MICROSCOPIC HEMATURIA

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BCRenal

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NO DISCLOSURES

OBJECTIVES

Definition

Different types of urine testing and indications

Approach/causes

Indications for specialist referral

WORKUP OF MICROSCOPIC HEMATURIA

- External Review Ongoing

Working group members

1. Chair: Dr. Kennard Tan, Medical Microbiologist, Vancouver
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3. Dr. Peter Birks , Nephrology, Fraser Health
4. Dr. Michael Chen, Medical Biochemist, Victoria
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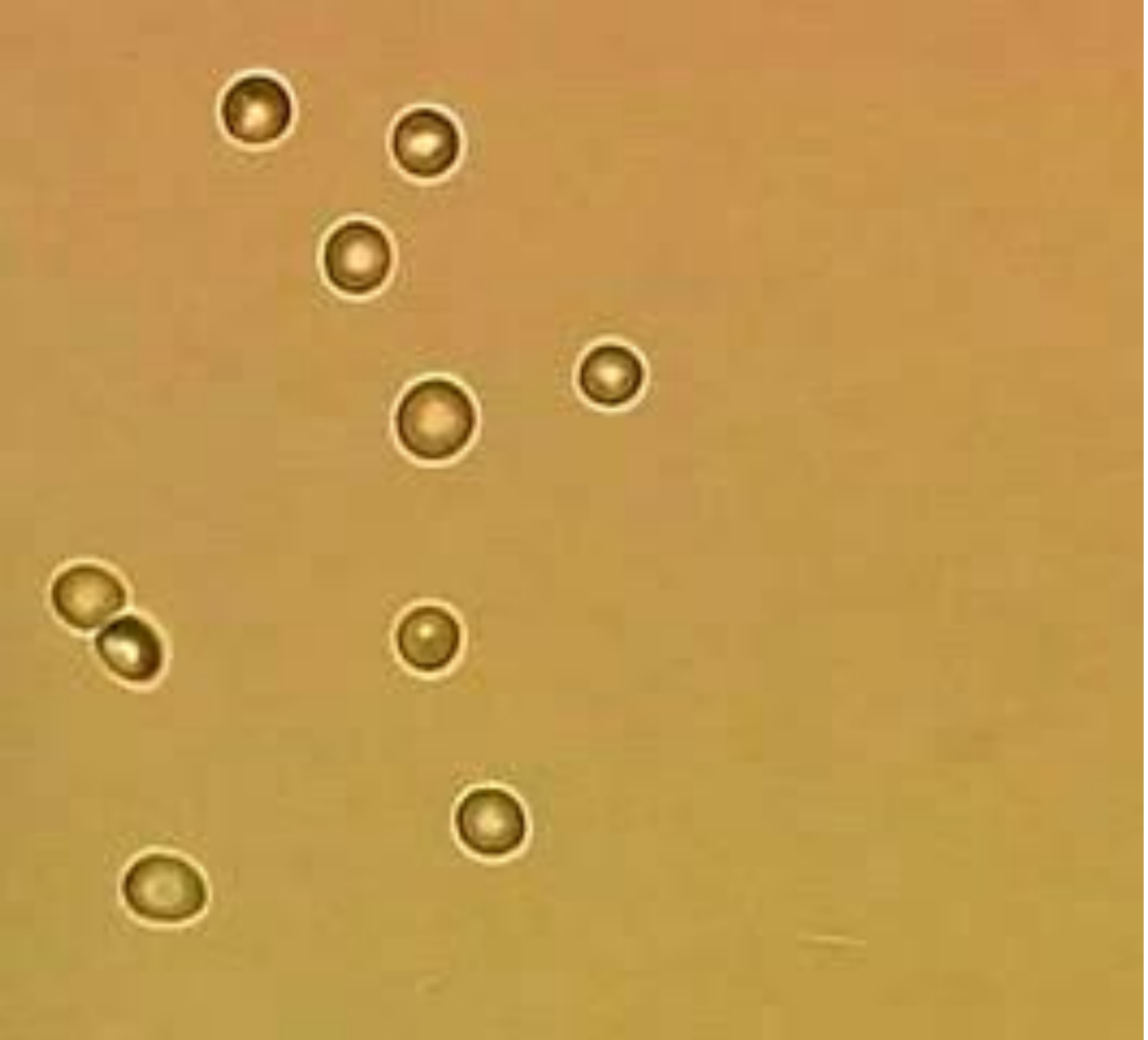
9. Katey Townsend Research Officer, Ministry of Health, Victoria

