# Etiology and evaluation of hematuria in adults

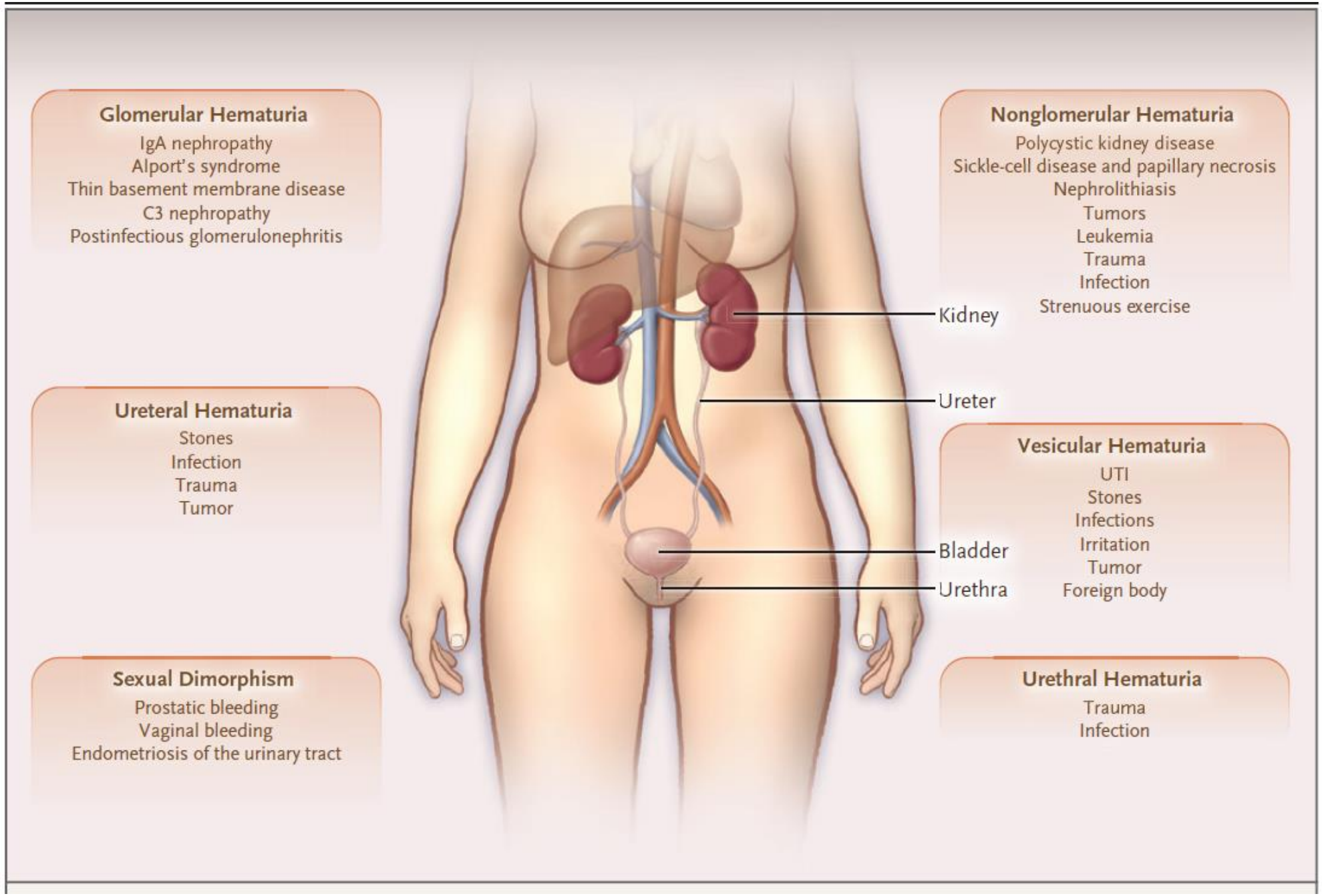
Atefeh Amouzegar, MD
Nephrologist
Firoozgar Hospital, IUMS, Tehran, Iran
20-08-1400

# Introduction

- Hematuria is a condition that frequently presents to the emergency department (ED).
- There are many possible causes both benign and life-threatening.
- A thorough history and physical examination focusing on identifying the possible life-threatening causes often drives the workup.
- Laboratory studies are the mainstay of the diagnostic workup and, sometimes, imaging is warranted.

# Introduction

- The definition of hematuria is the excretion of red blood cells (RBCs) in the urine.
- A problem arising in **the genitourinary tract anywhere from the glomerulus to the urethral meatus can result in RBCs in the urine**.
- Hematuria is defined by the American Urological Association as greater than 3 to 5 RBCs per high-powered field undermicroscopy.
- Hematuria may be visible to the **naked eye** (called **gross hematuria**) or detectable only on examination of the urine sediment by microscopy (called **microscopic hematuria**).


Glomerular Hematuria
IgA nephropathy
Alport's syndrome
Thin basement membrane disease
C3 nephropathy
Postinfectious glomerulonephritis
Nonglomerular Hematuria
Polycystic kidney disease
Sickle-cell disease and papillary necrosis
Nephrolithiasis
Tumors
Leukemia
Trauma
Infection
Strenuous exercise
Kidney
Ureteral Hematuria
Stones
Infection
Trauma
Tumor
Ureter
Vesicular Hematuria
UTI
Stones
Infections
Irritation
Tumor
Foreign body
Bladder
Urethra
Sexual Dimorphism
Prostatic bleeding
Vaginal bleeding
Endometriosis of the urinary tract
Urethral Hematuria
Trauma
Infection

# Gross hematuria

- **Gross hematuria** is suspected because of the presence of red or brown urine.
- The color change does not necessarily reflect the degree of blood loss, since as little as 1 mL of blood per liter of urine can induce a visible color change.
- In addition, the intermittent excretion of red to brown urine can be seen in a variety of clinical conditions other than bleeding into the urinary tract.
- Gross hematuria with passage of **clots** **usually indicates a lower urinary tract source** but can be seen with some forms of intra-renal bleeding (eg, kidney cancer).

