

Hematuria in Adults

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2023/10/23

REVIEW ARTICLE

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Hematuria in Adults

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This article was updated on July 13, 2021,
at NEJM.org.

N Engl J Med 2021;385:153-63.

DOI: 10.1056/NEJMra1604481

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Outline

- Epidemiology
- Detection of hematuria
- Confirmed visible hematuria
- Confirmed microhematuria
- Biomarkers
- Further evaluation

Epidemiology

- The reported prevalence of microhematuria varies greatly, 1% up to around 40 %.
- The American Urological Association (AUA) guidelines: **prevalence** from **2.1 to 31.4%**.
- Consideration of individual patient circumstances and geographic region
→ northern Africa, (**Schistosoma haematobium** endemic) -> microhematuria
- Difference of etiology between men and women → evaluation to **cancer concern**

Detection of Hematuria

- Color: **Red, pink, “rusty,” or brown urine**
- **Dipstick tests** detect red cells, as well as hemoglobin and myoglobin.
- Pseudoperoxidase activity of hemoglobin will oxidize the benzidine compound: **blue**.

Detection of Hematuria

- **False positive**
 - a. sodium hypochlorite (漂白水)
 - b. peroxidases from vegetable or bacterial sources, and
 - c. **semen**
- **False negative**: very high ascorbic acid(Vit C.) levels in urine

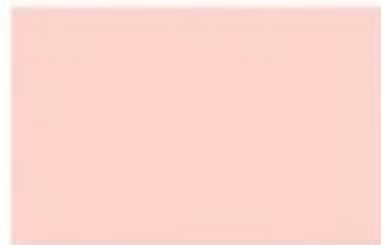
Table 1. Selected Nonheme Causes of Pigmenturia, as Compared with Red Cells or Free Hemoglobin.*

Variable	Red Cells	Hemoglobin	Myoglobin	Porphyria	Bile Pigments	Alkaptonuria
Urine color	Red to rusty	Pink to red	Rusty	Turns black, brown, or red in sunlight	Brown	Turns dark in sunlight
Heme test	Positive	Positive	Positive	Negative	Negative	Negative
Usual microscopic findings	Red cells, casts	No cells	No red cells; casts may be present	Normal	Normal	Normal
Plasma	Normal	Pink	Normal	Normal	Icteric	Normal

* Shown are selected endogenous causes of pigmenturia. A heme test for exogenous causes, including beets, rhubarb, azo dye, sulfonamides, and phenolphthalein, is negative.