BACKGROUND

Prevalence microscopic hematuria is 2.4-31.1%

Often incidental, but may be associated with urologic malignancy in up to 10%

May be associated with nephrologic disease

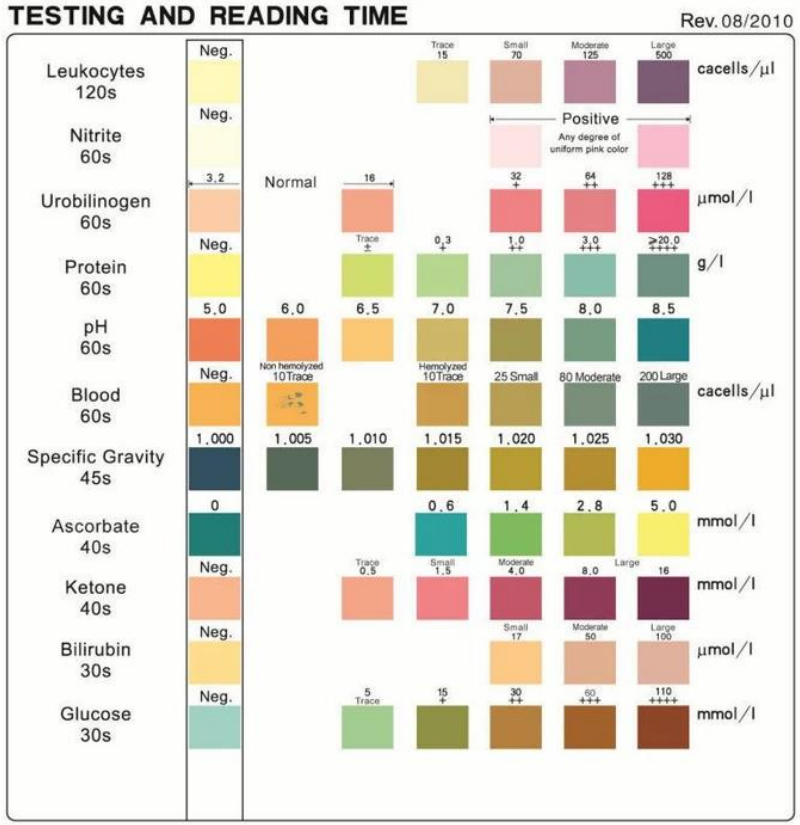


DEFINITION OF MICROSCOPIC HEMATURIA

- Significant microscopic hematuria is defined as **≥ 3 RBC per high power field** on urine microscopy

URINE TESTING

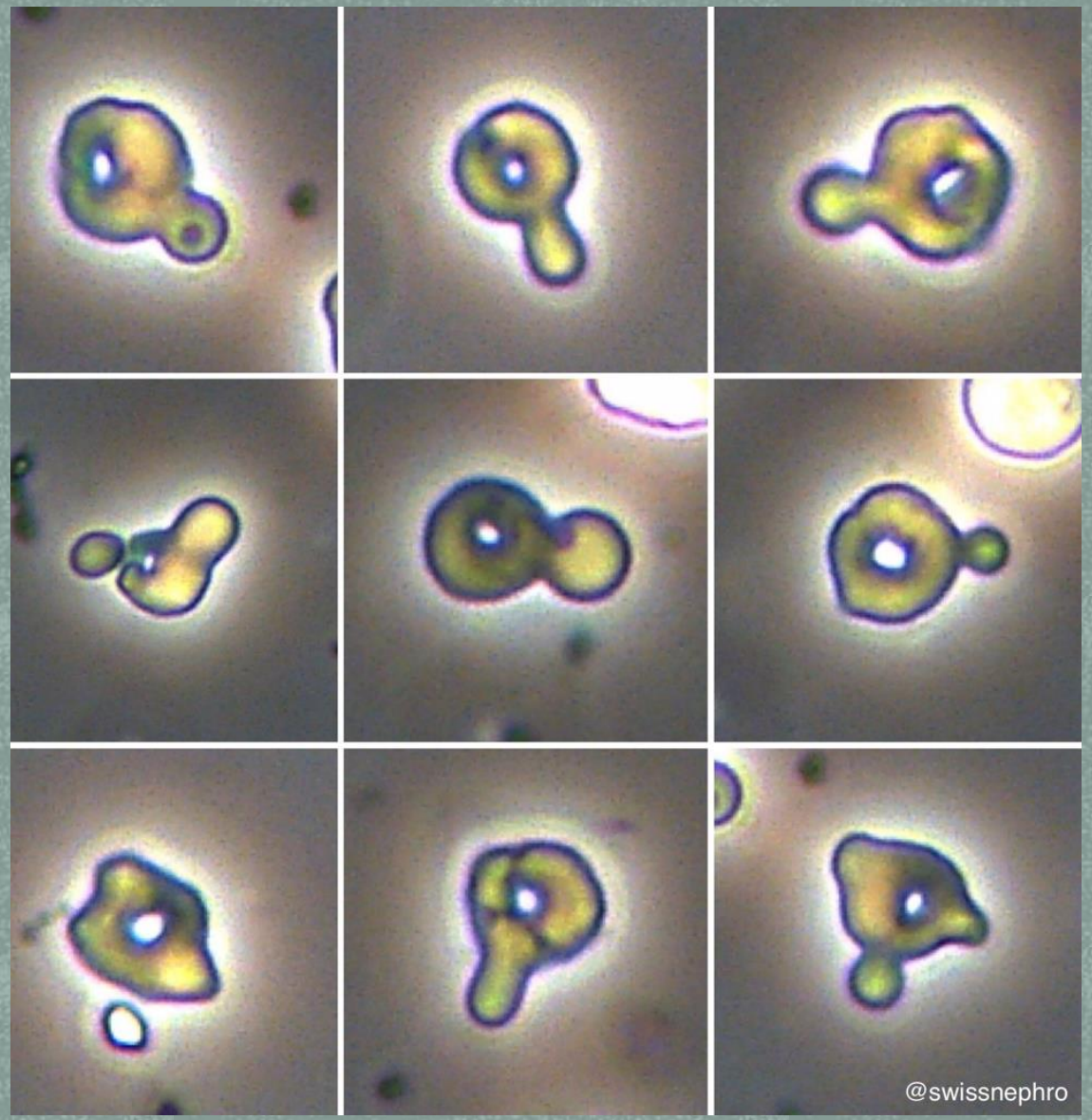
- Urinalysis
  - Includes dipstick and microscopy
  - Proper collection: midstream specimen in clean container without prior cleansing of genitalia
- Dipstick (Macroscopic urinalysis)
  - Picks up Heme
  - Sensitive but not specific (good rule out test…but needs to be confirmed)
  - False positive with myoglobin, semen, high urine pH



