hematuria

Dr esmat abdollahpour

Nephrologist, assistant professor of TUMS

Introduction and definition

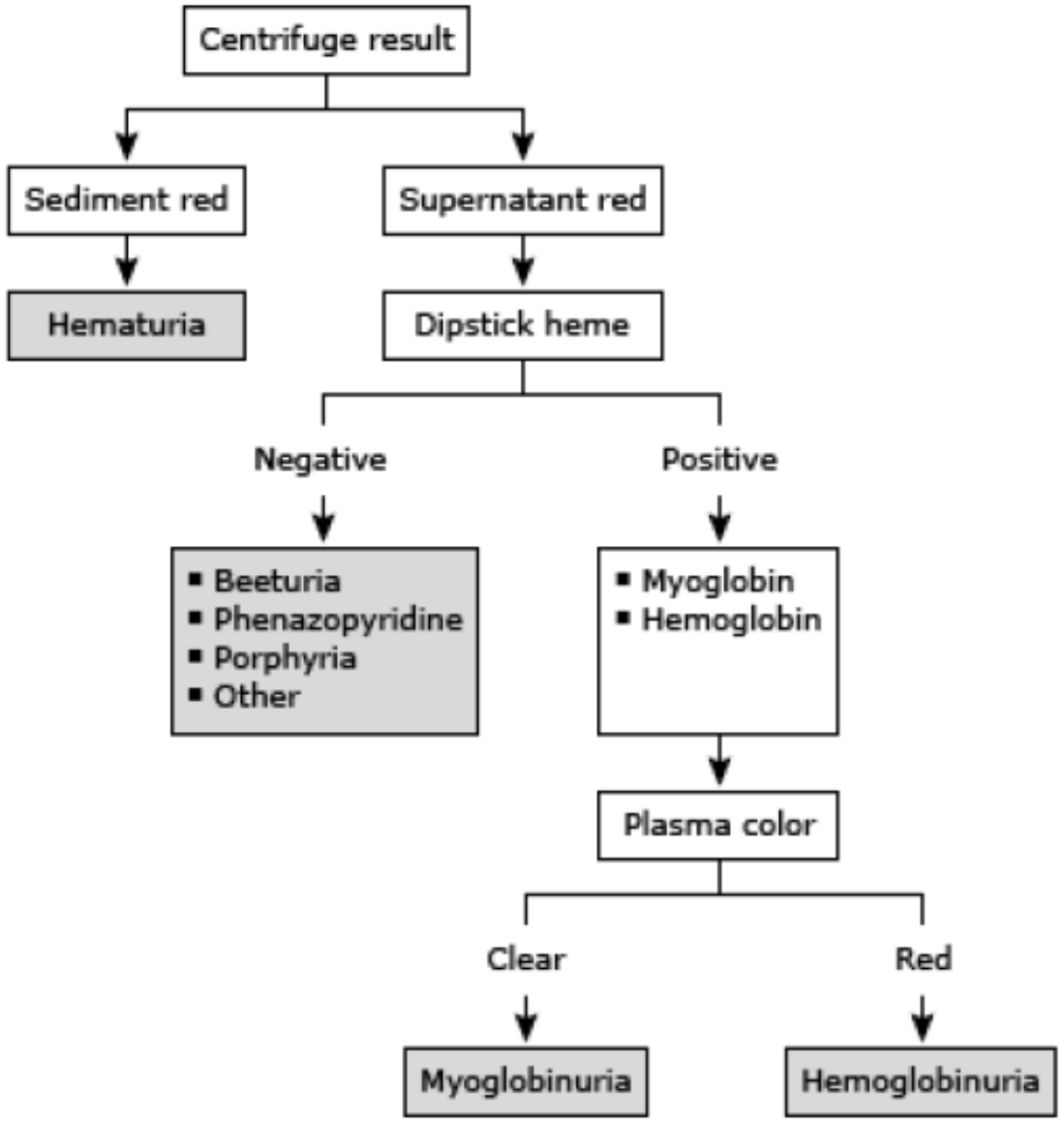
- Unexplained hematuria is fairly common
- Appreciable risk of malignancy over age 35 years
- Urologic cause for hematuria often not be identified (61%)
- Gross hematuria vs microscopic hematuria

Gross hematuria

- Gross hematuria with passage of clots: lower urinary tract source
- Contamination with blood
- AKI in gross hematuria with underlying glomerular disease
- Distension of renal tubules with RBCs & ATN
- Ig A nephropathy, TBM, LN
- Initial step in evaluation of red urine: centrifugation of specimen

Approach to the patient with red or brown urine

Exception: RBC lysis in very dilute urine



Causes of heme-negative red urine

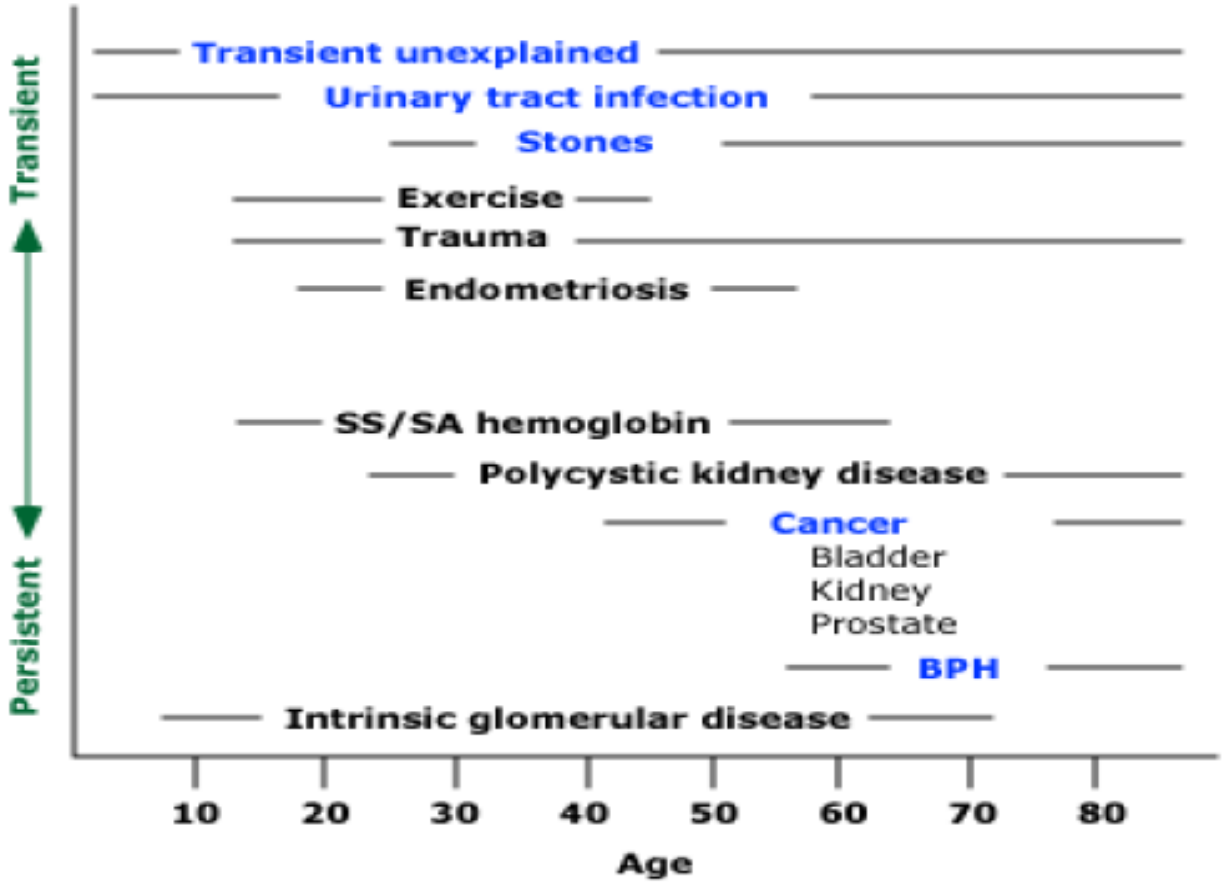
Medications
Doxorubicin
Chloroquine
Deferoxamine
Ibuprofen
Iron sorbitol
Nitrofurantoin
Phenazopyridine
Phenolphthalein
Rifampin
Food dyes
Beets (in selected patients)
Blackberries
Food coloring
Metabolites
Bile pigments
Homogentisic acid
Melanin
Methemoglobin
Porphyrin
Tyrosinosis
Urates