Red



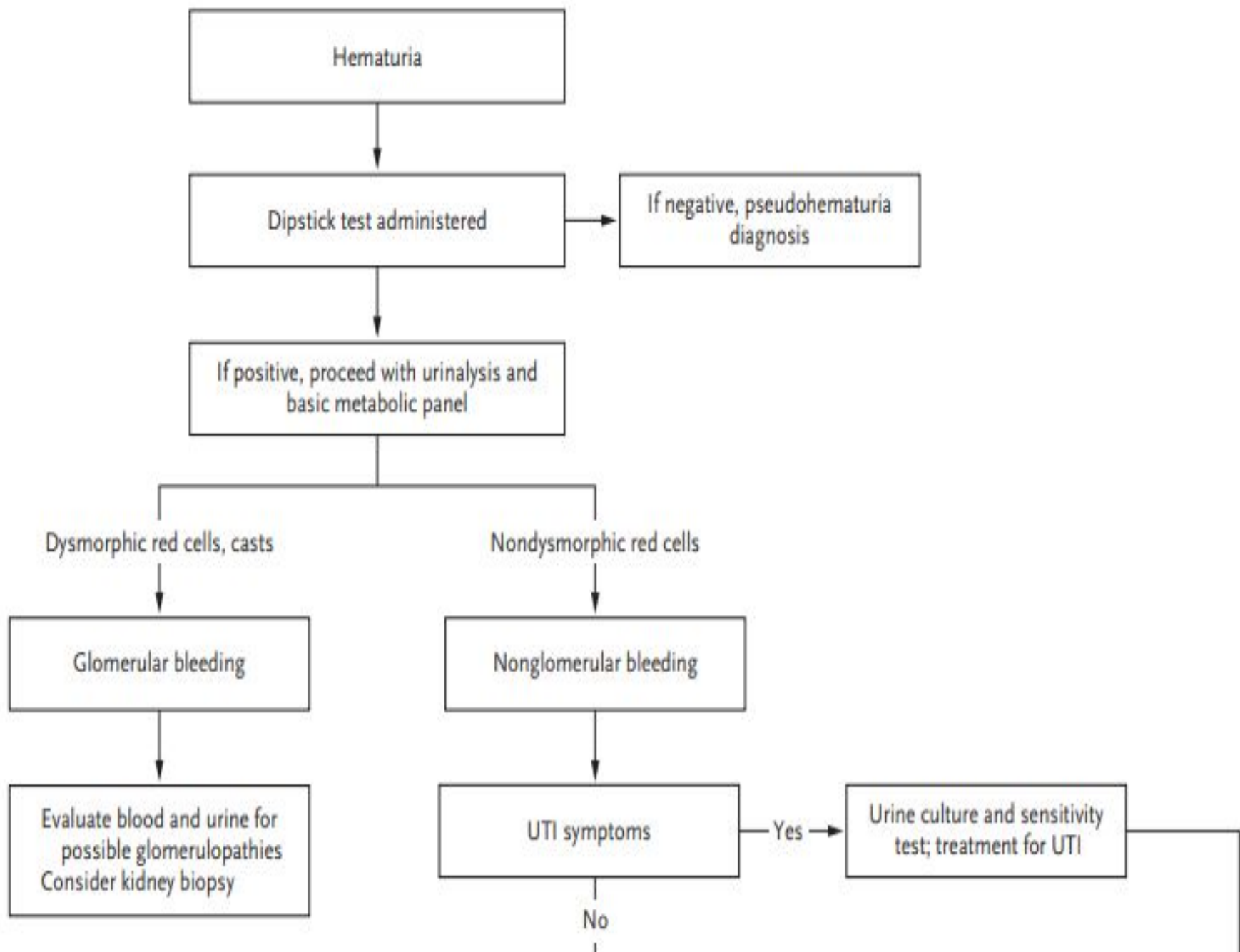
Pink



Brown



Black



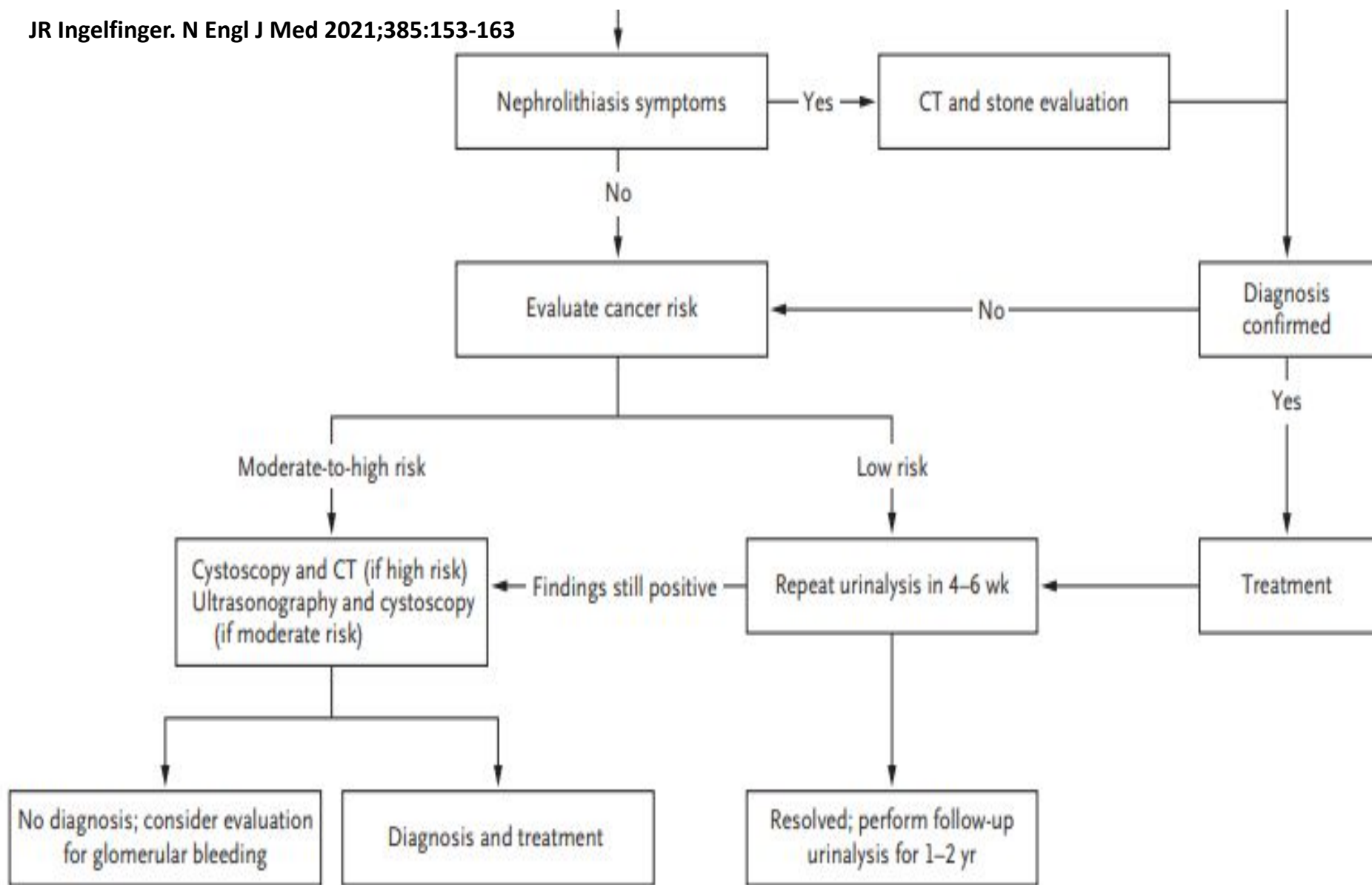


Figure 2. Algorithm Incorporating Risk Assessment in the Evaluation of Hematuria.

The algorithm is based on the current American Urological Association guidelines. UTI denotes urinary tract infection.

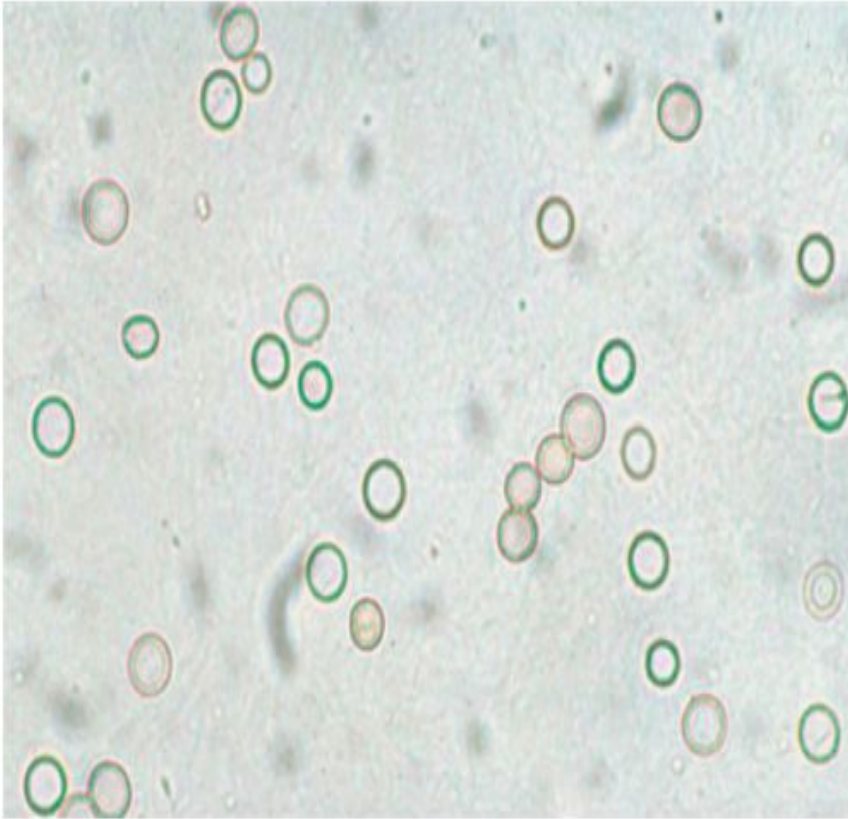
Distinguish blood from myoglobin

- **Centrifugation** : red cells will sediment, leaving a clear supernatant, whereas myoglobin /free hemoglobin will not.
- In all the absence of red cells in the sediment of a “heme-positive” specimen → **isolated hemoglobinuria or myoglobinuria**
- Myoglobinuria
 - **ammonium sulfate precipitation**
 - electrophoretic test
 - immunologic test

Definition of microhematuria

- If a positive dipstick test -> must **microscopic examination**
- **> 2-3 RBC/HPF**, and on **two or three** separate urinalyses sample.
- Even a single urinalysis is positive, a patient should have **follow-up urinalyses for at least a year**, so as to avoid missing an intermittent source of microhematuria.