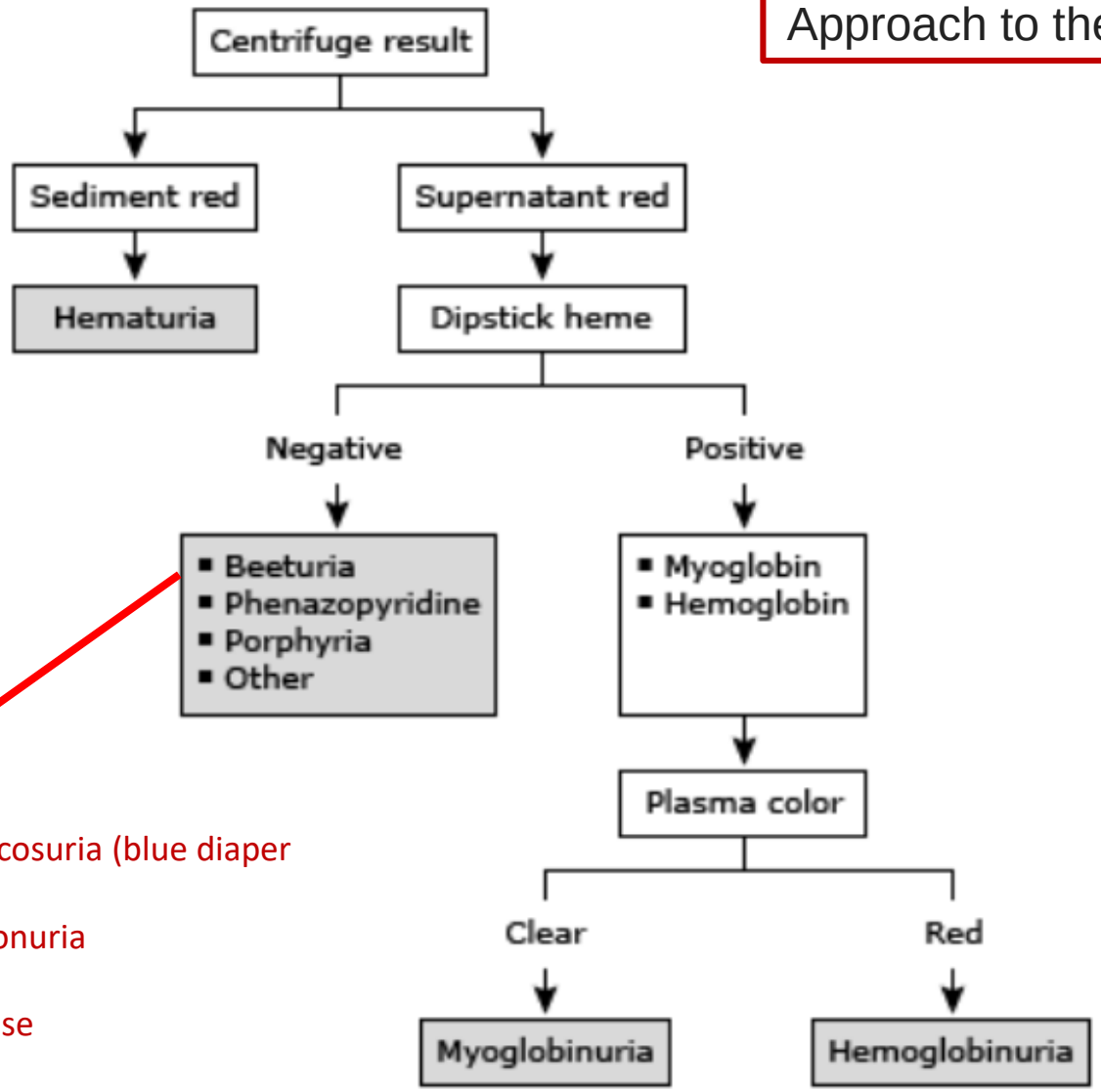
# Microscopic hematuria

- **Microscopic hematuria** may be discovered by accident when blood (either red blood cells or hemoglobin) is found on a urinalysis or dipstick done for other purposes.
- Hematuria is defined as two to five RBCs per high-power field (HPF) and can be detected by dipstick.
- Up to 18% of normal individuals have some form of hematuria on random Screening.
- The prevalence of microscopic hematuria in asymptomatic patients varies by age anywhere between 2% and 21%.

# Evaluation

- Available dipstick tests detect **red cells**, as well as **hemoglobin** and **myoglobin**, necessitating microscopic examination of the urine if a dipstick test is heme-positive, followed by other tests to confirm hematuria and, potentially, to determine its cause. (Dipstick testing for blood relies on the peroxidase activity of hemoglobin; a positive result occurs when hemoglobin pigment oxidizes the test-strip reagent producing a color change)
- The initial step in the evaluation of patients with red urine is **centrifugation** of the specimen to see if the red or brown color is in the urine sediment or the supernatant.

# Approach to the patient with red or brown urine




Pigmenturia
Melanin
Porphyria
Hypercalciuria/hyperuricosuria (blue diaper syndrome)
Phenylketonuria/alkaptonuria
Tyrosinosis
Maple syrup urine disease
Hartnups disease
Bilirubinuria
Hepatocellular (eg, Dubin-Johnson, Rotor)

## TABLE 24-1 Causes of Red or Brown Urine

| ENDOGENOUS SUBSTANCES | FOODS | DRUGS |
|---|---|---|
| Red blood cells | Artificial food coloring | Adriamycin |
| Hemoglobin | Beets | Chloroquine |
| Myoglobin | Blackberries | Deferoxamine |
| Bilirubin | Blueberries | Levodopa |
| Porphyrins | Fava beans | Methyldopa |
| Melanin | Paprika | Metronidazole |
| | Rhubarb | Nitrofurantoin |
| | | Phenazopyridine (Pyridium) |
| | | Phenolphthalein |
| | | Phenytoin |
| | | Prochlorperazine |
| | | Quinine |
| | | Rifampin |
| | | Sulfonamides |

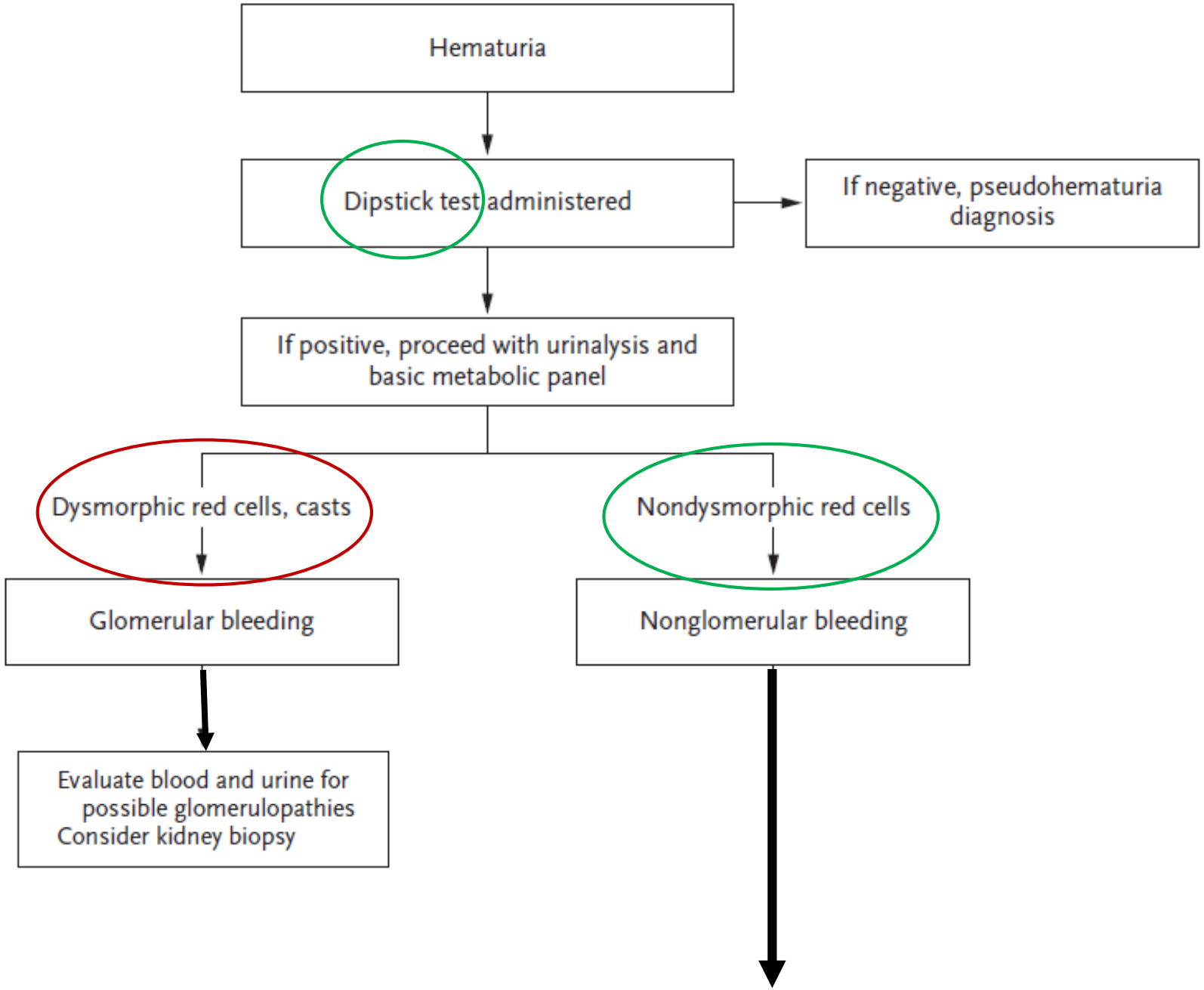

Hematuria
Dipstick test administered
If negative, pseudohematuria diagnosis
If positive, proceed with urinalysis and basic metabolic panel
Dysmorphic red cells, casts
Nondysmorphic red cells
Glomerular bleeding
Nonglomerular bleeding
Evaluate blood and urine for possible glomerulopathies
Consider kidney biopsy