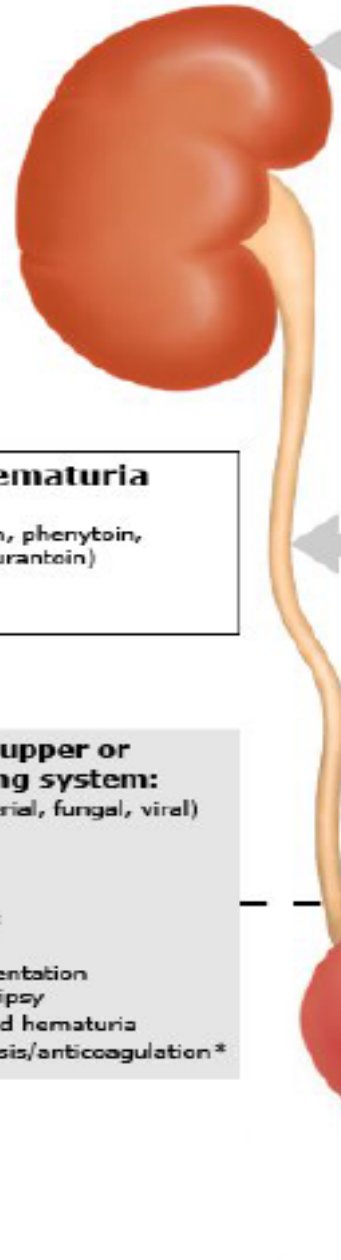
Microscopic hematuria

- Three or more RBCs Per HPF in a spun urine sediment
- Urine sediment (direct counting): gold standard
- Dipstick for heme: detect 1-2 RBCs per HPF
- More false positive: semen, alkaline urine PH>9, oxidizing agents, myoglobinuria or hemoglobinuria
- Positive dipsticks must be confirmed with microscopic examination
- RBC lysis in very dilute urine: not false positive
- False negative is unusual: ingestion of large amounts vit C

Etiology

Major causes of hematuria by age and duration





Renal

- Benign renal mass (angiomyolipoma, oncocytoma, abscess)
- Malignant renal mass (renal cell carcinoma, transitional cell carcinoma)
- Glomerular bleeding (IgA nephropathy, thin basement membrane disease, Alport syndrome)
- Structural disease (polycystic kidney disease, medullary sponge kidney)
- Pyelonephritis
- Hydronephrosis/distension
- Hypercalciuria/hyperuricosuria
- Malignant hypertension
- Renal vein thrombus/renal artery embolism
- Arteriovenous malformation
- Papillary necrosis (sickle cell disease)

Ureter

- Malignancy
- Stone
- Stricture
- Fibroepithelial polyp
- Post-surgical conditions (ureteroiliac fistula)

Mimics of hematuria

- Menstruation
- Drugs (pyridium, phenytoin, rifampin, nitrofurantoin)
- Pigmenturia
- Beeturia

Renal and/or upper or lower collecting system:

- Infection (bacterial, fungal, viral)
- Malignancy
- Urolithiasis
- Tuberculosis
- Schistosomiasis
- Trauma
- Recent instrumentation including lithotripsy
- Exercise-induced hematuria
- Bleeding diathesis/anticoagulation*

Upper collecting system

Lower collecting system

Bladder

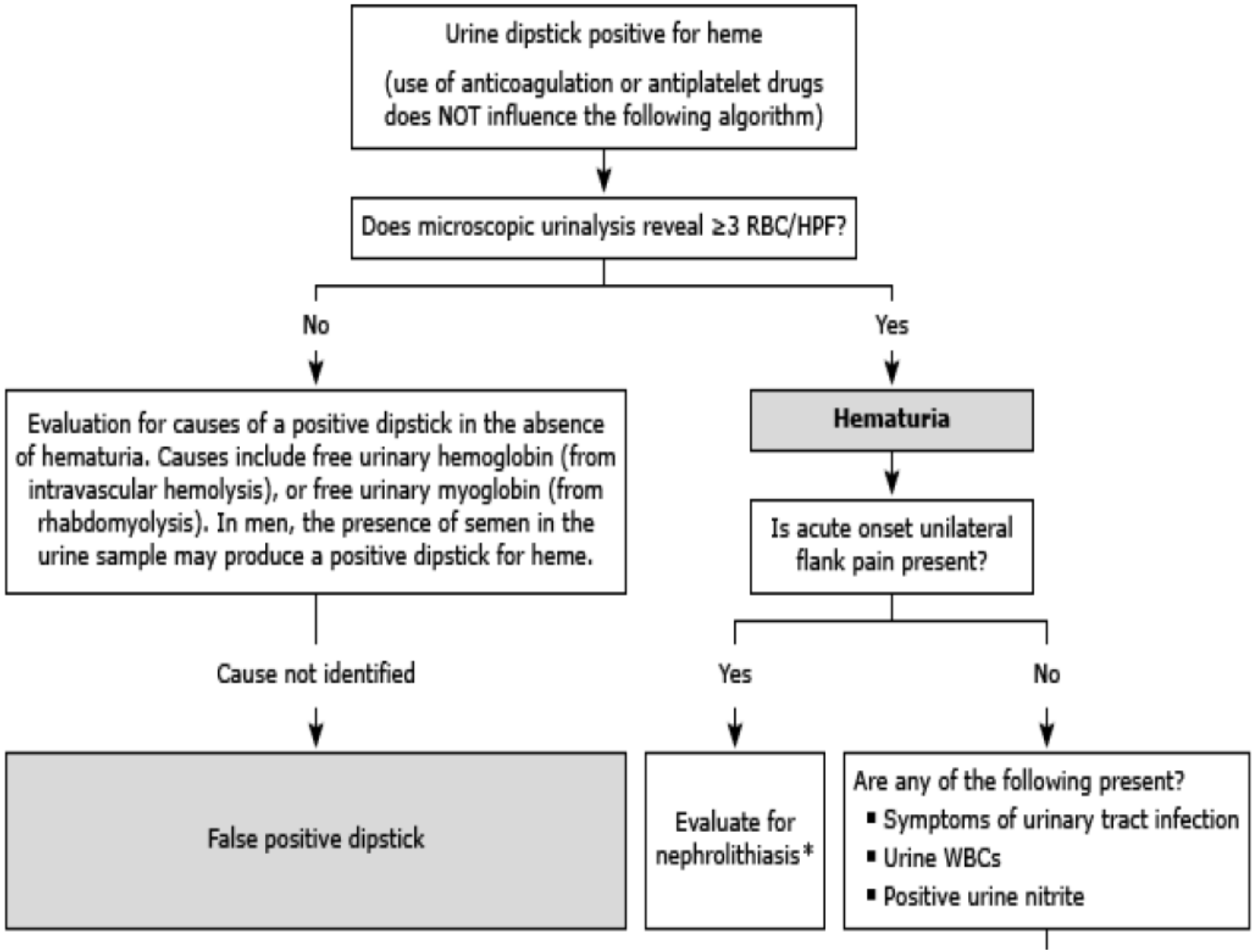
- Malignancy (transitional cell carcinoma, squamous cell carcinoma)
- Radiation
- Cystitis
- Bladder stones