URINE TESTING

- Urine Microscopy
  - Detects cells, casts, crystals
  - Look at cell appearance (isomorphic vs dysmorphic)
- **Microscopy is not needed at initial screening in most cases and should be ordered in response to a positive dipstick**

Finding	Positive result indicates[3,18]
Urine Dipstick	
Specific Gravity	Indicates relative hydration/dehydration.
pH	Alkaline urine suggests presence of urea-splitting organism.
Leukocytes, white blood cells, pyuria	Measured by Leukocyte Esterase. Dipstick is positive in the presence of > 5-15 WBC/high-power field.
Nitrite	Detects presence of certain bacteria that convert nitrates into nitrites. Dipstick is positive when bacteria > 10^5 CFU/mL.
Protein	Proteinuria is defined as 10-20 mg per dL. 1+ = approximately 30 mg protein per dL 2+ = 100 mg per dL 3+ = 300 mg per dL 4+= 10000 mg per dL
Glucose	Presence indicates glycosuria.
Ketones	Measured by acetic acid. Presence indicates ketonuria.
Blood	Detects presence of > 1-4 red blood cells/high-power field.
Urine Microscopy	
Red Blood Cells (RBCs)	Urinary tract inflammation or glomerular bleeding. For a list of other causes, see Urinalysis: A Comprehensive Review.[18] In the case of isolated microscopic hematuria, refer to the BC Guideline: Microscopic Hematuria.
White Blood Cells (WBCs)	Infection, interstitial nephritis.
Hyaline casts	Normal when found absence of other casts.
Granular casts	Acute tubular necrosis (ATN).
RBC casts	Glomerulonephritis.
WBC casts	Acute interstitial nephritis or pyelonephritis.
Waxy casts	Non-specific, acute or chronic kidney impairment.
Fatty casts	Marked proteinuria or nephrotic syndromes.
Renal tubular epithelial cells	Acute tubular necrosis (ATN).
Bacteria	Infection, contamination and/or overgrowth.
Schistosome ova/miracidia	Detection of *Schistosoma haematobium* requires a special request.
Urate or other crystals	Interpret based on crystal found.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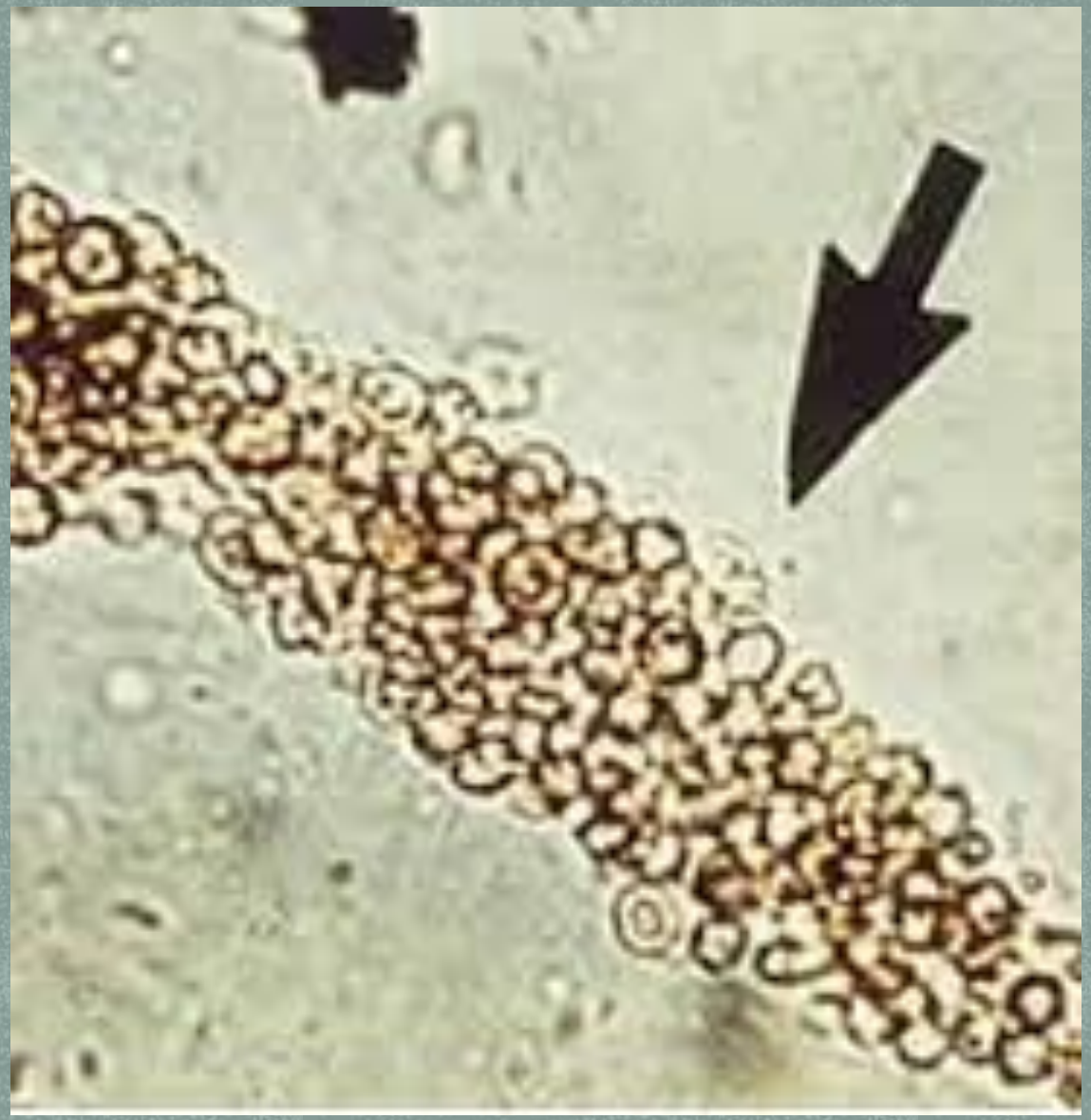
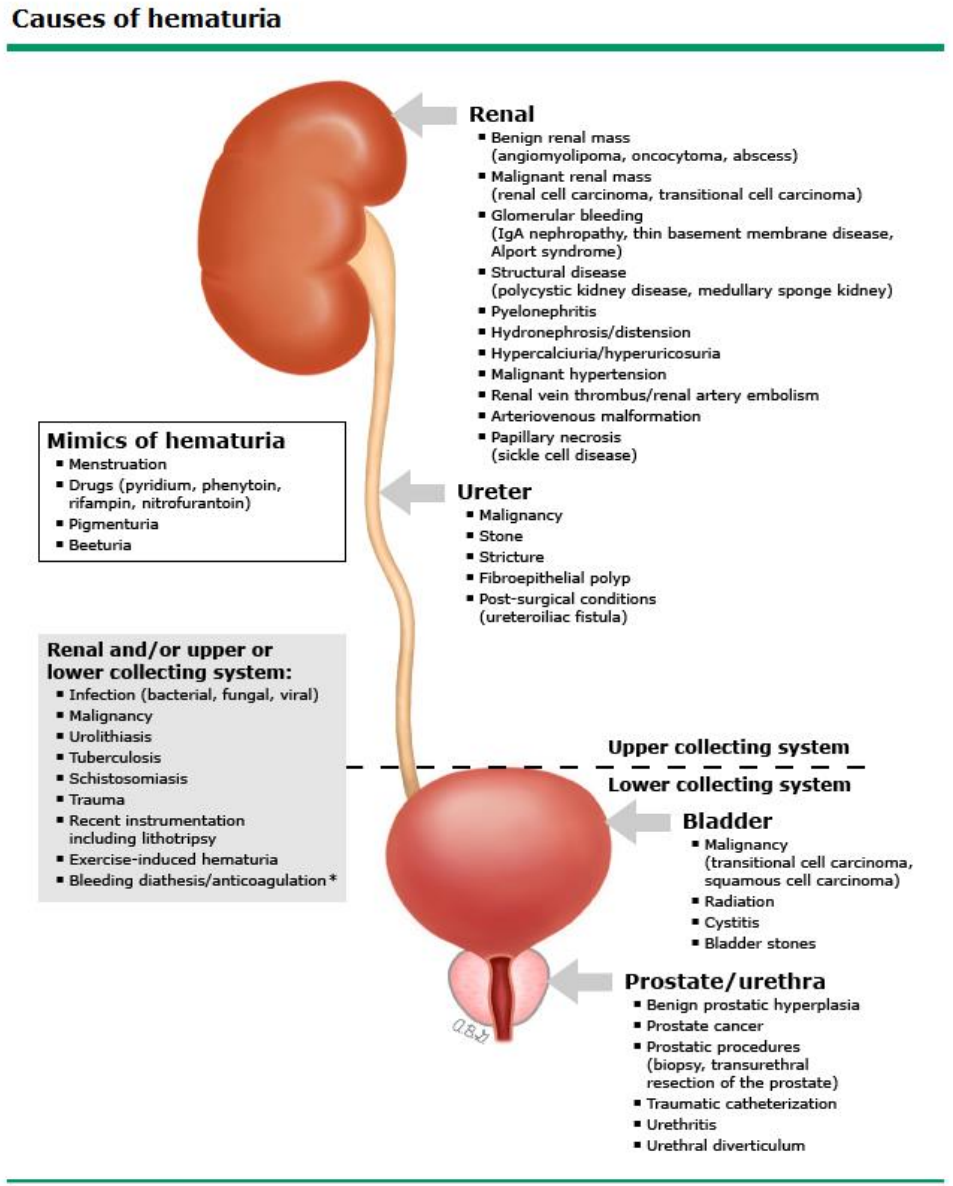