A Nondysmorphic Red Cells



B Dysmorphic Red Cells

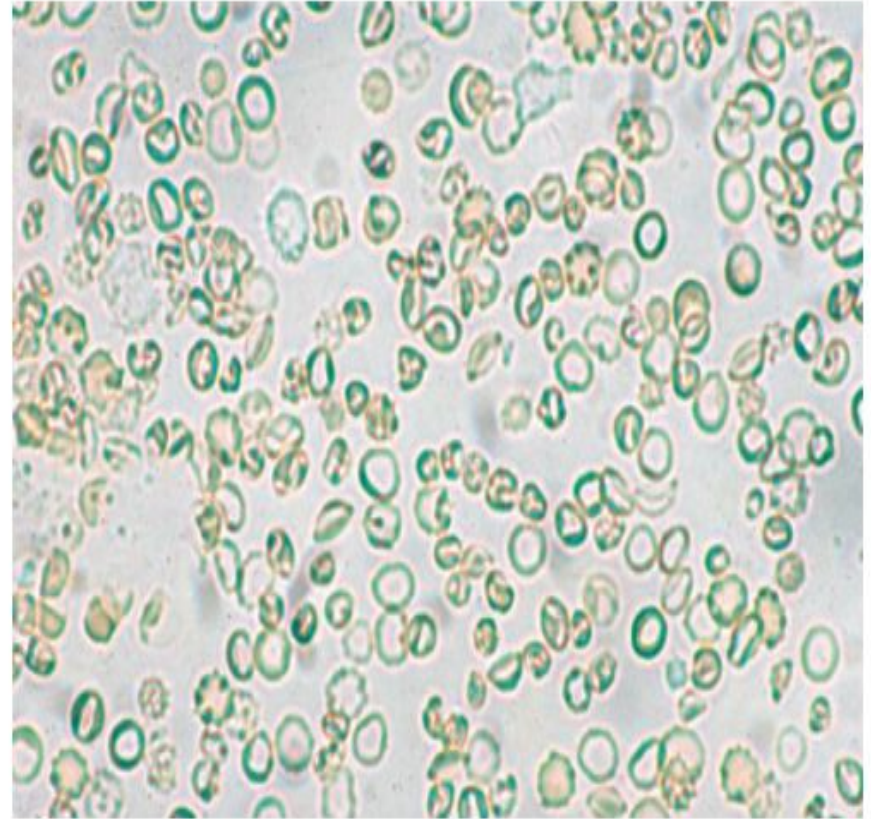


Figure 1. Nondysmorphic and Dysmorphic Red Cells in Freshly Voided Urine.

Panel A shows nondysmorphic red cells, and Panel B shows dysmorphic red cells, which have characteristic blebs. Micrographs are courtesy of the estate of the late Michael Linshaw, M.D.

Cause of microhematuria

- Bacteria in the unspun urine: UTI
- Crystals: nephrolithiasis
- If normal-appearing red cells → imaging and urologic referral.
- In patients with **risk factors for cancer**
-> **urethrocystoscopy + CT-urography** or **ultrasonography + cystoscopy**.

Glomerular hematuria

- A marker of changes in the glomerular filtration apparatus or of inflammation, → **isolated glomerular hematuria** may not always be innocuous.
-
- Army recruits: increased risk of ESRD.

Glomerular hematuria

- Kidney donors: increased risk of kidney dysfunction
-
- The mechanism of kidney injury
→ **tubular inflammation** and **oxidative stress** induced by breakdown products of red cells.