**Table 1**
**Renal causes of hematuria**

| Origin | Cause | Disease |
|---|---|---|
| *Trauma* | | Renal trauma (contusion, hematoma, laceration, rupture) |
| *Glomerular* | | |
| Glomerulonephritis | | IgA nephropathy<br>Membranoproliferative/mesangial<br>Nephrotic syndrome<br>Post-strep (other postinfectious nephritides)<br>Rapid progressive/nephrotic |
| Familial | | Alport syndrome<br>Fabry disease<br>Nail-Patella syndrome<br>Thin basement membrane disease |
| Systemic/autoimmune | | Goodpasture disease<br>Systemic lupus erythematosus |
| Vasculitis | | Henoch-Schonlein purpura<br>Periarteritis nodosa<br>Wegeners' granulomatosis |
| *Nonglomerular* | | |
| Familial | | Polycystic kidney disease<br>Medullary sponge kidney |
| Infectious | | Pyleonephritis<br>Tuberculosis schistosomiasis |
| Neoplasm | | Wilms (pediatrics)<br>Genitourinary (renal carcinoma) |

- Glomerular hematuria may result from immune-mediated injury to the glomerular capillary wall or, in non-inflammatory glomerulopathies such as thin basement membrane nephropathy, from localized gaps in the glomerular capillary wall

**Signs of glomerular bleeding include: RBC casts, a dysmorphic appearance of some RBCs, and, in patients with gross hematuria, a brown, cola-colored urine.**

- Glomerular bleeding is indicated by proteinuria exceeding 500 mg/day that is temporally related to the onset of hematuria;
- However, new-onset hematuria in the setting of prior chronic proteinuria should elicit consideration of a nonglomerular or urologic source.

# Red cell casts

- The presence of RBC casts is virtually diagnostic of glomerulonephritis or vasculitis, although such casts are infrequently seen in acute interstitial nephritis. The absence of these casts, however, does not exclude glomerular hematuria


Source: Usatine RP, Smith MA, Mayeaux EJ, Chumley HS: *The Color Atlas of Family Medicine, Second Edition*: www.accessmedicine.com