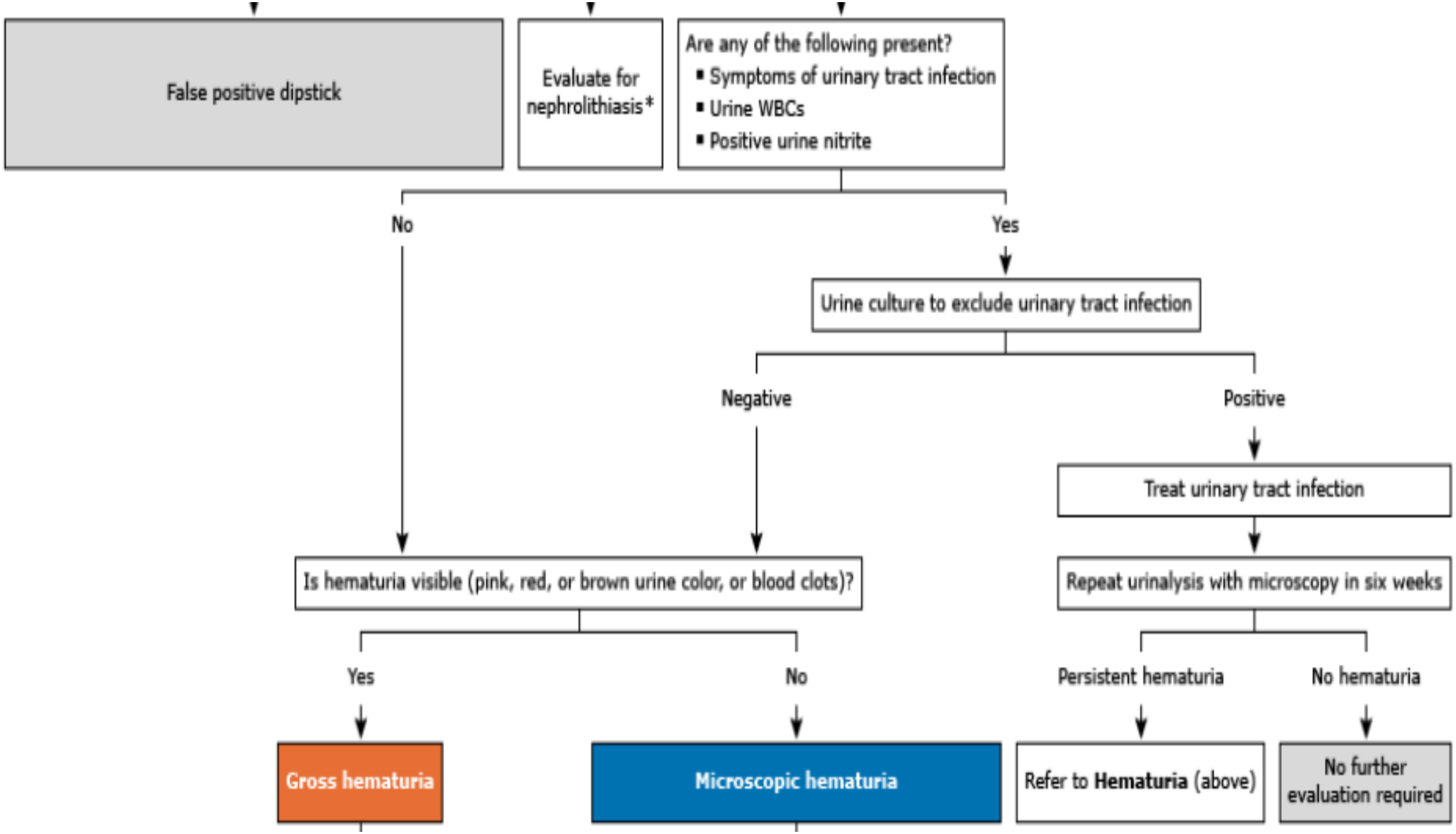
Prostate/urethra

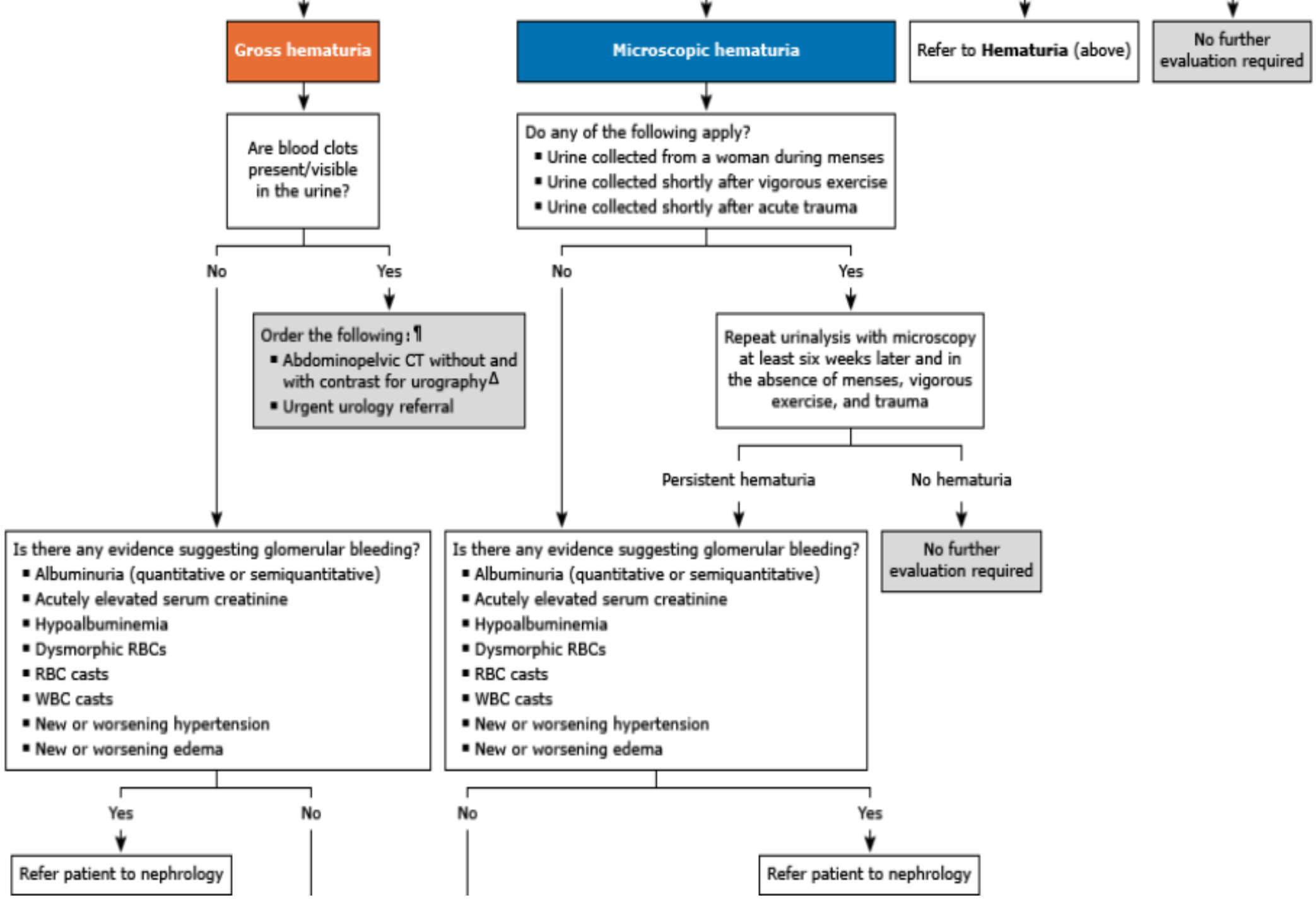
- Benign prostatic hyperplasia
- Prostate cancer
- Prostatic procedures (biopsy, transurethral resection of the prostate)
- Traumatic catheterization
- Urethritis
- Urethral diverticulum

