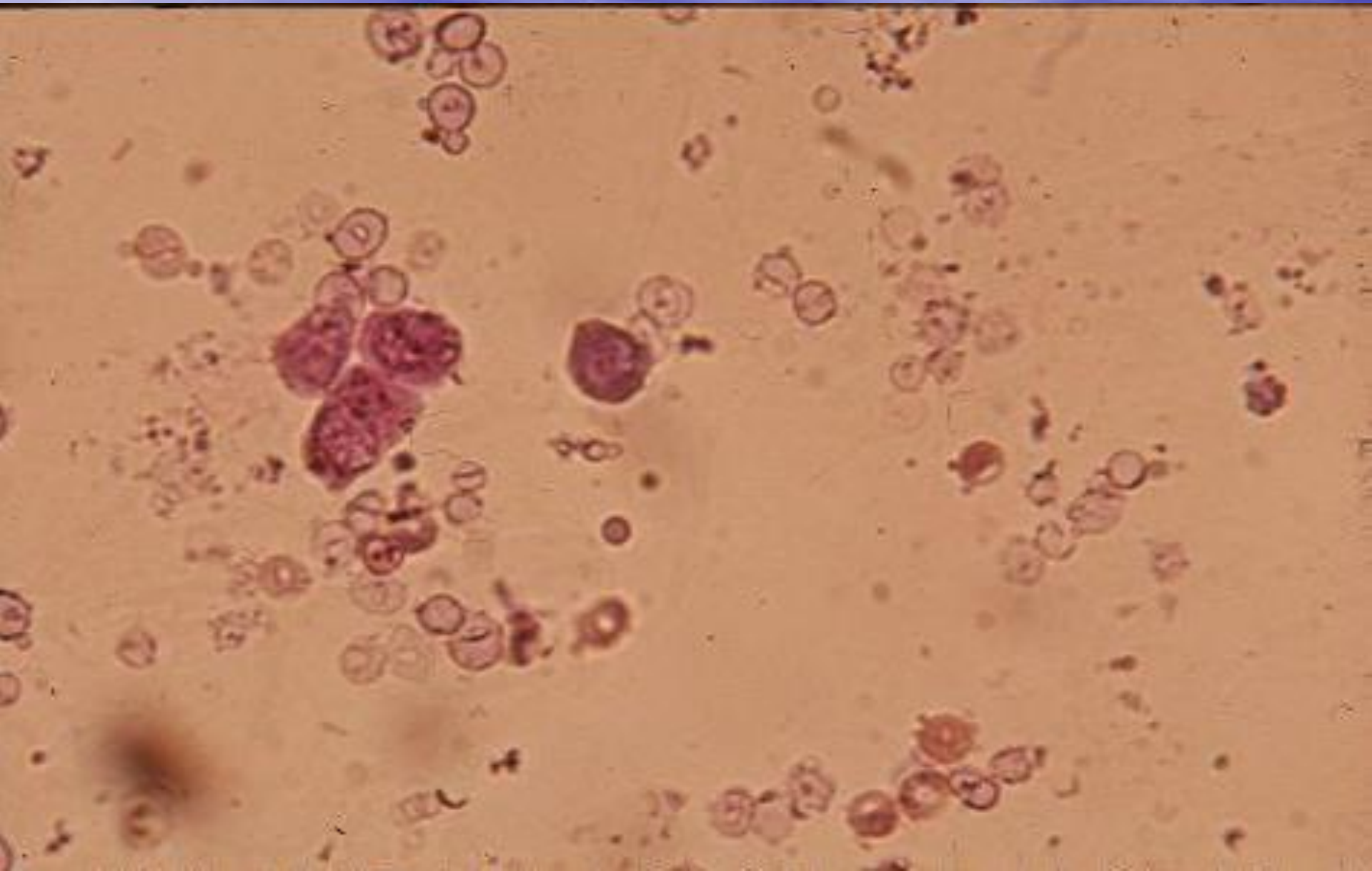
- Beets
- Blackberries
- Food coloring
- Phenolphthalein
- Chloroquin
- Deferoxamine
- Ibuprofen
- Iron sorbitol
- Rifampin
- Doxorubicin
- Nitrofurantoin
- Urate crystal
- Porphyrin
- Methemoglobin
- Homogentisic acid
- Tyrosinosis