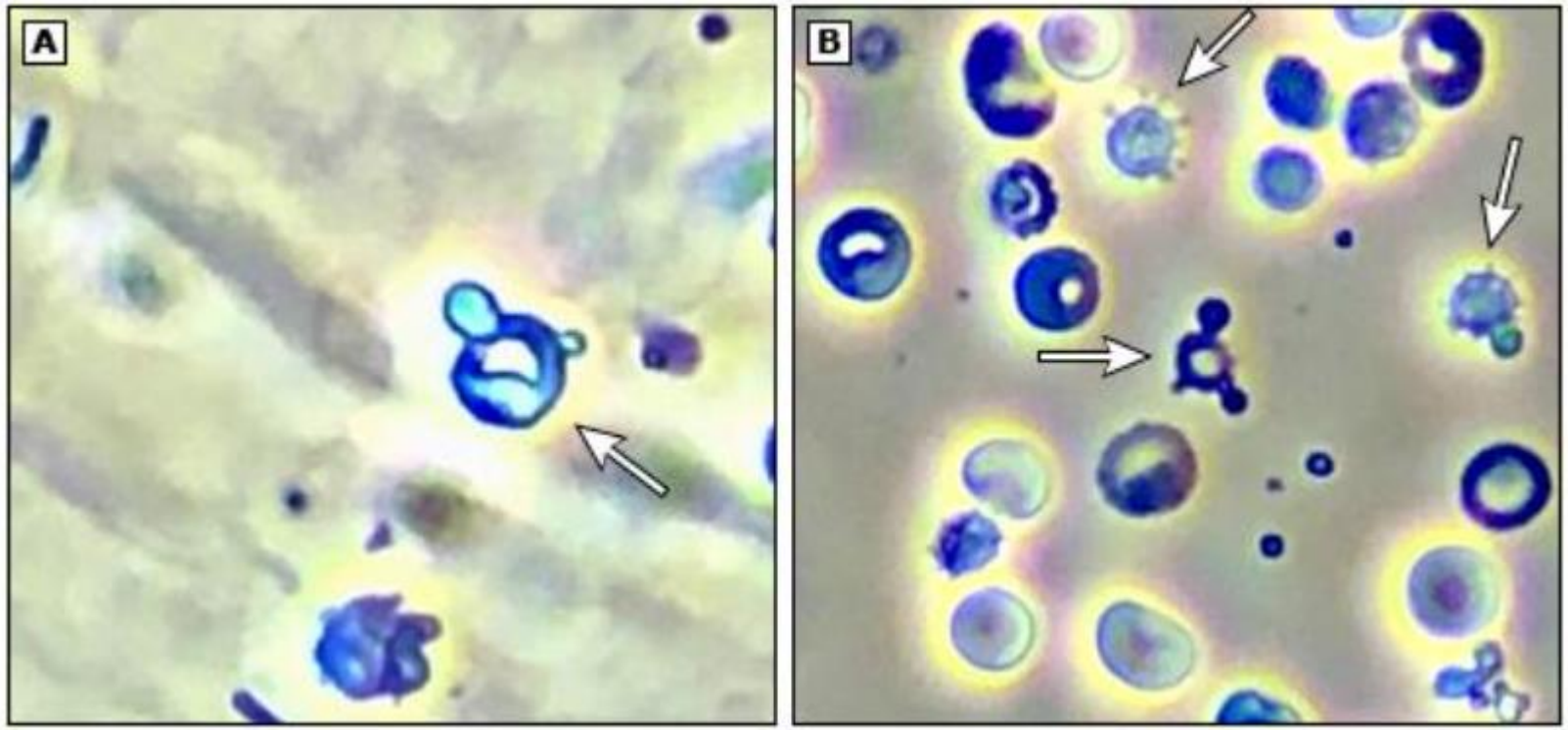

# Red Cell Morphology

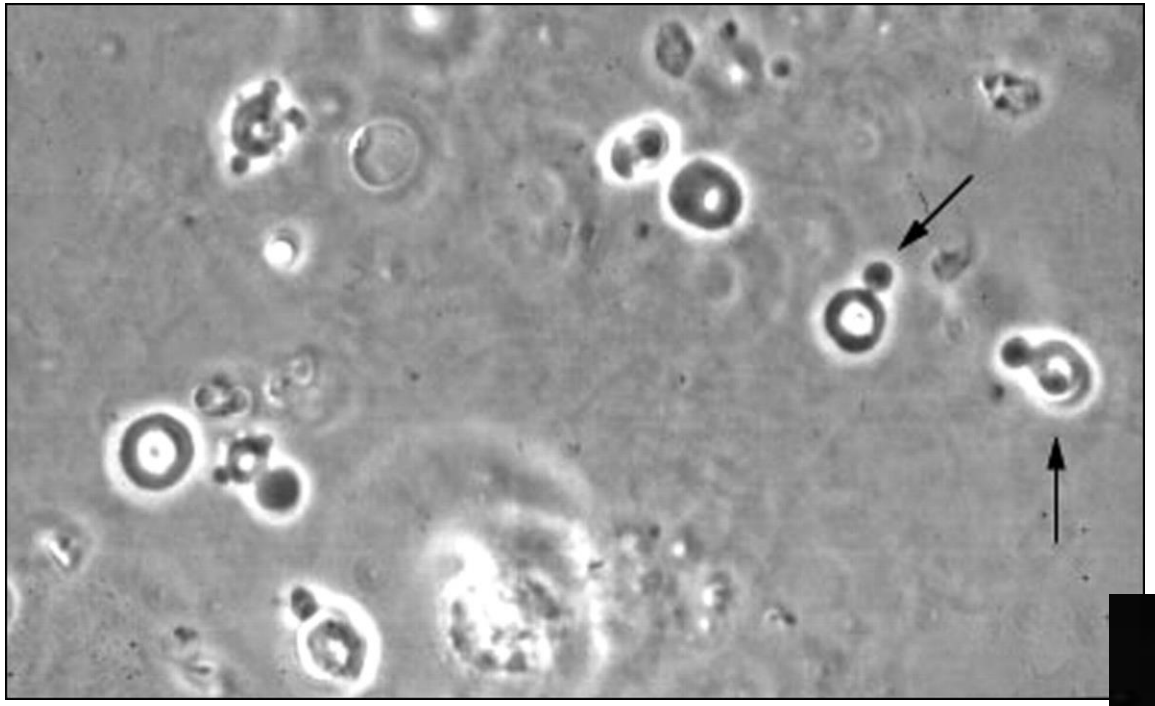
- Evaluation of RBC morphology may be helpful in identifying the cause of hematuria.
- **Extr-arenal bleeding:** The RBCs are typically uniform and round (as in a peripheral blood smear)
- **Renal lesions**: The RBCs usually have a dysmorphic appearance with, particularly in glomerular diseases. This change in morphology is manifested by **blebs**, **budding**, and segmental loss of membrane, resulting in marked variability in RBC shape and a reduction in mean RBC size.
- RBC injury in this setting may be due both to **mechanical trauma** as the cells pass through rents in the glomerular basement membrane and to **osmotic trauma** as the cells flow through the nephron.

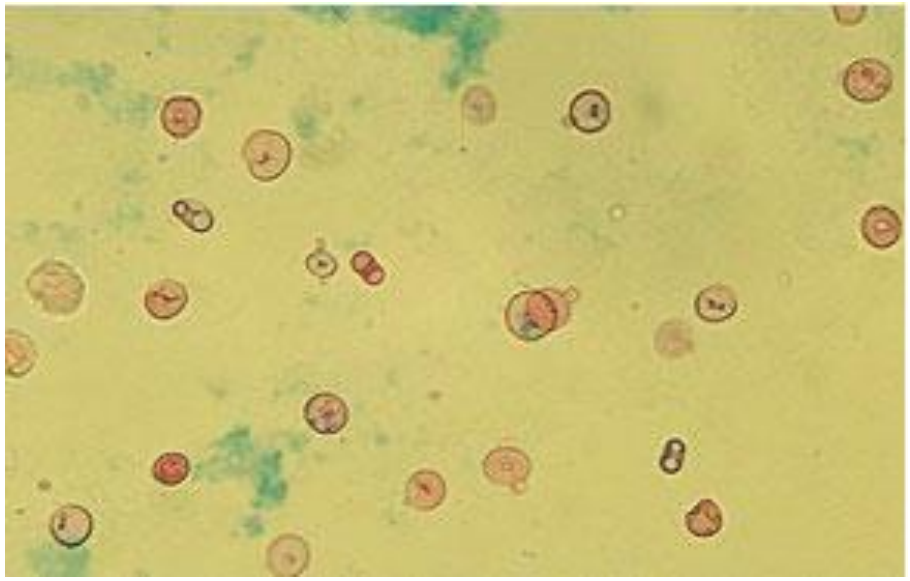
# Signs and Symptoms of Medical Renal Disease

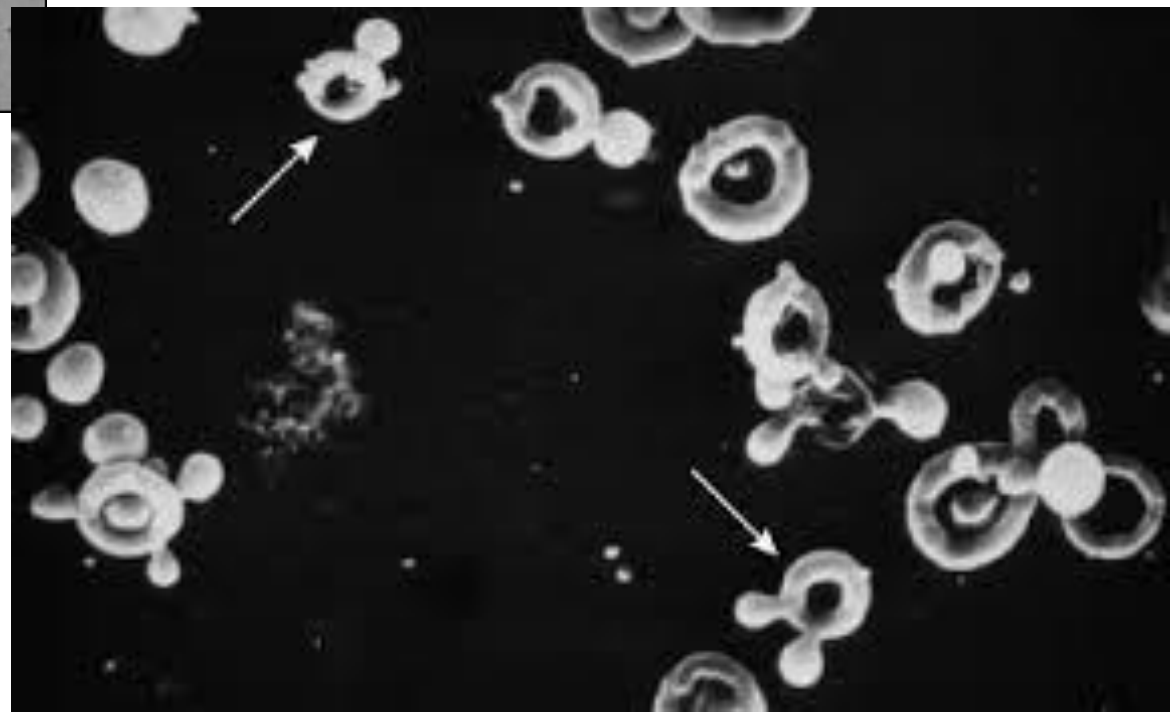
- The presence of microscopic hematuria and **dysmorphic red blood cells**, **cellular casts**, **proteinuria**, **elevated creatinine level**, or **hypertension** should raise suspicion for medical renal etiologies, such as **IgA nephropathy**, **Alport syndrome**, **benign familial hematuria**, or other nephropathy.
- If any of these are suspected, concurrent nephrologic workup is warranted.