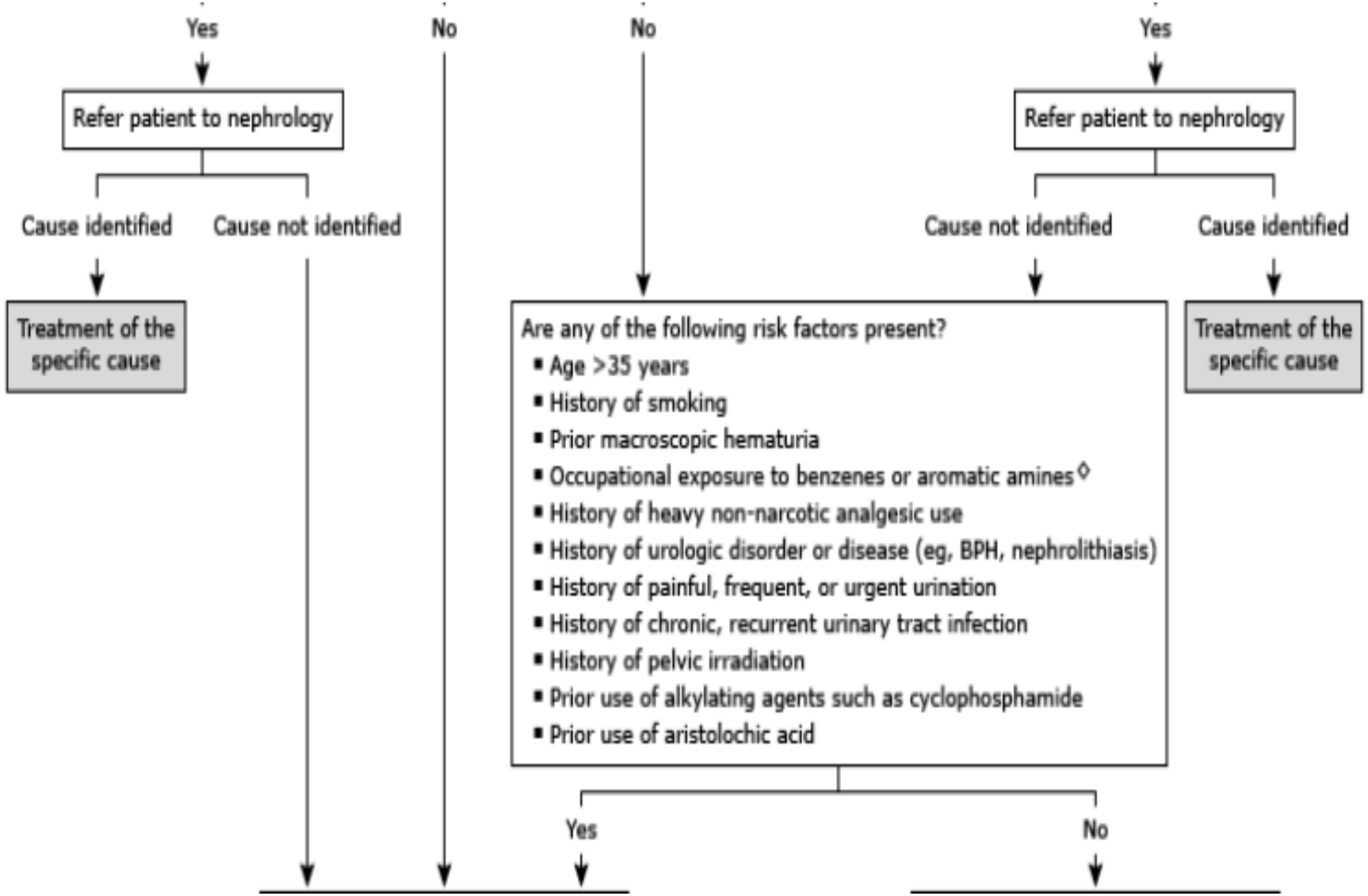
Evaluation

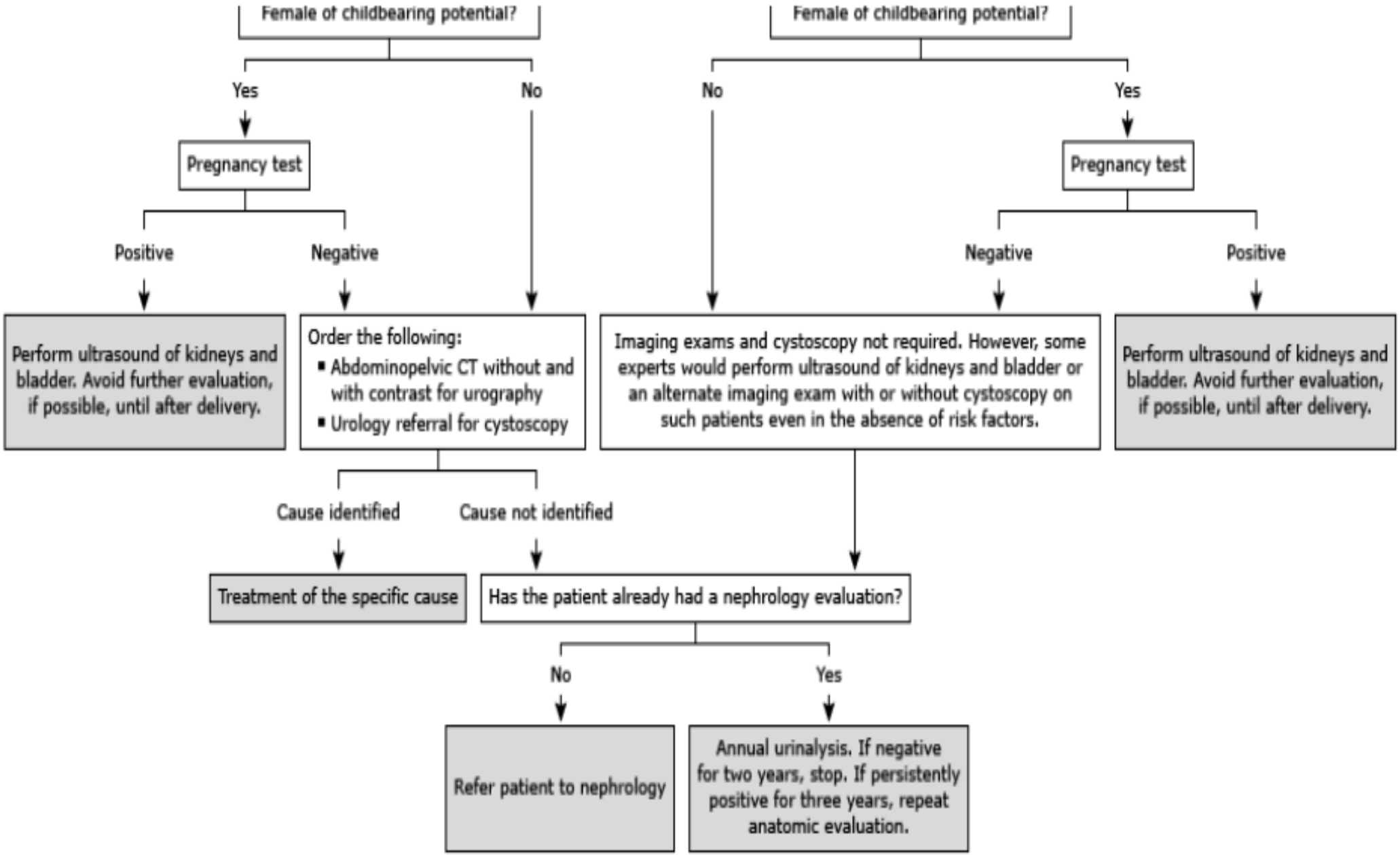
- Hematuria not imminently dangerous unless urinary retention and anemia in brisk nonglomerular bleeding
- First step: confirm by microscopic analysis
- Other causes of blood in the urine must be excluded
- Hematuria in the setting of vigorous exercise and trauma: repeated urinalysis after 4-6 weeks