APPROACH TO MICROSCOPIC HEMATURIA

- Mimics
  - Menstrual
  - Drugs/foods causing red urine
- Systemic
  - Coagulopathy
- Renal
- Ureter
- Bladder
- Prostate
- Urethra

APPROACH TO MICROSCOPIC HEMATURIA



SCREENING

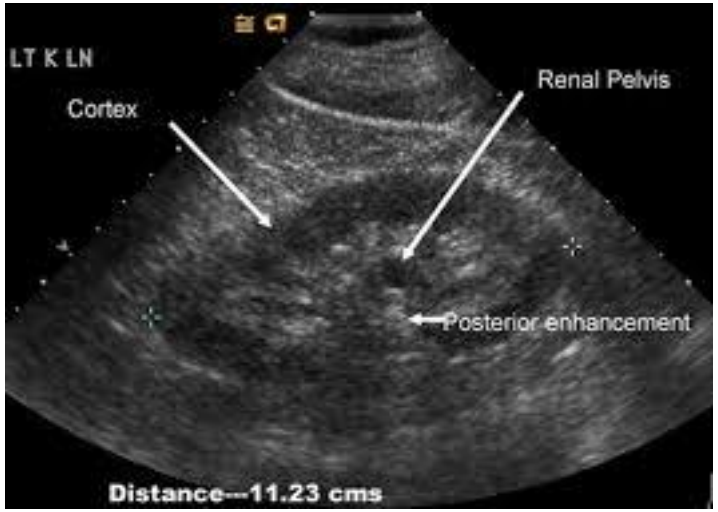
- Screening the general population not recommended (AUA 2012)
  - Higher risk patients should be screened
- Urine cytology is no longer recommended (AUA guidelines 2012)
- Positive urine dipstick should prompt urine microscopy
- Significant microscopic hematuria requires further workup