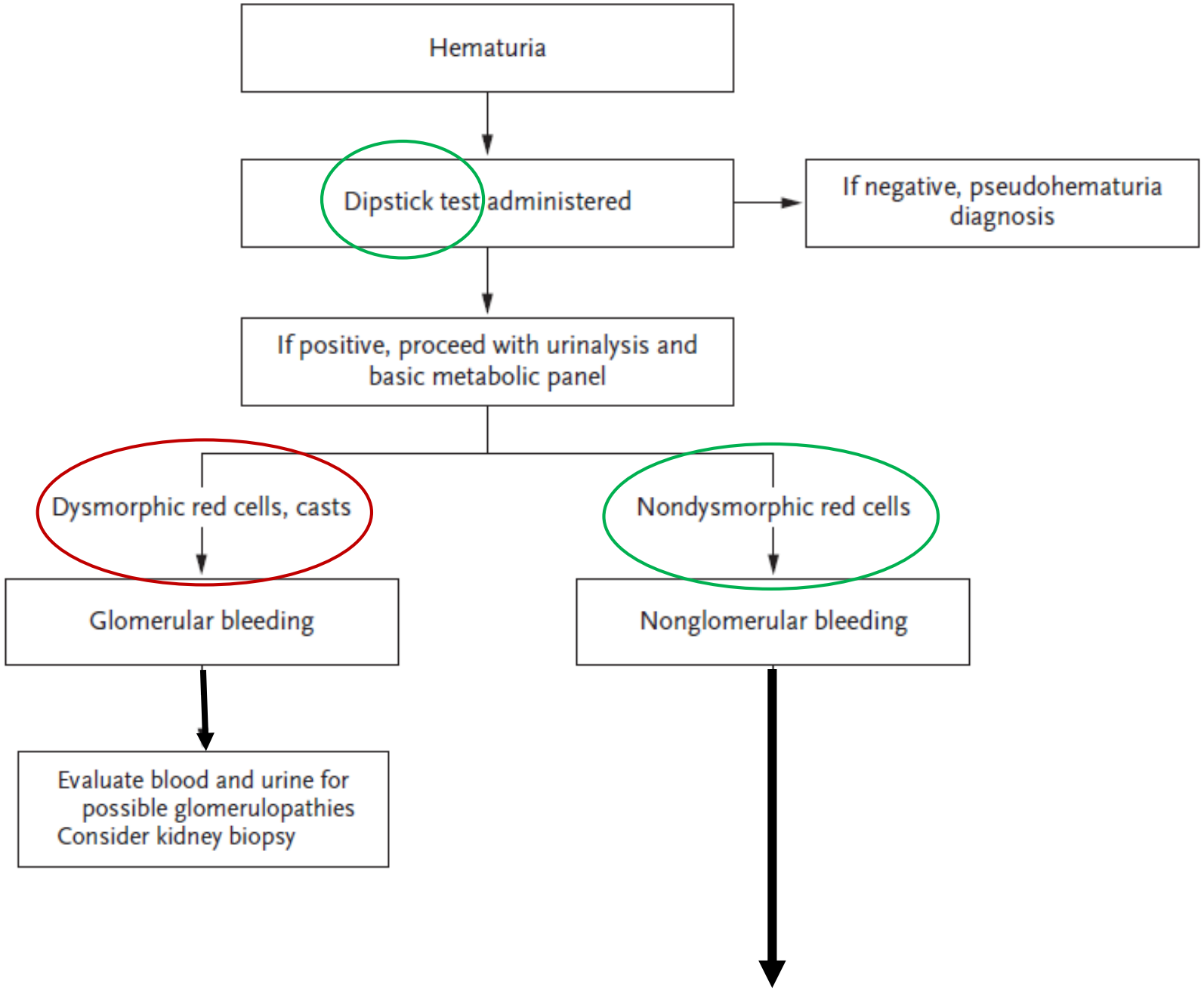
Phase-contrast micrograph showing dysmorphic RBCs in urine sediment










Hematuria
Dipstick test administered
If negative, pseudohematuria diagnosis
If positive, proceed with urinalysis and basic metabolic panel
Dysmorphic red cells, casts
Nondysmorphic red cells
Glomerular bleeding
Nonglomerular bleeding
Evaluate blood and urine for possible glomerulopathies
Consider kidney biopsy

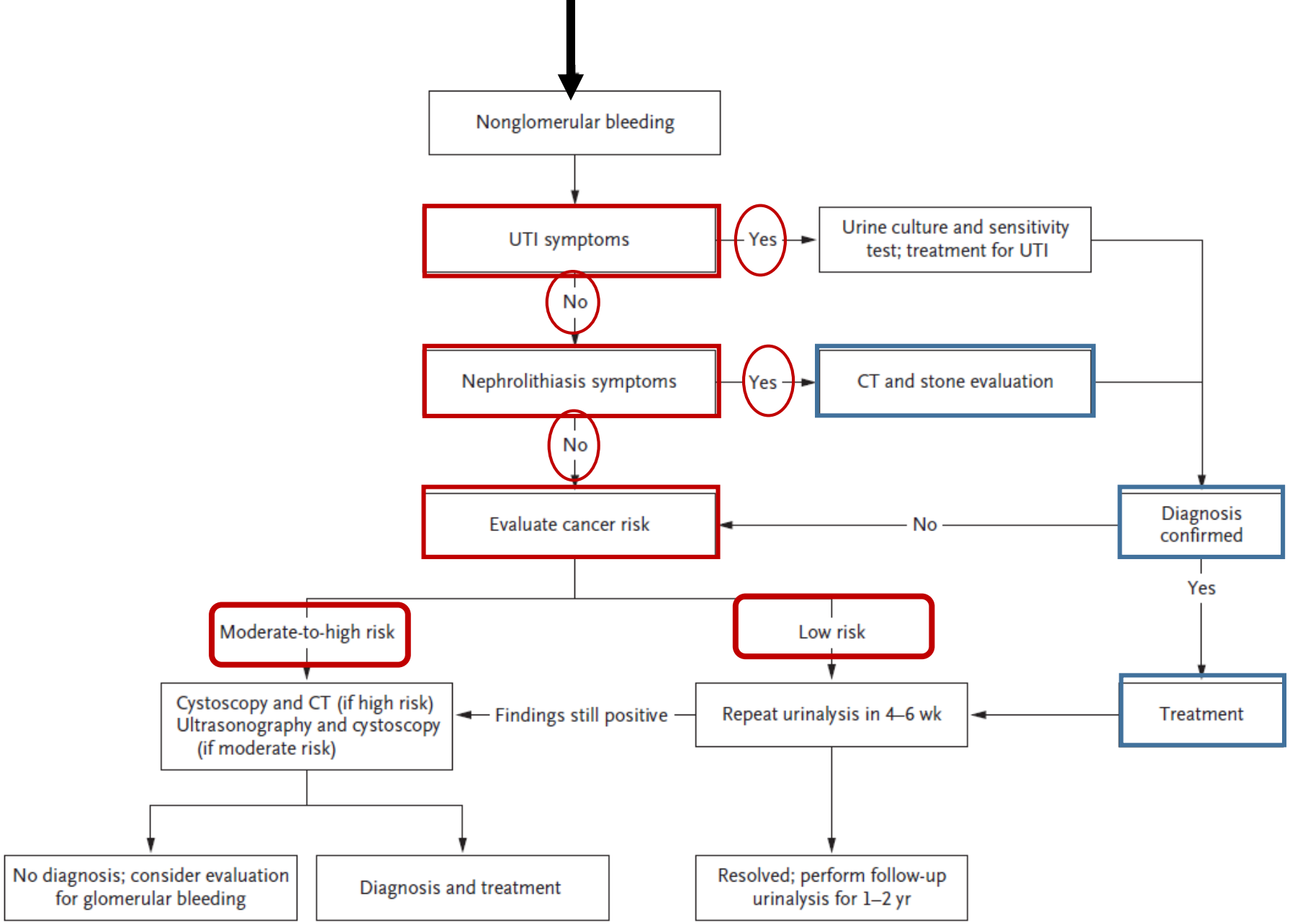
# Common Causes of Non-Glomerular Hematuria