Confirmed Visible Hematuria

- DDX: the passage of a kidney stone, acute hemorrhagic cystitis, or a sickle-cell crisis
- In **adults over the age of 40** years (some sources suggest a cutoff age of 35 years), an unexplained episode of visible hematuria may signify **bladder or upper urinary tract cancer.**

History and PE

- Trauma: renal contusion, vascular injury, or infarction
- Urinary tract infection or renal colic
- Just undergone surgery
- Anticoagulants
- Strenuous activity, eg. long-distance run
- Voiding pattern change
- Flank pain or suprapubic pain or dysuria
- **Man: digital rectal examination**, prostate
- **Woman: MC, GYN survey**

Image study

- **Ultrasonography + cystoscopy**
- **CT urography** with contrast material
- MRI is not generally recommended

Confirmed Microhematuria

- The most common causes of microhematuria are **nonmalignant**.
- GN (e.g., IgAN or thin GBM disease)
- Inflammatory/Infectious conditions of the urethra, prostate, and bladder
- Renal calculi
- Benign prostatic hypertrophy (BPH)

Glomerular Hematuria

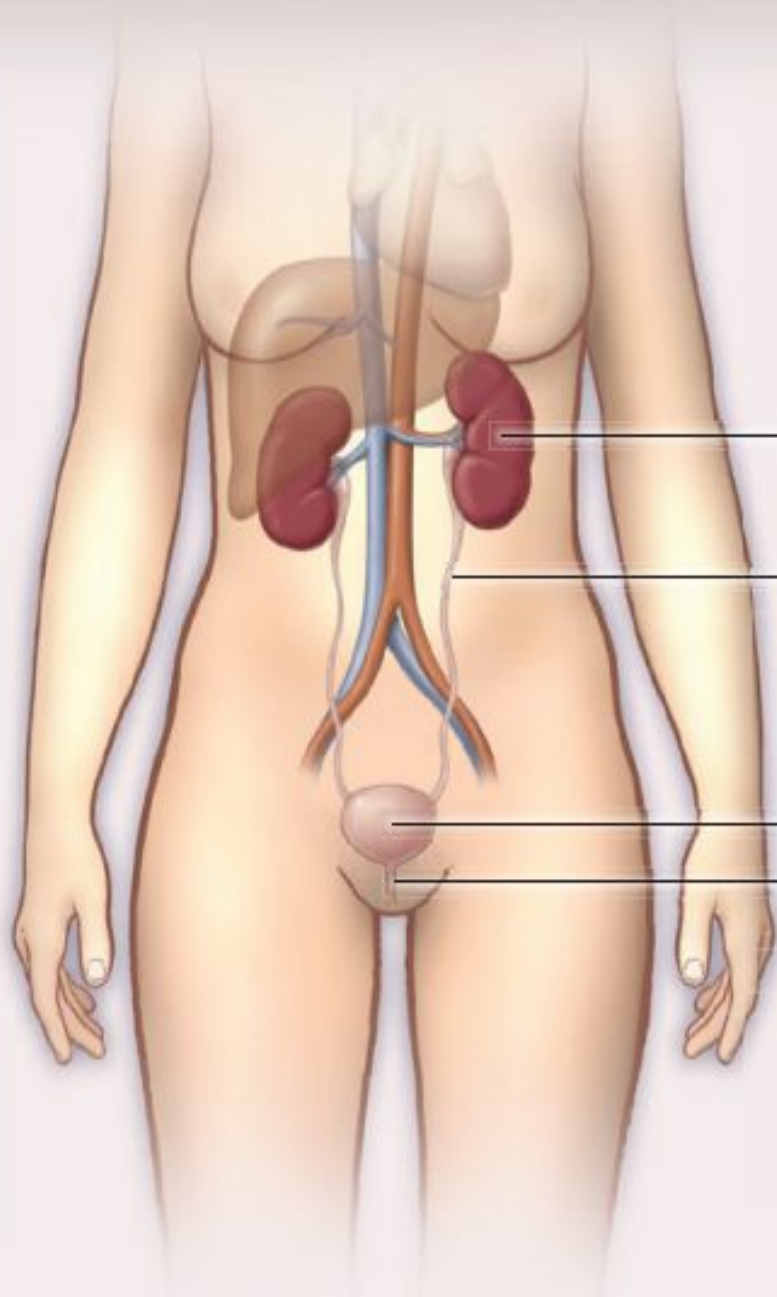
- IgA nephropathy
- Alport's syndrome
- Thin basement membrane disease
- C3 nephropathy
- Postinfectious glomerulonephritis