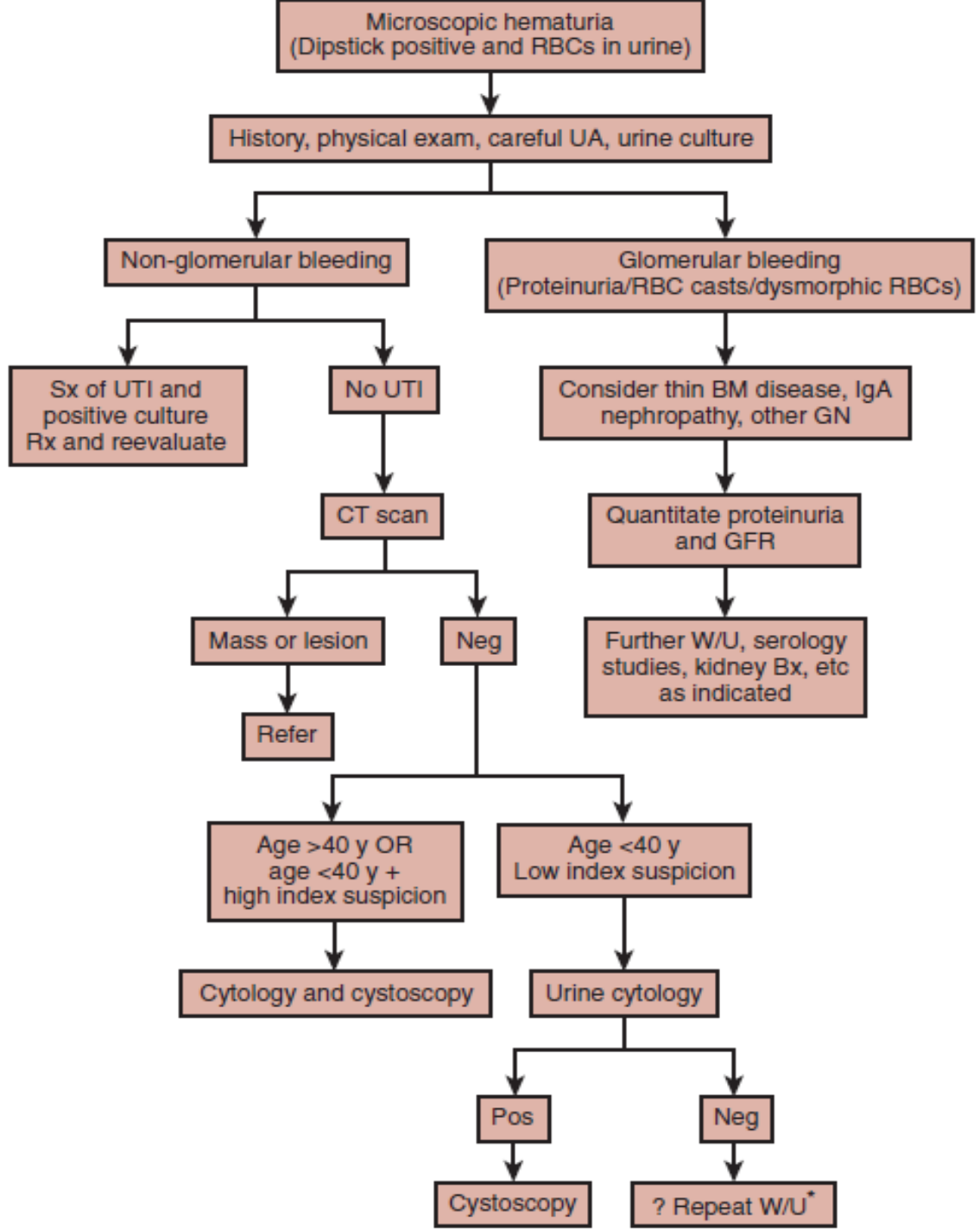

Urine dipstick positive for heme
(use of anticoagulation or antiplatelet drugs does NOT influence the following algorithm)
Does microscopic urinalysis reveal ≥3 RBC/HPF?
No
Yes
Evaluation for causes of a positive dipstick in the absence of hematuria. Causes include free urinary hemoglobin (from intravascular hemolysis), or free urinary myoglobin (from rhabdomyolysis). In men, the presence of semen in the urine sample may produce a positive dipstick for heme.
Hematuria
Is acute onset unilateral flank pain present?
Cause not identified
Yes
No
False positive dipstick
Evaluate for nephrolithiasis*
Are any of the following present?
Symptoms of urinary tract infection
Urine WBCs
Positive urine nitrite


False positive dipstick
Evaluate for nephrolithiasis*
Are any of the following present?
Symptoms of urinary tract infection
Urine WBCs
Positive urine nitrite
No
Yes
Urine culture to exclude urinary tract infection
Negative
Positive
Treat urinary tract infection
Repeat urinalysis with microscopy in six weeks
Is hematuria visible (pink, red, or brown urine color, or blood clots)?
Yes
No
Persistent hematuria
No hematuria
Gross hematuria
Microscopic hematuria
Refer to Hematuria (above)
No further evaluation required


Gross hematuria
Microscopic hematuria
Refer to **Hematuria** (above)
No further evaluation required
Are blood clots present/visible in the urine?
Do any of the following apply?
Urine collected from a woman during menses
Urine collected shortly after vigorous exercise
Urine collected shortly after acute trauma
No
Yes
No
Yes
Order the following: ¶
Abdominopelvic CT without and with contrast for urography Δ
Urgent urology referral
Repeat urinalysis with microscopy at least six weeks later and in the absence of menses, vigorous exercise, and trauma
Persistent hematuria
No hematuria
No further evaluation required
Is there any evidence suggesting glomerular bleeding?
Albuminuria (quantitative or semiquantitative)
Acutely elevated serum creatinine
Hypoalbuminemia
Dysmorphic RBCs
RBC casts
WBC casts
New or worsening hypertension
New or worsening edema
Is there any evidence suggesting glomerular bleeding?
Albuminuria (quantitative or semiquantitative)
Acutely elevated serum creatinine
Hypoalbuminemia
Dysmorphic RBCs
RBC casts
WBC casts
New or worsening hypertension
New or worsening edema
Yes
No
No
Yes
Refer patient to nephrology
Refer patient to nephrology


Yes
Refer patient to nephrology
Cause identified
Cause not identified
Treatment of the specific cause
No
No
Are any of the following risk factors present?
Age >35 years
History of smoking
Prior macroscopic hematuria
Occupational exposure to benzenes or aromatic amines◊
History of heavy non-narcotic analgesic use
History of urologic disorder or disease (eg, BPH, nephrolithiasis)
History of painful, frequent, or urgent urination
History of chronic, recurrent urinary tract infection
History of pelvic irradiation
Prior use of alkylating agents such as cyclophosphamide
Prior use of aristolochic acid
Yes
No
Yes
Refer patient to nephrology
Cause not identified
Cause identified
Treatment of the specific cause


Female of childbearing potential?
Yes
No
Pregnancy test
Positive
Negative
Perform ultrasound of kidneys and bladder. Avoid further evaluation, if possible, until after delivery.
Order the following:
Abdominopelvic CT without and with contrast for urography
Urology referral for cystoscopy
Cause identified
Cause not identified
Treatment of the specific cause
Female of childbearing potential?
No
Yes
Pregnancy test
Negative
Positive
Imaging exams and cystoscopy not required. However, some experts would perform ultrasound of kidneys and bladder or an alternate imaging exam with or without cystoscopy on such patients even in the absence of risk factors.
Perform ultrasound of kidneys and bladder. Avoid further evaluation, if possible, until after delivery.
Has the patient already had a nephrology evaluation?
No
Yes
Refer patient to nephrology
Annual urinalysis. If negative for two years, stop. If persistently positive for three years, repeat anatomic evaluation.


Microscopic hematuria
(Dipstick positive and RBCs in urine)
History, physical exam, careful UA, urine culture
Non-glomerular bleeding
Glomerular bleeding
(Proteinuria/RBC casts/dysmorphic RBCs)
Sx of UTI and
positive culture
Rx and reevaluate
No UTI
Consider thin BM disease, IgA
nephropathy, other GN
CT scan
Quantitate proteinuria
and GFR
Mass or lesion
Neg
Further W/U, serology
studies, kidney Bx, etc
as indicated
Refer
Age >40 y OR
age <40 y +
high index suspicion
Age <40 y
Low index suspicion
Cytology and cystoscopy
Urine cytology
Pos
Neg
Cystoscopy
? Repeat W/U*

Evaluation, historical clue

- Pyuria and dysuria: UTI or malignancy
- Recent URI or symptom: post infectious GN, Ig A Nephropathy, vasculitis, anti GBM disease
- Positive family history: hereditary nephritis, SCD,PCKD
- Unilateral flank pain: ureteral obstruction due to a calculus or blood clot(malignancy or Ig A nephropathy)
- History of excessive anticoagulant therapy, vigorous exercise, BPH
- Sterile pyuria with hematuria: TB, Analgesic nephropathy, interstitial disease

Evaluation, glomerular vs nonglomerular

- Clear evidence of glomerular hematuria: no evaluation of serious urologic disease
- Glomerular bleeding: proteinuria> 500 mg/day
- New-onset hematuria in prior chronic proteinuria: consideration of urologic source
- RBC casts: GN or vasculitis, rarely interstitial nephritis
- Absence of RBC cast not exclude glomerular hematuria