Hematuria: Site of Bleeding

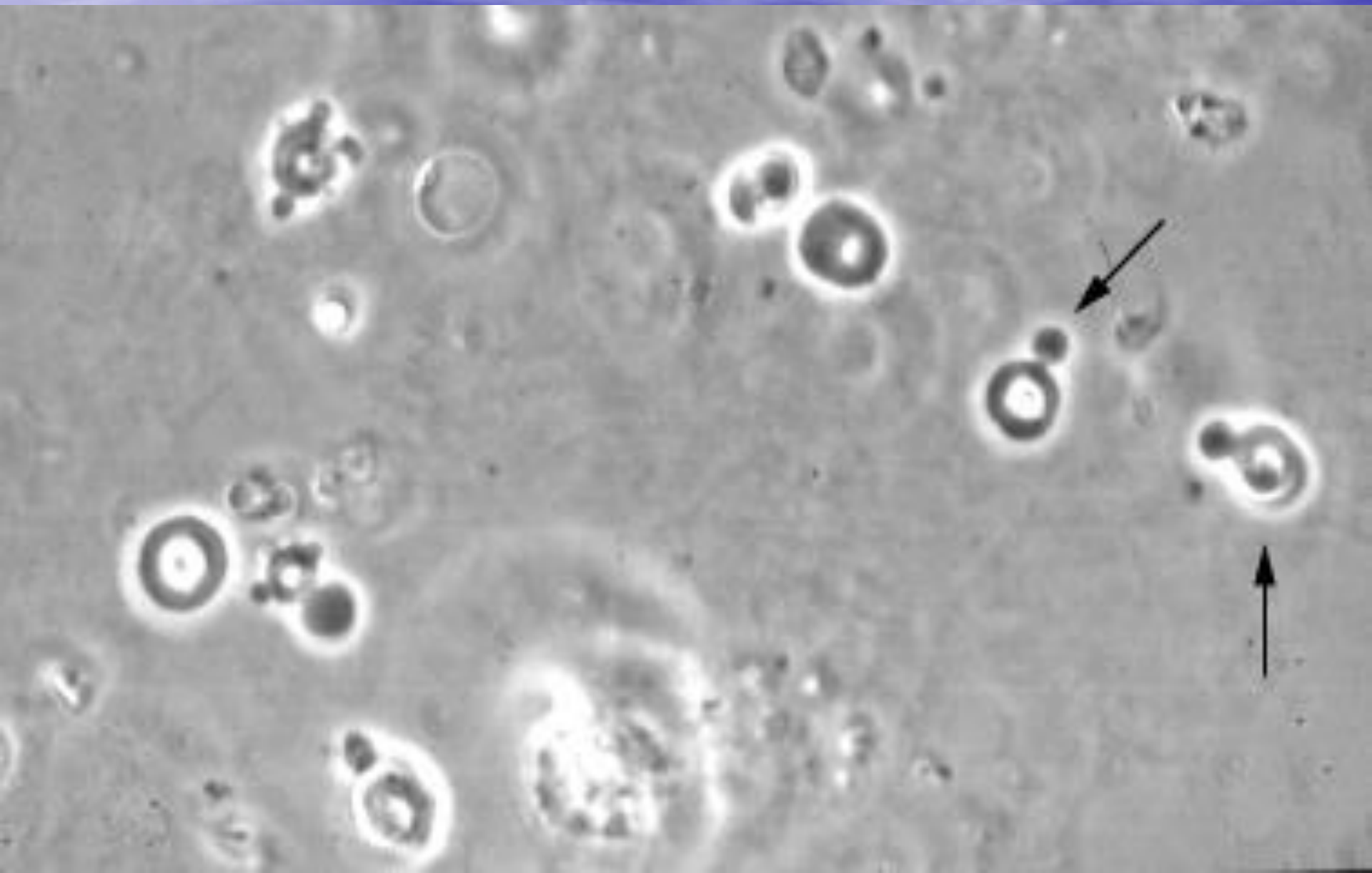
- *Glomerular hematuria*
  - tea or cola color
  - rbc cast, cellular cast
  - proteinuria $\geq$ 2 +, > 500 mg/d (no gross hematuria)
  - dysmorphic rbc > 30%
  - acanthocyte > 5%