INVESTIGATION OF MICROSCOPIC HEMATURIA

- After detection, rule out contributing factors such as infection, menstruation, vigorous exercise, trauma to urethra
  - If present: repeat after resolution
- Assure urine culture has been performed
- If dipstick remains + → confirm with microscopy
- All patients should have a renal imaging with **Kidney-Bladder Ultrasound**
  - CT reasonable if high suspicion malignancy or stones

RENAL IMAGING

- Patient with confirmed microscopic hematuria should be imaged
- **KUB Ultrasound** is preferred initial investigation in most cases
- IVP is not generally used anymore
- CT IVP provides better detection of mass and stones
  - Non contrast CT KUB and single-phase enhanced CT are not adequate investigations for hematuria
  - BC guidelines recommends ultrasound first, then refer
  - CT reasonable for very high-risk patients
- No imaging test can completely assess lower tract disease….**Cystoscopy** is required



FINDINGS CONCERNING FOR RENAL PARENCHYMAL DISEASE

- Abnormal renal function
- Proteinuria (urine dipstick or urine ACR)
- RBC casts
- Dysmorphic RBC
- Other abnormal urine sediment including sterile pyuria
- *Recent URTI or pharyngitis*
- *Family history of renal disease such as ADPKD/Alport*
- These findings should prompt a **nephrology referral**

UROLOGIST REFERRAL

- All patients age > 40
- Patients with positive imaging findings
- Unexplained persistent microscopic hematuria
- Patients with risk factors for urothelial cancer

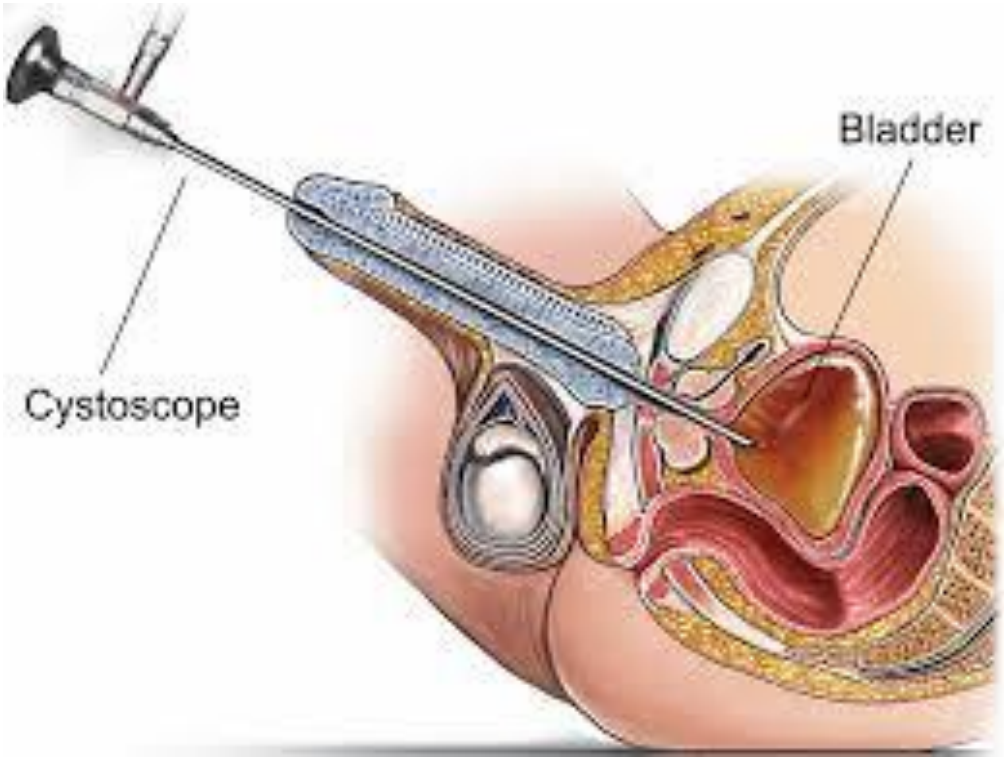
Risk Factors for Urothelial Cancer
Demographics
Age >40 years; risk increases with age
Male gender (2-3 times as high in men)
Caucasian ethnicity
Patients with a personal history of bladder cancer
Environmental
Smoking, past or present including exposure to second hand smoke
Occupational exposure to chemicals or dyes (e.g. benzenes or aromatic amines)**
Exposure to certain drugs (phenacetin, cyclophosphamide)
Overuse of analgesic drugs
Exposure to pelvic radiation
Urologic History
History of gross hematuria
Chronic inflammation of lower urinary tract. (e.g. chronic indwelling foreign body, chronic urinary tract infection, urethral or suprapubic catheter, ureteric stent, bladder stone and chronically infected stone)
History of irritative voiding symptoms
Schistosomiasis haematobium infection (exceedingly rare in North America; endemic to Middle East and Africa)