Ureteral Hematuria

- Stones
- Infection
- Trauma
- Tumor

Sexual Dimorphism

- Prostatic bleeding
- Vaginal bleeding
- Endometriosis of the urinary tract



Nonglomerular Hematuria

- Polycystic kidney disease
- Sickle-cell disease and papillary necrosis
- Nephrolithiasis
- Tumors
- Leukemia
- Trauma
- Infection
- Strenuous exercise

Vesicular Hematuria

- UTI
- Stones
- Infections
- Irritation
- Tumor
- Foreign body

Urethral Hematuria

- Trauma
- Infection

History taking

- Any symptom ? What ?
- Urinary tract infection(UTI)
- Menstruating
- Just exercised
- Recent sexual activity
- Exposure to instrumentation (e.g., post cystoscopy examination).

Urinary sediment examination

- **Midstream** urine (ideally, the **first void** of the day) and examine it **within 1 to 2 hours**.
- Spinning the sample at 4000 rpm for 5 minutes after obtaining a dipstick reading.
- **Normal: <2-3 RBC/HBF**
- Repeat testing over a period of a year. **(QxM and then once or twice yearly)**

Urinary sediment examination

- Dysmorphic RBCs: > 25% GN
- **Low urinary RBC MCV**
- Most common GN: **IgAN and Alport's syndrome** (familial nephritis)

Further examination

- Urine cytology: visible hematuria (2/2278)
- Image: CT urography, cystoscopy, CT + cystoscopy, and **Echo + cystoscopy (preferred)**.
- **Cystoscopy: Microhematuria + Age > 35**
 - The 2012 AUA guidelines
 - The 2020 AUA guidelines: if increased risk.

Risk factors to malignancy

- **Male**
- **Age > 40**
- **> 25 RBC/HPF**
- Occupational exposure: aromatic amines and hydrocarbons
- **Analgesic abuse (phenacetin)**
- Pelvic irradiation
- Alkylating agents (e.g., **cyclophosphamide**)
- Exposure to foreign bodies (e.g., catheters)

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

Biomarkers

- Bladder cancer is heterogeneous
 - Urothelial carcinomas : 90-95% (bladder)
 - Squamous-cell : 3 to 7% (renal pelvis and ureters)
 - Adenocarcinoma : < 3% (trigonal region)
- FDA approved: **bladder tumor-associated antigen (BTA) + nuclear matrix protein 22 (NMP22)** in bladder cancer
- Circulating tumor DNAs (**ctDNAs**)
- Renal-cell carcinoma: **cell-free DNA**

- NMP22檢測對尿路上皮癌的Sensitivity為90.9%，而尿細胞學檢查的Sensitivity僅為54.5%。
- 當Cut-off值設定為10U/ml時，尿NMP22對尿路上皮癌的陽性率為80.9%，而治療後和良性疾病的陽性率為35.7%。
- 在**健康個體中NMP22具有100%的Specificity**。
- 依據台灣兩家醫學院所做的研究結果，NMP22對膀胱癌的陽性預測值(**PPV**)為**53.2%**；陰性預測值(**NPV**)為**94.9%**，其NPV優於尿細胞學檢查。

- Nuclear Matrix Protein 22(NMP22)是針對膀胱癌高專一性的癌症腫瘤標記，因為**膀胱癌患者會釋放此種蛋白質至尿液中**。NMP22 BladderChek[®]試驗已獲得美國FDA認可核准，可協助診斷與監控膀胱癌。
- 優點: 僅需要少數尿液檢體，且**不受血尿的干擾**
- 缺點: **泌尿系統感染**導致死亡細胞釋放NMP22而產生**假陽性**。
- 可應用於**低風險族群的篩檢**，若NMP22篩檢結果為陽性時，仍應以膀胱鏡進行膀胱癌確認診斷。

Conclusions

- Given the association of both visible hematuria and microhematuria with bladder and kidney cancer, the focus of evaluation has long been to **rule out cancer**.
- Older age(**> 40 years**), greater hematuria(**>25 RBC/HPF**), and **male** gender increase the risk of cancer.
- **Ultrasonography plus cystoscopy** is preferred to further evaluation the cause of hematuria.

Take home messages

- Hematuria with cancer/GN risk.
- Age > 40, hematuria(>25 RBC/HPF), and male gender
- Ultrasonography plus cystoscopy

Thank you!