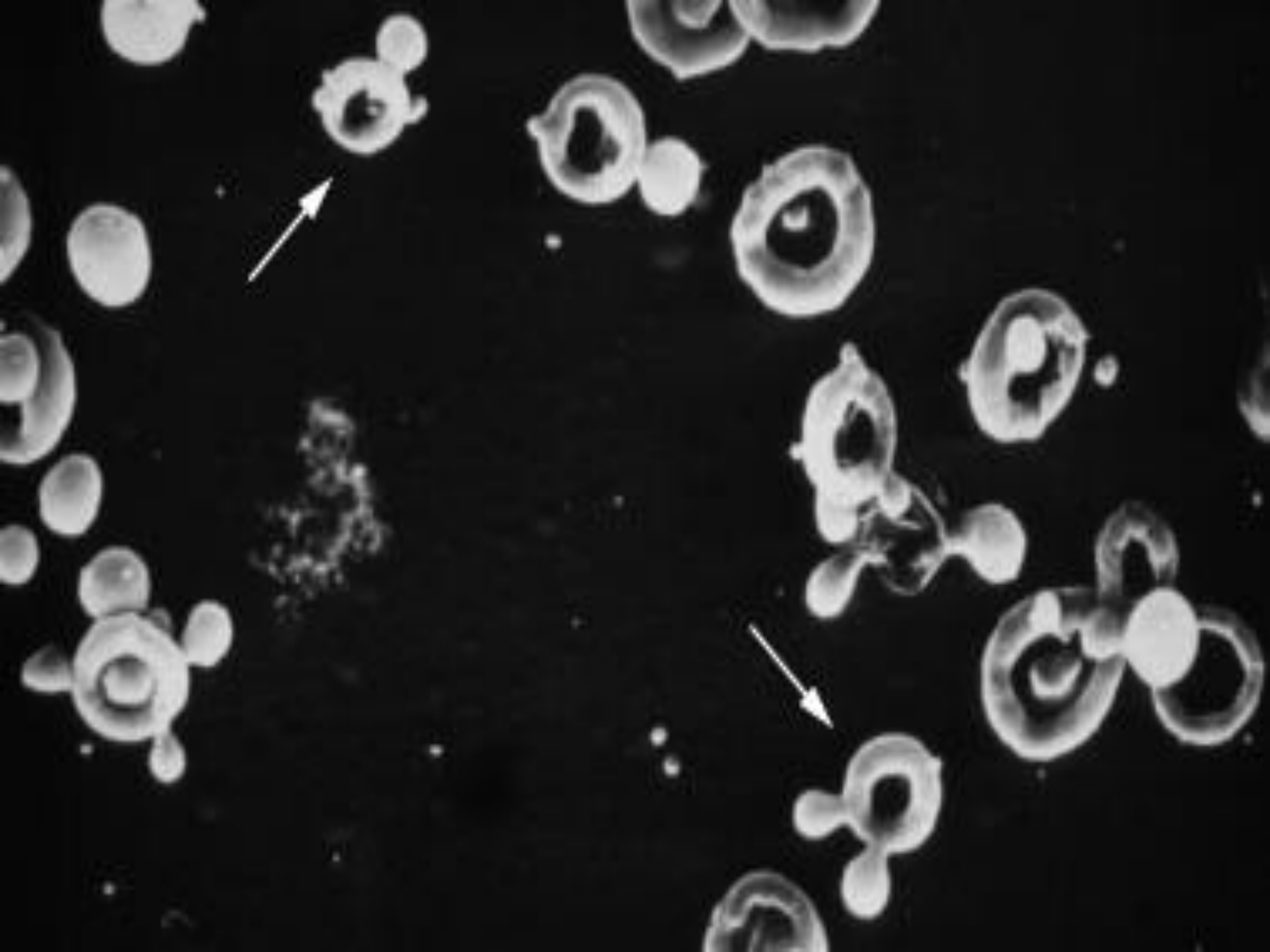
- *Non-glomerular hematuria*
  - pink or red color
  - Initial, terminal hematuria
  - blood clot
  - proteinuria $\leq$ 2+ (no gross hematuria)
  - normal rbc morphology