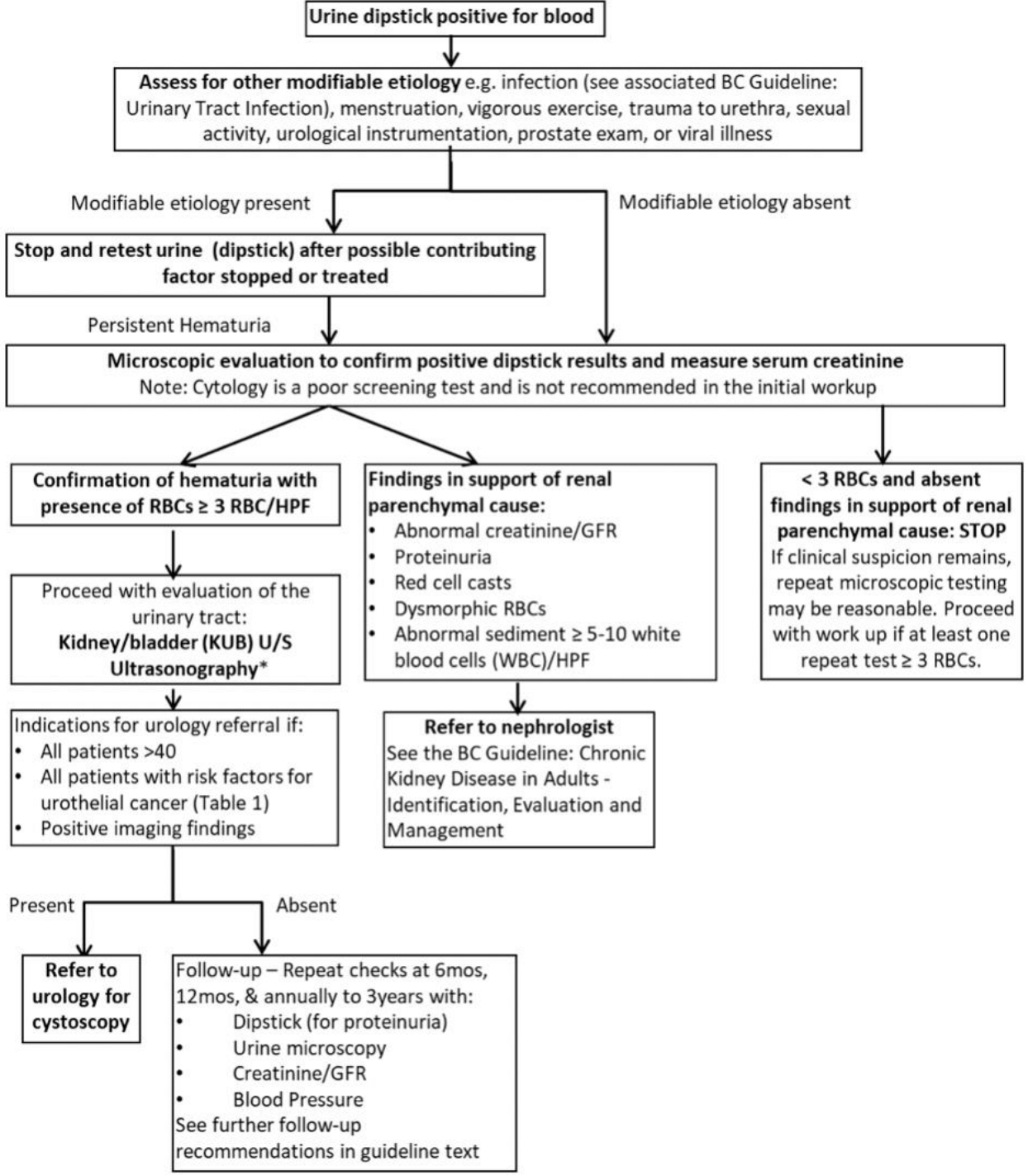
UROTHELIAL CANCER RISK

- Smoking is the most important risk factor for bladder cancer
- Men are 2-3x more likely to get bladder cancer

CYSTOSCOPY

- All patients > 40 with microscopic hematuria
- Patient of any age with microscopic hematuria and risk factors for urothelial cancer
- Patients of any age with suspicious findings for urologic malignancy




Urine dipstick positive for blood
Assess for other modifiable etiology e.g. infection (see associated BC Guideline: Urinary Tract Infection), menstruation, vigorous exercise, trauma to urethra, sexual activity, urological instrumentation, prostate exam, or viral illness
Modifiable etiology present
Modifiable etiology absent
Stop and retest urine (dipstick) after possible contributing factor stopped or treated
Persistent Hematuria
Microscopic evaluation to confirm positive dipstick results and measure serum creatinine
Note: Cytology is a poor screening test and is not recommended in the initial workup
Confirmation of hematuria with presence of RBCs ≥ 3 RBC/HPF
Findings in support of renal parenchymal cause:
• Abnormal creatinine/GFR
• Proteinuria
• Red cell casts
• Dysmorphic RBCs
• Abnormal sediment ≥ 5-10 white blood cells (WBC)/HPF
< 3 RBCs and absent findings in support of renal parenchymal cause: STOP
If clinical suspicion remains, repeat microscopic testing may be reasonable. Proceed with work up if at least one repeat test ≥ 3 RBCs.
Proceed with evaluation of the urinary tract:
Kidney/bladder (KUB) U/S
Ultrasonography*
Indications for urology referral if:
• All patients >40
• All patients with risk factors for urothelial cancer (Table 1)
• Positive imaging findings
Refer to nephrologist
See the BC Guideline: Chronic Kidney Disease in Adults - Identification, Evaluation and Management
Present
Absent
Refer to urology for cystoscopy
Follow-up – Repeat checks at 6mos, 12mos, & annually to 3years with:
• Dipstick (for proteinuria)
• Urine microscopy
• Creatinine/GFR
• Blood Pressure
See further follow-up recommendations in guideline text

ALGORITHM

NEGATIVE WORKUP?