**Upper Tract**

- Urolithiasis
- Pyelonephritis
- Renal cell carcinomas or other malignant/benign renal tumors
- Upper tract urothelial carcinoma
- Urinary obstruction (eg ureteropelvic junction obstruction, ureteral strictures)
- Trauma

**Lower Tract**

- Bacterial cystitis (UTI)
- Prostatitis
- Benign prostatic hyperplasia
- Strenuous exercise ("marathon runner's hematuria")
- Urothelial carcinoma of bladder/urethra
- Prostate Cancer
- Instrumentation
- Trauma
- Radiation cystitis
- • Benign hematuria (e.g. interstitial cystitis)


Nonglomerular bleeding
UTI symptoms
Yes
Urine culture and sensitivity test; treatment for UTI
No
Nephrolithiasis symptoms
Yes
CT and stone evaluation
No
Evaluate cancer risk
No
Diagnosis confirmed
Yes
Moderate-to-high risk
Low risk
Cystoscopy and CT (if high risk)
Ultrasonography and cystoscopy (if moderate risk)
Findings still positive
Repeat urinalysis in 4–6 wk
Treatment
No diagnosis; consider evaluation for glomerular bleeding
Diagnosis and treatment
Resolved; perform follow-up urinalysis for 1–2 yr

# Hematuria with Urinary Tract Infections

- If a patient has microscopic hematuria in the presence of **pyuria** or **bacteriuria**, a urine culture should be obtained to rule out urinary tract infection.
- Culture-directed antibiotics should be administered, and a microscopic urinalysis should be **repeated** in **six weeks** to assess for resolution of the hematuria.
- If the hematuria has resolved after the infection has cleared, no further workup is needed.
- If hematuria persists, diagnostic evaluation should commence.

# Risk Factors for Malignancy

- Male gender
- Age >35 years
- Past or current smoking history in which the risk correlates with the extent of exposure
- Occupational exposure to chemicals or dyes (benzenes or aromatic amines), such as printers, painters, and chemical plant workers
- History of gross hematuria
- History of irritative voiding symptoms
- History of chronic urinary tract infection
- History of pelvic irradiation
- History of exposure to cyclophosphamide
- History of a chronic indwelling foreign body
- History of analgesic abuse, which is also associated with an increased incidence of carcinoma of the kidney.

# Imaging

- Imaging is generally considered necessary in adults with gross hematuria, given the possibility of cancer, unless there is an obvious cause (e.g., hemorrhagic cystitis).
- For many patients, **ultrasonography** plus **cystoscopy** suffices.
- **CT urography** is recommended by some sources but is more costly than ultrasonography and usually includes the administration of contrast material.
- The use of MRI is not generally recommended. However, advances in technology may increase the use of MRU in some populations because the sensitivity of detecting renal lesions is greater than 90%.


**Figure 2.** Unenhanced multiphasic computed tomography urography in a 46-year-old man with hematuria and colicky pain in the left flank demonstrates *(A)* left midureteral calculus with "tissue-rim sign" *(arrow)* and *(B)* proximal hydronephrosis with minimal perinephric fat stranding *(arrows)*.

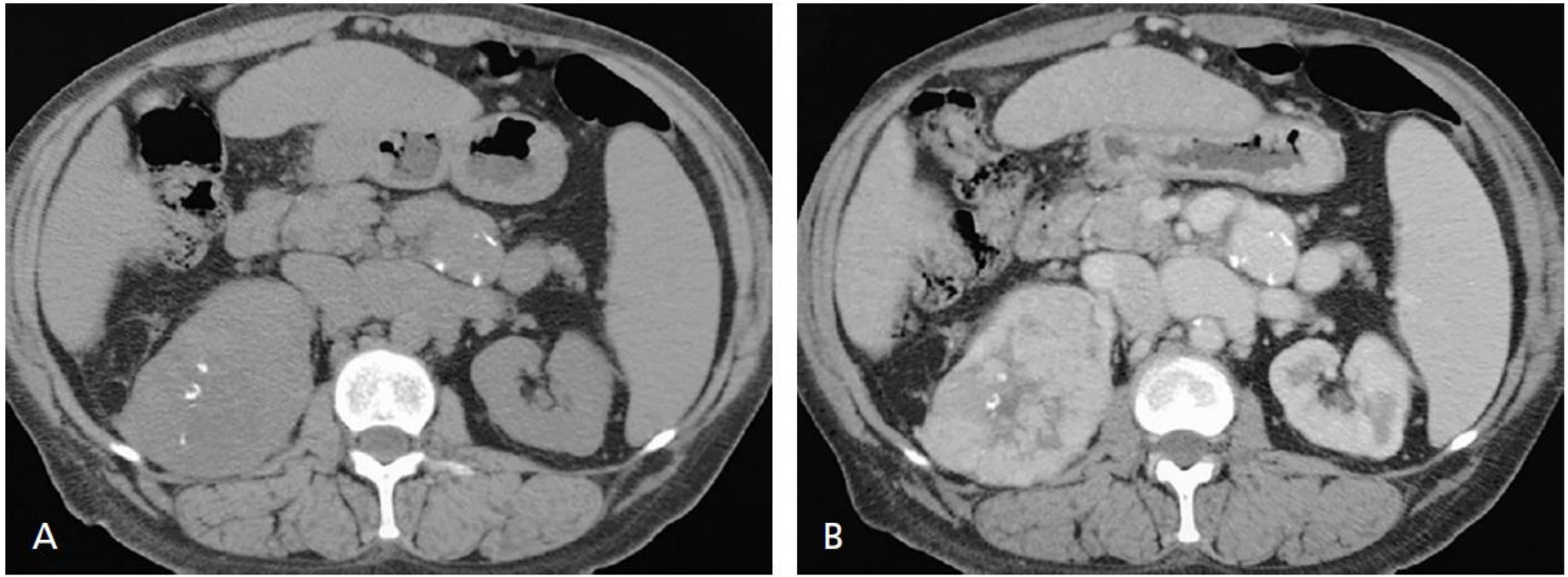



**Figure 3.** Multiphasic computed tomography urography in a 52-year-old woman with hematuria shows renal cell carcinoma. *(A)* Unenhanced image demonstrates right renal mass with calcification. *(B)* Contrast-enhanced images demonstrate a hypervascular enhancing mass.