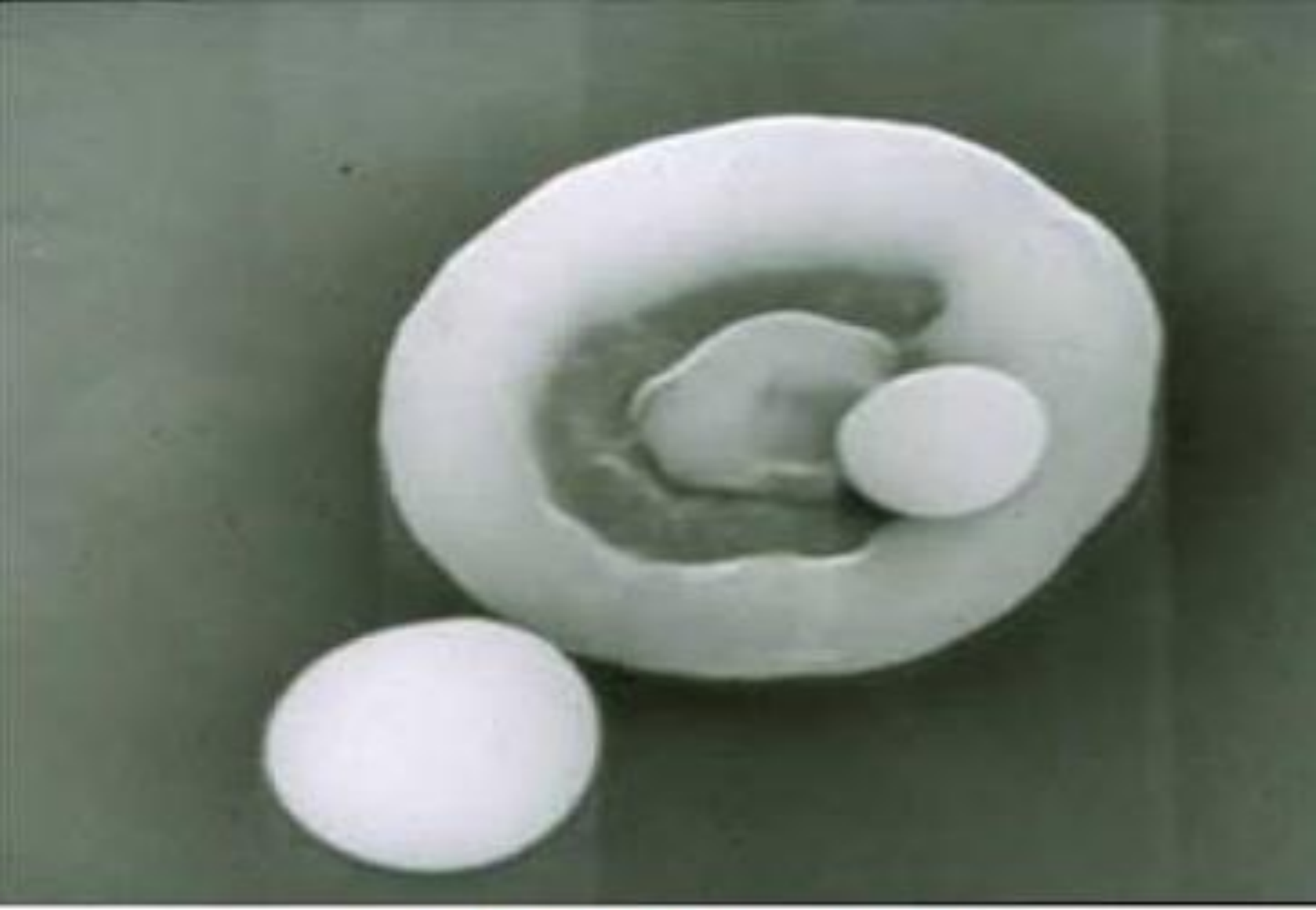
Urine: Microscopic Examination



Dysmorphic Red Cells

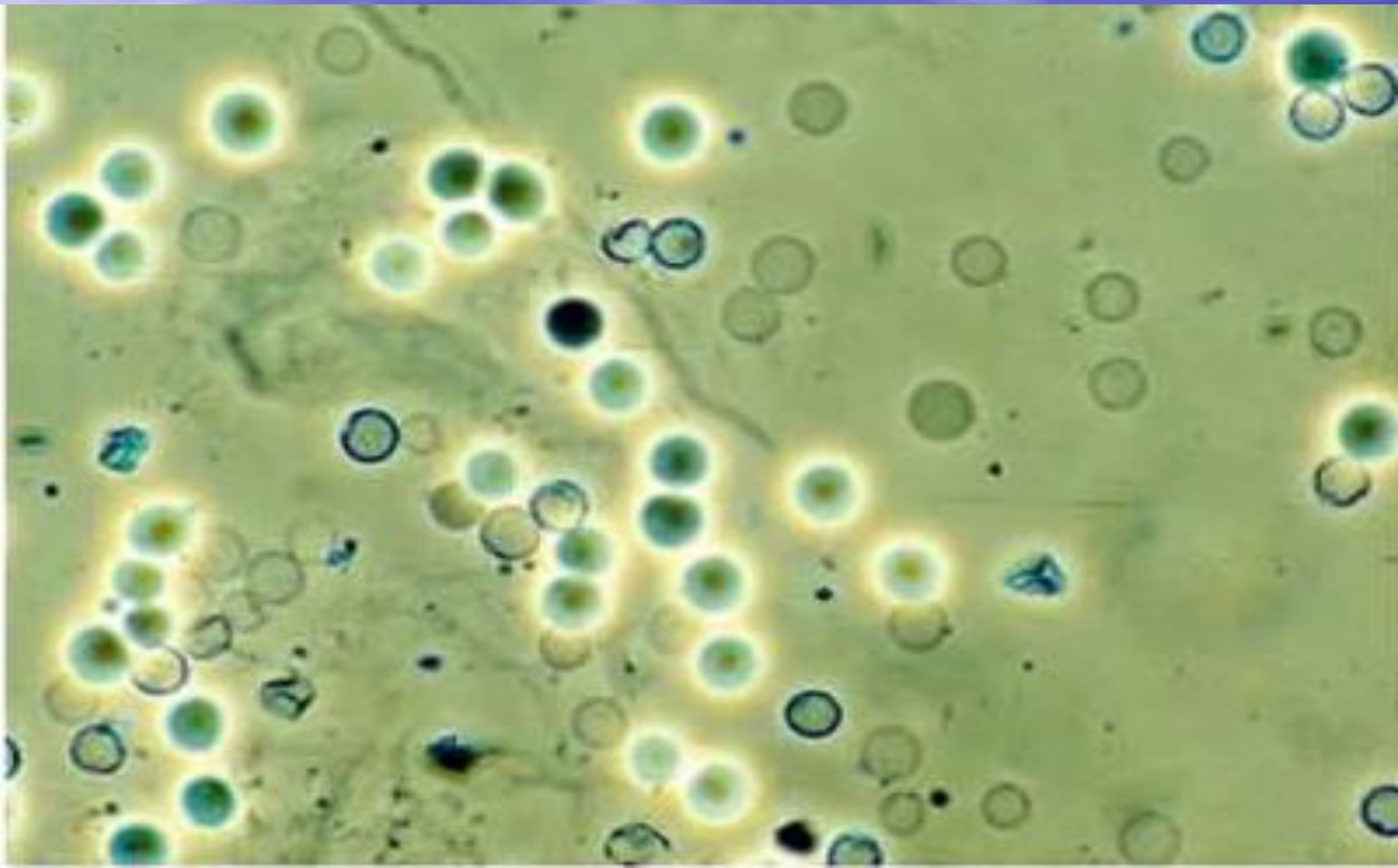


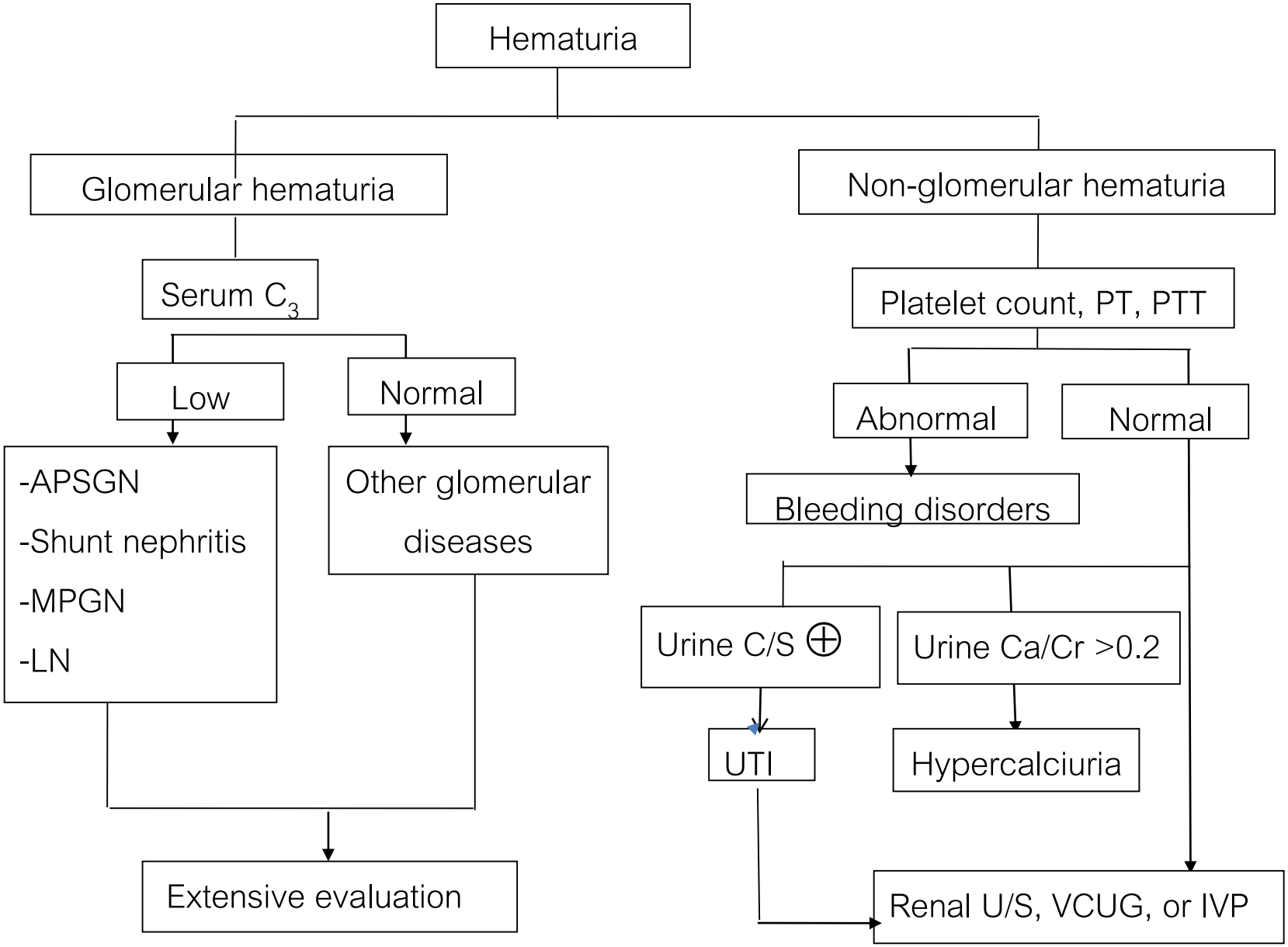




ACANTHOCYTE (SEM)

Normal RBC Morphology in Urine




Hematuria
Glomerular hematuria
Non-glomerular hematuria
Serum C_3
Platelet count, PT, PTT
Low
Normal
Abnormal
Normal
-APSGN
-Shunt nephritis
-MPGN
-LN
Other glomerular diseases
Bleeding disorders
Urine C/S ⊕
Urine Ca/Cr >0.2
UTI
Hypercalciuria
Extensive evaluation