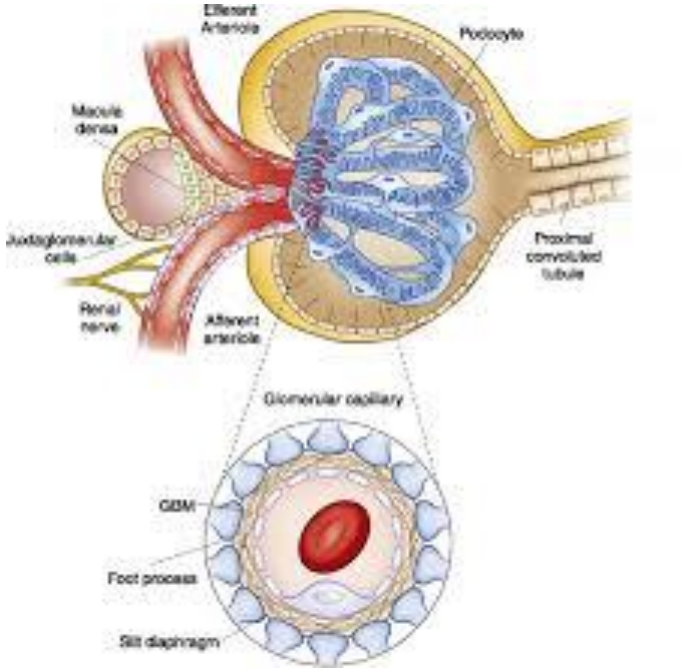
- Common
- Suggest at 6 and 12 months:
  - Urine ACR
  - Creatinine/GFR
  - Blood Pressure
- If 2 consecutive annual urine microscopies are negative, then routine follow up can be discontinued
- Re-initiate investigation if new gross hematuria, increase in amount RBC/HPF, symptoms

RENAL PARENCHYMAL DISEASES

- Glomerulonephritis (GN)
- Thin Basement Membrane
- Alport Syndrome
- Acute interstitial nephritis (AIN)
- Polycystic kidney disease
- Sickle cell disease
- Other
  - Loin pain hematuria syndrome
  - Nutcracker syndrome

GLOMERULONEPHRITIS - TERMINOLOGY

- Glomerular disease: Inherited or acquired disease of glomerulus
- Glomerulonephritis: Inflammation in the glomerulus
- Glomerular disease presents with some combination of proteinuria, hematuria, or change in renal function
  - Can present more on the nephritic or nephrotic spectrum depending on the cause and location of the glomerular pathology