Distinguishing extraglomerular from glomerular hematuria

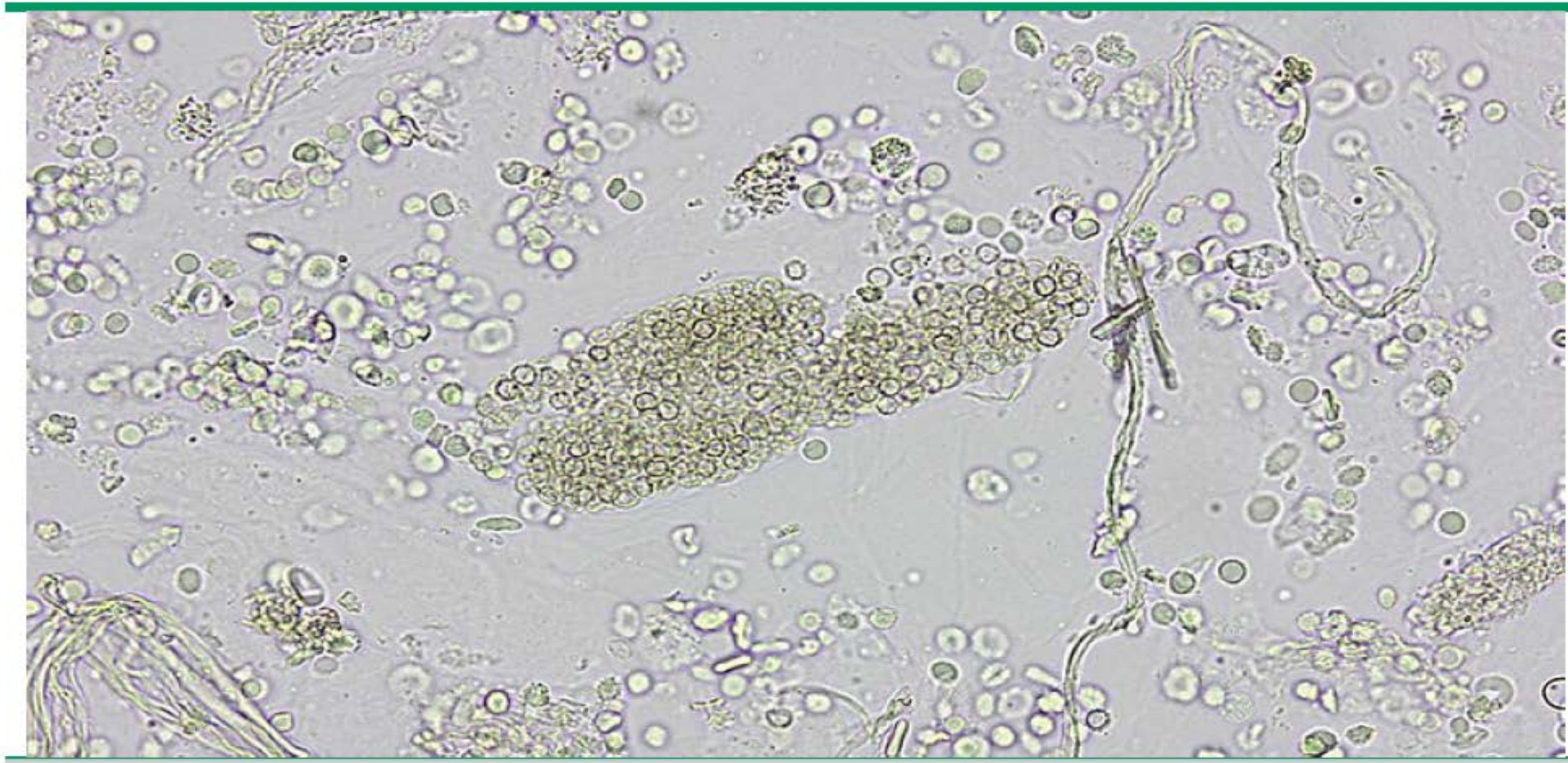
	Extraglomerular	Glomerular
Color (if macroscopic)	Red or pink	Red, smoky brown, or "Coca-Cola"
Clots	May be present	Absent
Proteinuria	<500 mg/day	May be >500 mg/day
RBC morphology	Normal	Some RBCs are dysmorphic
RBC casts	Absent	May be present

RBC: red blood cell.

Evaluation, glomerular vs nonglomerular

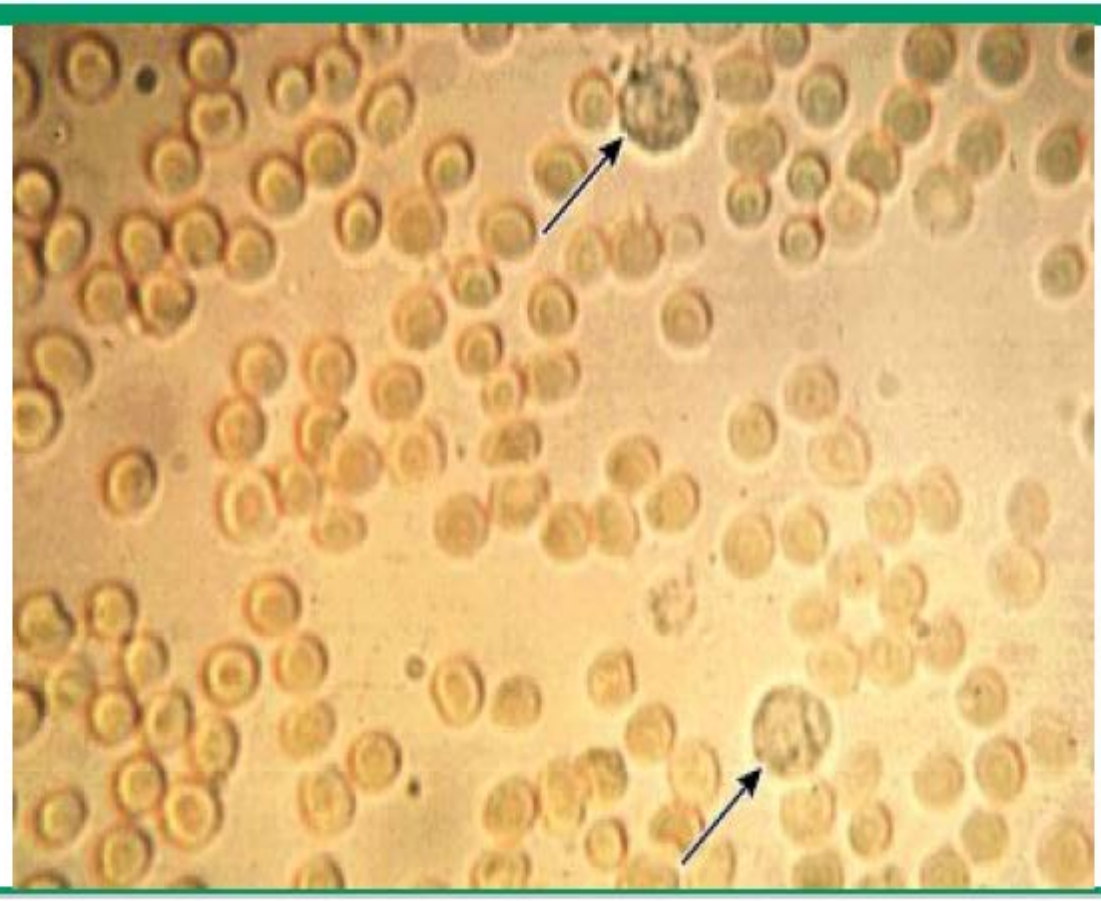
- Normomorphic RBCs occasionally in GN in the setting of forced diuresis, advanced RF or gross hematuria
- Magnitude of dysmorphic hematuria is best expressed in absolute terms rather than as a percentage of urinary RBCs
- Type of dysmorphic RBC may be of diagnostic importance
- Dysmorphic RBCs alone may be predictive of only renal bleeding
- Acanthocytes (ring-shaped RBCs with vesicle-shaped protrusion in phase-contrast microscopy): most predictive of glomerular disease
- Acanthocytes ≥5 percent of excreted RBCs (sensitivity and specificity 52 and 98 percent)