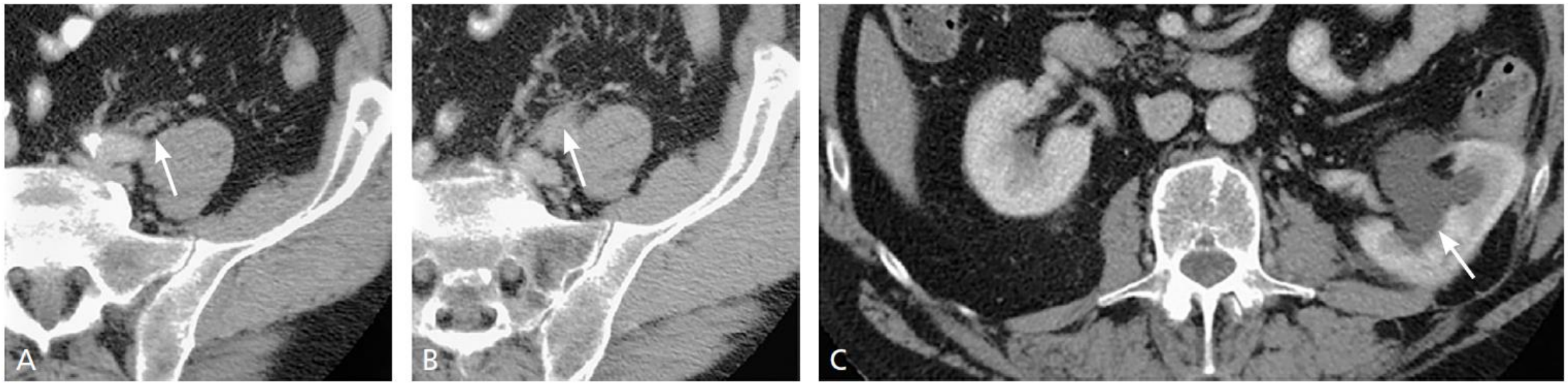



**Figure 4.** *(A and B)* Multiphasic computed tomography urography in a 53-year-old man with hematuria secondary to a transitional cell carcinoma of the left ureter shows thickened, enhancing ureteric wall *(arrow)* with periureteric fat stranding *(arrow)* suggestive of a urothelial lesion with extramural spread of the disease. *(C)* Proximal hydronephrosis with hydroureter *(arrow)* is noted.

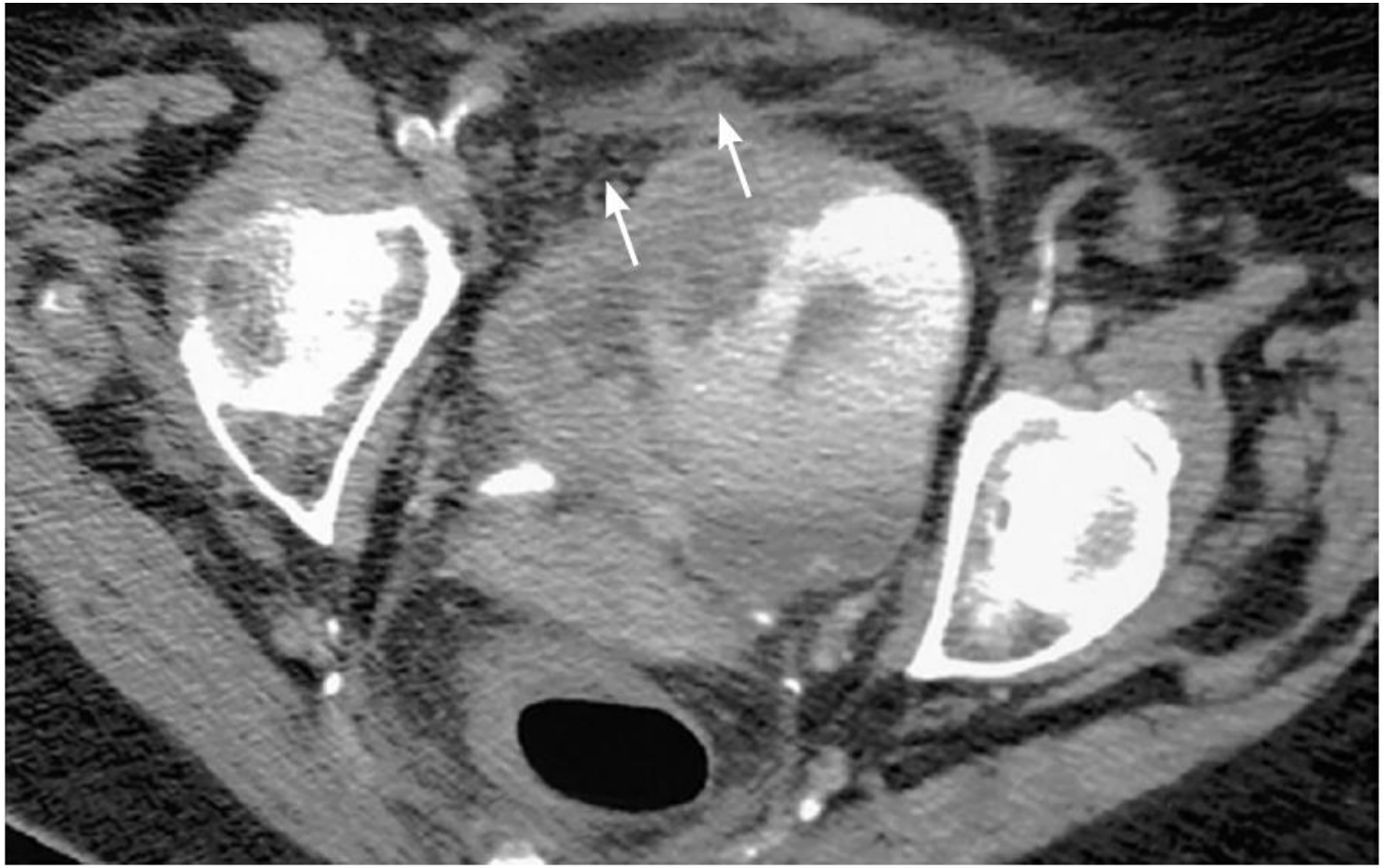


**Figure 5.** Multiphasic computed tomography urography in a 71-year-old woman with gross hematuria secondary to transitional cell carcinoma of the urinary bladder. A large polypoidal mass is visible arising from the right lateral wall with subtle perivesical fat stranding *(arrows)* suggestive of extramural spread.

# Cystoscopy

- For patients who have gross hematuria without an obvious cause, **cystoscopy is generally recommended in order to rule out cancer, most often bladder cancer.**
- The 2012 AUA guidelines recommended cystoscopy for all patients with microhematuria **who are older than 35 years of age**, but the **2020 AUA guidelines added risk levels** and recommended immediate cystoscopy only **for patients at increased risk**.