Renal U/S, VCUG, or IVP

Differential Diagnosis

Glomerular diseases

- -APSGN
- -LN
- -MPGN
- -IgA nephropathy
- -HSP
- -HUS
- -Benign familial hematuria
- -Alport syndrome

Differential Diagnosis

Non-glomerular diseases

- -Hypercalciuria
- -Urolithiasis
- -UTI
- -Renal vein thrombosis
- -Polycystic kidney disease
- -Wilm's tumor
- -Hydronephrosis
- -Bleeding disorders

APSGN

Clinical manifestations

- β-hemolytic streptococcus gr.A
- Pharyngitis, pyoderma
- Latent period 1-3 weeks
- Acute nephritis syndrome

Lab

- High ASO titer, anti-DNase B
- Low C_3, normal (or low) C_4

Lupus nephritis

Clinical manifestation

- SLICC criteria

Lab

-ANA, Antids-DNA, Anti-Smith, (LE cell)

-Low C3, C4

-Antiphospholipid Ab (lupus anticoagulant, anticardiolipin, VDRL)

-Renal biopsy (WHO Class I-VI)

MPGN

Clinical manifestation

-Microscopic hematuria

-Acute nephritis syndrome

-NS

-RPGN

Lab

-Low, normal C_3, C_4

-Renal biopsy

IgA nephropathy (Berger nephropathy)

Clinical manifestations

- -M > F
- -Synpharyngitis, diarrhea (1-3 d)
- -Microscopic hematuria
- -Microscopic hematuria & proteinuria
- -Recurrent gross hematuria
- -Acute nephritis syndrome
- -NS
- -Mixed

Lab

- -Normal C_3, C_4
- -Renal biopsy

HSP

Clinical manifestation

- Age < 20 yr at onset
- Palpable purpura
- Bowel angina
- Joint symptoms

Lab

- Normal C_3, C_4
- Skin or renal biopsy

HUS

- Bloody diarrhea
- Shigella dysenteriae, EHEC
- Hematuria
- Triad: thrombocytopenia, MAHA, renal failure

Benign Familial Hematuria (Thin basement membrane disease)