Photomicrograph of urine sediment with a red cell cast



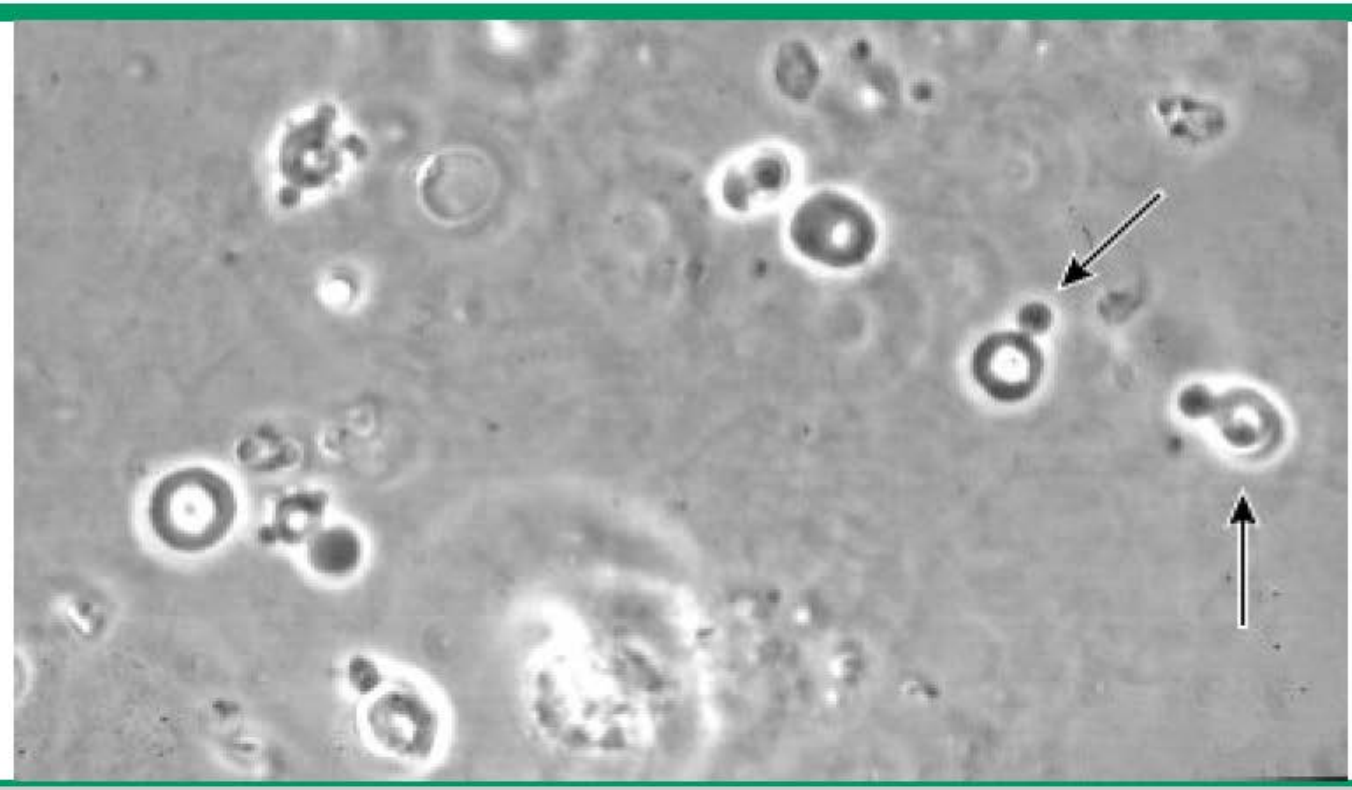
Urine sediment showing free red cells and a red cell cast that is tightly packed with red cells. It is more common for red cell casts to have fewer red cells trapped within a hyaline or granular cast. Red cell casts are virtually diagnostic of glomerulonephritis or vasculitis.

Phase-contrast micrograph showing monomorphic red cells in urine sediment



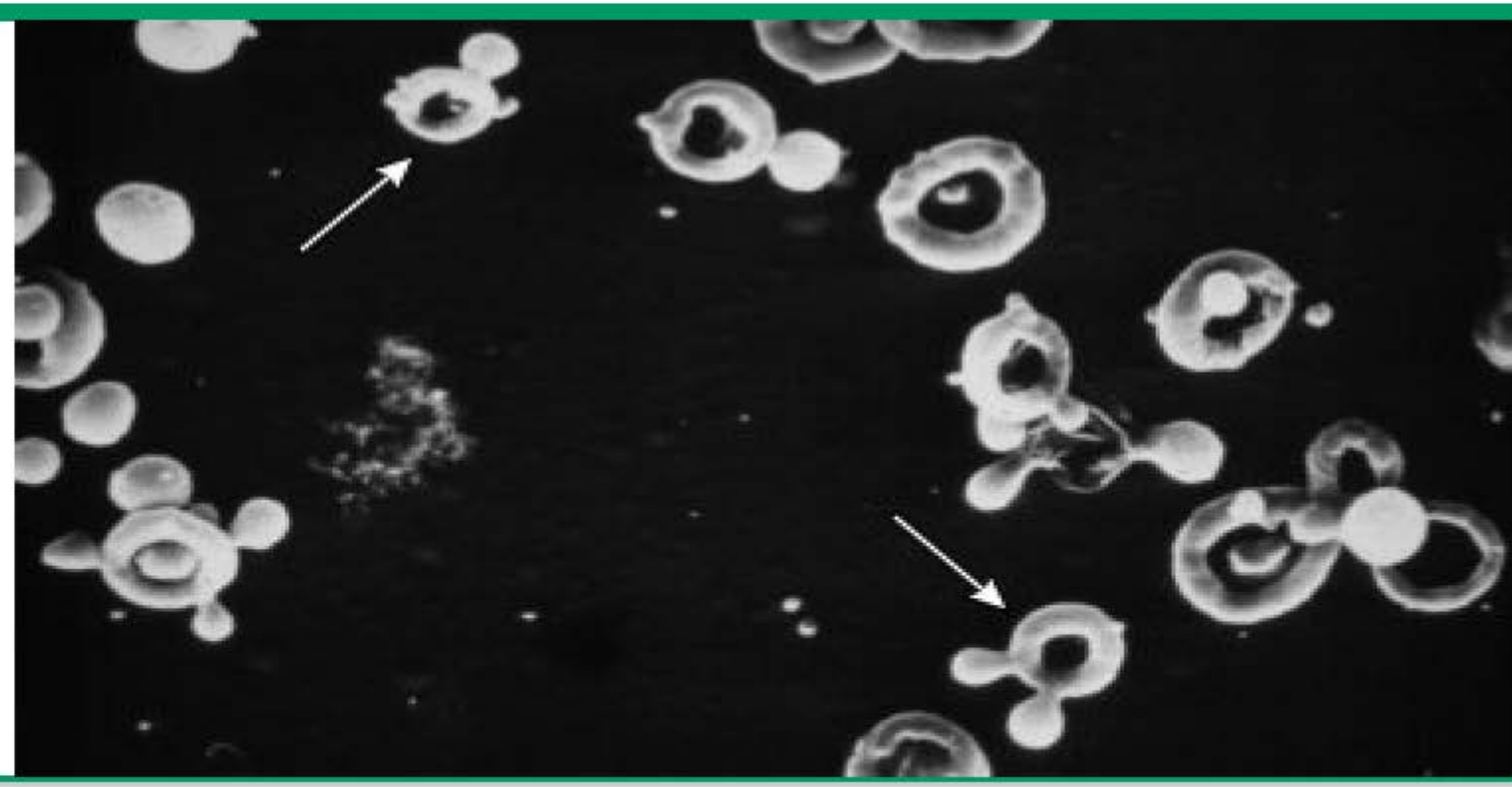
Urine sediment viewed by phase-contrast microscopy showing many red cells and an occasional larger white cell with a granular cytoplasm (arrows). The red cells have a uniform size and shape, suggesting that they are of nonglomerular origin.

Phase-contrast micrograph showing dysmorphic red cells in urine sediment



Phase-contrast microscopy showing dysmorphic red cells in a patient with glomerular bleeding. Acanthocytes can be recognized as ring forms with vesicle-shaped protrusions (arrows).