**Table 2.** Risk Stratification for Bladder Cancer.

**Low risk (all criteria must be met)**

<40 Yr of age for men, <50 yr of age for women

Never smoked or <10 pack-yr of smoking

3–10 Red cells per high-power field on one urinalysis

No risk factors for urothelial cancer

**Intermediate risk (one criterion raises the risk to intermediate)**

40–59 Yr of age for men and women

10–30 Pack-yr of smoking

11–25 Red cells per high-power field on repeat urinalysis

Additional risk factors for urothelial cancer

**High risk (one criterion raises the risk to high)**

≥60 Yr of age for men and women

>30 Pack-yr of smoking

>25 Red cells per high-power field on single urinalysis

History of gross hematuria

**Additional risk factors for urothelial cancer**

Irritative lower urinary tract symptoms

Previous pelvic radiation therapy

Previous chemotherapy with cyclophosphamide or ifosfamide

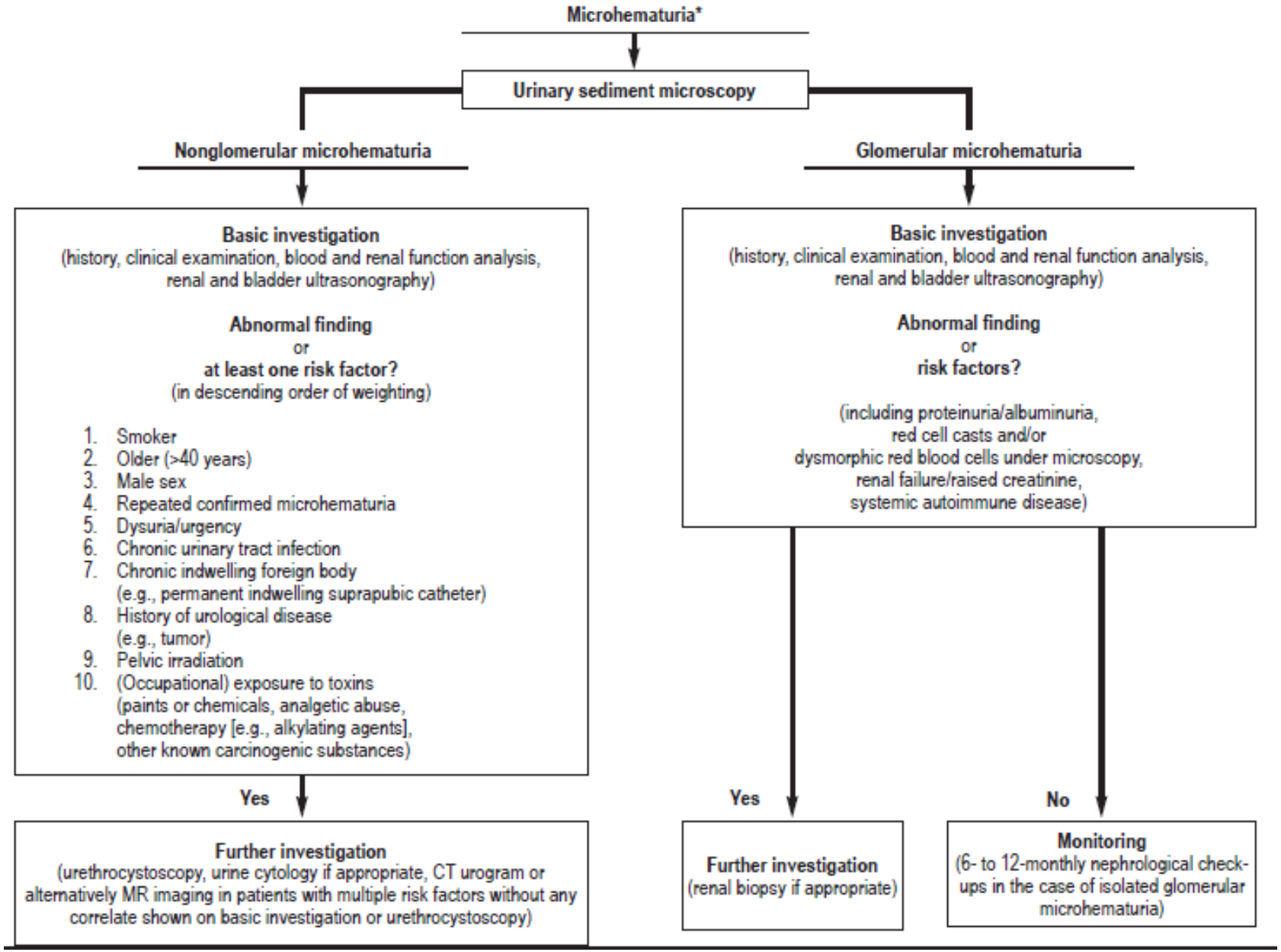
Family history of urothelial cancer or Lynch syndrome

Occupational exposure to benzene or aromatic amines

Chronic indwelling foreign body in the urinary tract

## SORT: KEY RECOMMENDATIONS FOR PRACTICE

| *Clinical recommendation* | *Evidence rating* |
|---|---|
| There is insufficient evidence to recommend screening urinalysis for the detection of bladder cancer in the absence of clinical indicators. | C |
| Further evaluation is recommended for individuals with three or more red blood cells per high-power field in a properly collected urine specimen in the absence of infection. | C |
| Concurrent nephrologic and urologic referral is indicated in the presence of hypertension, elevated creatinine level, and dysmorphic red blood cells, cellular casts, or proteinuria on urinalysis. | C |
| Computed tomography urography is the preferred method for radiologic imaging in the evaluation of microscopic hematuria. | C |
| Urine cytology and other bladder tumor markers are not recommended for the initial evaluation of microscopic hematuria. | C |


Microhematuria*
Urinary sediment microscopy
Nonglomerular microhematuria
Glomerular microhematuria
Basic investigation
(history, clinical examination, blood and renal function analysis, renal and bladder ultrasonography)
Abnormal finding
or
at least one risk factor?
(in descending order of weighting)
1. Smoker
2. Older (>40 years)
3. Male sex
4. Repeated confirmed microhematuria
5. Dysuria/urgency
6. Chronic urinary tract infection
7. Chronic indwelling foreign body (e.g., permanent indwelling suprapubic catheter)
8. History of urological disease (e.g., tumor)
9. Pelvic irradiation
10. (Occupational) exposure to toxins (paints or chemicals, analgetic abuse, chemotherapy [e.g., alkylating agents], other known carcinogenic substances)
Yes
Further investigation
(urethrocystoscopy, urine cytology if appropriate, CT urogram or alternatively MR imaging in patients with multiple risk factors without any correlate shown on basic investigation or urethrocystoscopy)
Basic investigation
(history, clinical examination, blood and renal function analysis, renal and bladder ultrasonography)
Abnormal finding
or
risk factors?
(including proteinuria/albuminuria, red cell casts and/or dysmorphic red blood cells under microscopy, renal failure/raised creatinine, systemic autoimmune disease)
Yes
Further investigation
(renal biopsy if appropriate)
No
Monitoring
(6- to 12-monthly nephrological check-ups in the case of isolated glomerular microhematuria)

# Follow-up

- If appropriate workup does not reveal nephrologic or urologic disease, then **annual** urinalysis should be performed for at least two years after initial referral.
- If these two urinalyses do not show persistent hematuria, the risk of future malignancy is less than 1% and the patient may be released from care.
- However, if asymptomatic microscopic hematuria persists on follow-up urinalysis, a full repeat evaluation should be considered within **three to five years** of the initial evaluation.
- Patients' risk factors for urologic malignancy should guide clinical decision making about reevaluation.

**Definitions and recommended actions to investigate asymptomatic microhematuria (aMH), based on international guideline recommendations (1, 8, 14–20)**

| Parameter | Definition/recommended actions |
|---|---|
| **Microhematuria** | ≥ 3 red blood cells per high-power field* |
| **Nephrology referral** | If proteinuria, albuminuria, red blood cell casts, and/or dysmorphic red blood cells shown by microscopy and/or renal failure/raised creatinine present |
| **Age threshold** | Investigate in patients >40 years |
| **Urine cytology** | For all patients >50 years with negative ultrasound and cystoscopy findings |
| **Urethrocystoscopy** | Age >40 years or other risk factors (*Figure 3*), patients with atypical or positive cytology |
| **Imaging** | According to guideline recommendation, CT urography if basic investigation or urethrocystoscopy fails to show a correlate (*Figure 3*), or in patients with positive ultrasound findings<br><br>In the opinion of the present authors, CT urography is only justified in patients with multiple risk factors. |
| **Monitoring – who?** | Patients >40 years, (ex-)smokers, history of exposure to chemicals |
| **Monitoring – what?** | Urinanalysis, cytology, and blood pressure measurement at 6, 12, 24, and 36 months after a negative initial investigation |

# Key messages

- Every case of hematuria requires investigation. Macrohematuria requires more extensive investigation.
- Findings of **red cell casts**, large numbers of **dysmorphic red blood** cells, or more than 5% acanthocytes indicate the presence of glomerular hematuria, which requires a nephrology referral.
- For a basic investigation, for all patients a **history** should be taken and clinical and **laboratory tests** carried out, and possibly also red cell morphology studies and renal and bladder ultrasonography.
- Patients who have been exposed to **exogenous toxins** (including tobacco smoke), are **older**, are of **male sex**, or have **macrohematuria**, should be further investigated by **urethrocystoscopy** and perhaps **CT urography.**