Clinical manifestations

- AD (mostly)
- α-3, α-4 chains of type IV collagen in GBM
- FH of hematuria (mostly microscopic)
- Normal eyes & ears

Lab

- Gene
- EM

Alport Syndrome

Clinical manifestations

- XD (mostly)
- α-5 chain of type IV collagen in GBM
- SNHL
- Anterior lenticonus
- FH of deafness, renal failure esp. in male

Lab

- Monoclonal Ab to α-5 chain
- Gene sequence

Hypercalciuria

Clinical manifestations

-Hematuria (gross, microscopic)

-Dysuria

Lab

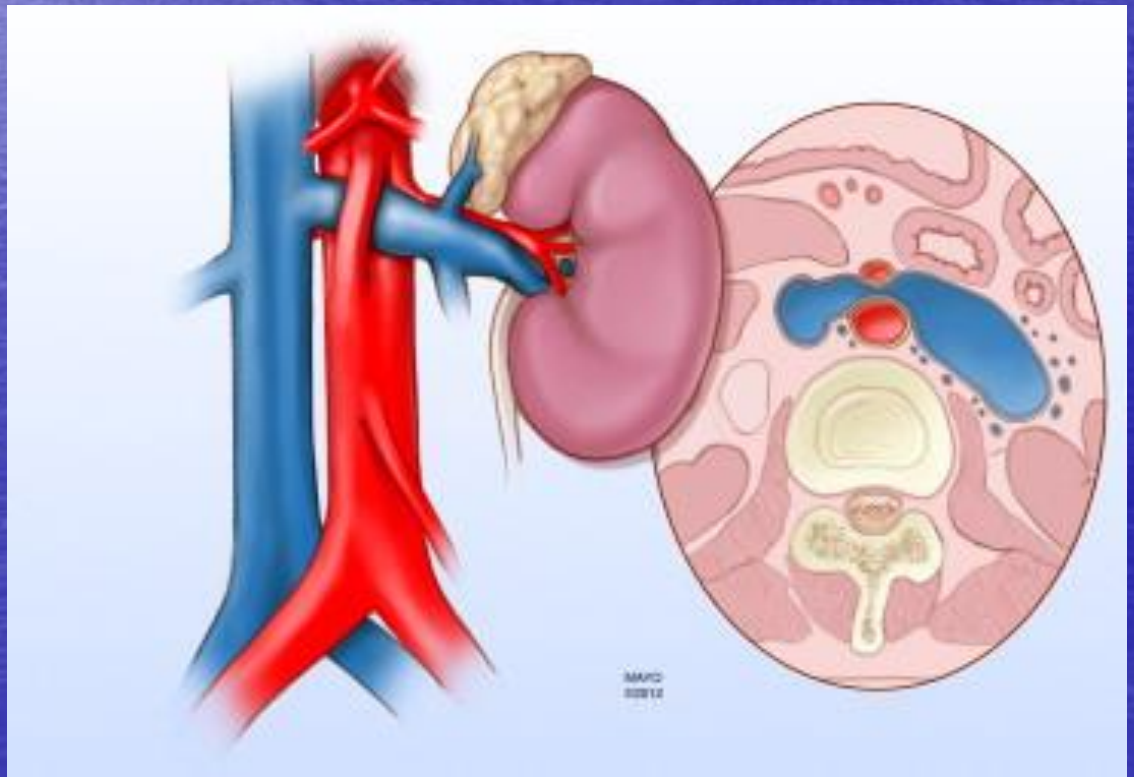
-24-hr urine calcium > 4 mg/kg/d

-Spot Urine Ca:Cr

age	< 7 mo	: > 0.86
	7-18 mo	: > 0.6
	19 mo – 6 yr	: > 0.42
	> 6 yr	: > 0.2

Nutcracker syndrome

- Left renal vein entrapment syndrome
- Hematuria, proteinuria, loin pain/asymptomatic
- Diagnosis: Doppler U/S, CT scan



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