Scanning electron micrograph showing dysmorphic red cells in urine sediment



Scanning microscopy showing dysmorphic red cells in a patient with glomerular bleeding. Acanthocytes can be recognized as ring forms with vesicle-shaped protrusions (arrows).

Evaluation, glomerular vs nonglomerular

- Mild to moderate proteinuria: both glomerular and nonglomerular hematuria
- Higher percentage of urine protein in the form of albumin: consistent with glomerular hematuria
- High urine albumin-to-protein ratio can help to distinguish glomerular from nonglomerular hematuria
- Urine albumin-to-protein ratio of ≥0.59: sensitivity of 97.1 % for glomerular hematuria

Evaluation, glomerular vs nonglomerular

- Typically red to pink urine: nonglomerular bleeding and alkaline urine in glomerular bleeding
- Smoky brown or cola color: glomerular bleeding
- Combination of prolonged transit time through the nephron and an acid urine: formation of methemoglobin
- Blood clots: almost always **nonglomerular** bleeding
- Microhematuria alone does **not** typically lead to a significant increase in protein excretion
- A dipstick test for protein greater than 1+: rarely observed with nonglomerular bleeding

Kidney biopsy

- Kidney biopsy is **not** usually performed for isolated glomerular hematuria (ie, no abnormal proteinuria, no elevation in serum creatinine, no elevation in blood pressure about a previous stable baseline, and no systemic manifestations or family history of renal disease)
- Most common findings are a normal biopsy or one of four disorders: IgA nephropathy, TBM disease, mild nonspecfic glomerular abnormalities, and hereditary nephritis
- Kidney biopsy is **not indicated** in patients with persistent, isolated **nonglomerular hematuria**

Monitoring

- If kidney biopsy not performed, Serum creatinine, urinalysis, and urine protein excretion: monitored yearly for at least five years

Transient or persistent hematuria

- Transient microscopic hematuria is a common problem in adults
- Repeat an abnormal urinalysis in a few days to determine if hematuria is transient or persistent
- Potential causes of transient hematuria: Fever, infection, trauma, and exercise, UTI
- Exception to the typically benign nature of transient hematuria: patients over age 40 years carries an increased risk of malignancy

Risk factors for malignancy

AUA recommendations and guidelines on asymptomatic microscopic hematuria

- Male gender
- Age >35 years
- Past or current smoking history ,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 (20% vs 1.9%)

Risk factors for malignancy

- 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 exposure to aristolochic acid
- History of analgesic abuse

Urine cytology

- No longer recommended due to variable sensitivity and specificity
- May be a role for urinary cytology in patients with suspected carcinoma in situ (ie, with risk factors for malignancy and irritative voiding symptoms)
- Not in simple asymptomatic microscopic hematuria

Imaging, CTU

- CT of the abdomen and pelvis without and with IV contrast for urography (CTU): in patients with otherwise unexplained hematuria
- Initially without contrast: nephrolithiasis and hydronephrosis
- IV contrast, parenchymal phase and excretory phase (7-10 min after iv bolus of contrast): renal and urothelial malignancy, in the context of hydronephrosis, impaired function of the obstructed kidney
- CTU is the preferred initial imaging modality in almost all patients

Imaging, CTU

- Exceptions:
- 1) young patient (<35 years), no risk factors for urinary tract malignancy, noncontrast images of the CTU demonstrate nephrolithiasis
- 2) Pregnant women (initial evaluation: ultrasound)
- 3) Decreased renal function (GFR<30, limited excretion rate): CT without contrast, if negative for nephrolithiasis, MRU without contrast
- Combination of CTU and cystoscopy, provide a complete evaluation of the urinary system, in patients with unexplained hematuria

Imaging, CTU and IVU

- CTU is more accurate than IVP or ultrasound for the diagnosis of renal masses, urinary tract calculi, and pelvicalyceal and ureteric transitional cell carcinomas
- Low-dose CTU confers a radiation dose comparable with a conventional single-phase abdominopelvic CT
- CTU imaging was more sensitive (100 versus 61 percent) and specific (97 versus 91 percent) than an IVP (IVU)

Imaging, ultrasound

- Ultrasound compared with CTU, demonstrates lower diagnostic yield and is less sensitive in detecting urothelium transitional cell carcinoma, small renal masses, and calculi
- Ultrasound detected only 26, 60, 82, and 85 % of CT-confirmed lesions <1 cm, 1-2 cm, 2-3 cm, and 3 cm or more in size, respectively
- Ultrasound rather than CT is more cost effective when combined with cystoscopy

Imaging, MRU

- Diagnostic accuracy of MRU is comparable in detecting renal lesions but less for urothelial tumors
- Stones or calcifications are nearly invisible on MRU
- MRU, even without contrast, is more sensitive than noncontrast CT in detecting small renal masses and identifying tumors causing hydronephrosis (90 versus 42 percent)
- MRU is useful in patients where iodinated contrast is contraindicated and nephrolithiasis has been excluded or thought unlikely
- Useful in localizing the anatomic site of obstruction in pregnant women with hydronephrosis diagnosed on ultrasound

Retrograde pyelography

- Retrograde pyelography, is comparable with CTU in diagnosis of upper tract urothelial tumors
- In patients with contraindications to IV contrast, retrograde pyelography, adjunct to cystoscopy is reasonable option

cystoscopy

- Entire bladder can be visualized for malignancy or other abnormalities
- Cystoscopy may identify the source of the bleeding among patients with gross hematuria
- Unilateral bleeding: AVM, fistula, venous varices, or unilateral renal or upper urinary tract tumors or stones
- Only modality that permits visualization of the prostate and urethra

cystoscopy

- Macroscopic hematuria and no evidence of glomerular disease or infection should undergo cystoscopy
- Gross hematuria with blood clots should have cystoscopy even if they have evidence of a glomerular lesion
- Microscopic hematuria, no evidence of glomerular disease, infection, or a known cause of hematuria such as exercise and at increased risk for malignancy
- Diagnostic yield of cystoscopy is lower in patients who have microscopic hematuria, negative imaging, negative urine cytology, and at low risk for malignancy (AUA recommend)

Unexplained hematuria

- Most likely causes of persistent isolated hematuria: mild glomerulopathy and a predisposition to stone disease (in young and middle-aged patients)
- Glomerular disease: IgA nephropathy, TBM nephropathy, Mesangioproliferative glomerulonephritis without IgA deposits, Alport syndrome
- Hypercalciuria (30-35%), hyperuricosuria (5-20%)
- Rare causes of hematuria: hereditary hemorrhagic telangiectasis, radiation cystitis, schistosomiasis, AVMs and fistulas, nutcracker syndrome, and the loin pain hematuria syndrome

Follow-up after initial negative evaluation

- Follow-up with urinalysis, blood pressure monitoring, and, in some cases, repeat imaging and cystoscopy
- Transient hematuria and high risk for malignancy:
- 1)Monitor with annual urinalyses
- 2)After two consecutive negative urinalyses, this follow-up may be concluded
- 3)If gross hematuria occurs at any time, the full evaluation be repeated
- 4)If hypertension, proteinuria, an increase in serum creatinine, or evidence of glomerular bleeding develops: reevaluate for renal disease

Follow-up after initial negative evaluation

- Persistent hematuria: most serious disorder, an undiagnosed carcinoma of the urinary tract
- 420 patients followed at six-month intervals for more than one year, 5% an identifiable cause for hematuria within three years, and 1 % detectable urinary tract malignancy
- Monitoring with annual urinalyses; if persisting for three to five years, repeating the initial urologic workup
- Repeat ultrasound and cystoscopy at one year in high-risk patients

Screening for hematuria

- Population- or office-based screening for hematuria in patients who have no symptoms suggestive of urinary tract disease and who have no known risk factors for urothelial malignancies or hereditable glomerular disease is **not recommended**

conclusion

- First step in evaluation of hematuria, urine sediment and confirm by microscopic analysis
- Evaluation for UTI or nephrolithiasis
- Definine glomerular and nonglomerular source of bleeding
- Kidney biopsy, imaging, urine cytology and cystoscopy
- Follow-up of unexplained hematuria should be considered