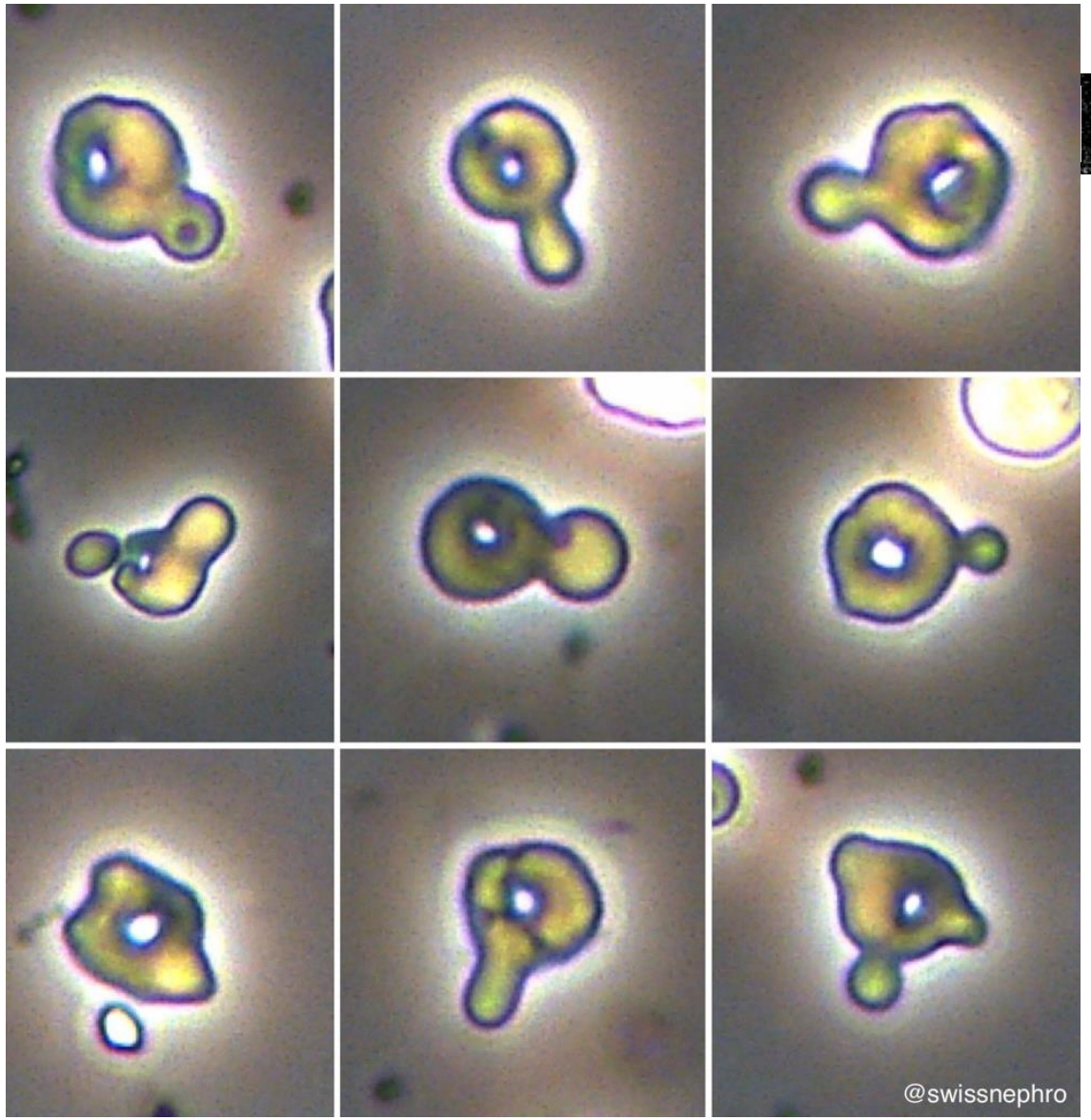
GLOMERULONEPHRITIS

Nephritic Syndrome

- **Hematuria**
  - Especially dysmorphic RBC and casts
- Renal insufficiency
- Oliguria
- Hypertension
- Proteinuria (non-nephrotic range)

Nephrotic Syndrome

- Proteinuria > 3.5g per day
- Edema
- Low albumin
- Hypertriglyceridemia
- Hypercoagulability
- Immunodeficiency
- *Typically no hematuria…but rarely can*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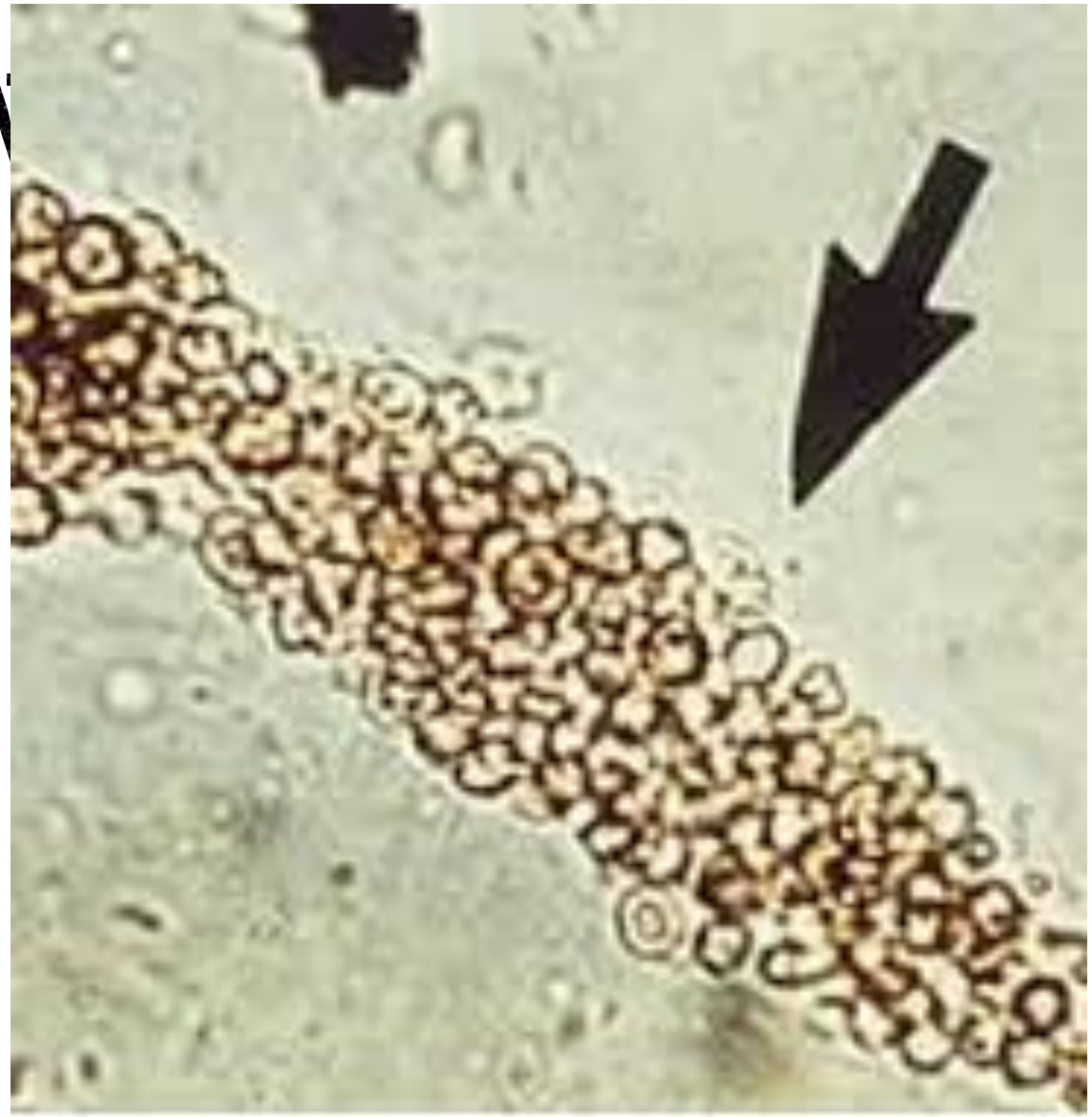


GLOMERULONEPHRITIS

Nephritic

- IgA /HSP
- ANCA Vasculitis (GPA, eGPA, MPA)
- Anti-GBM disease (Goodpasture's)
- SLE
- Post infectious GN (Strep/Staph)
- Endocarditis

Nephrotic

- Minimal change disease
- FSGS
- Membranous
- Diabetes
- Amyloidosis/myeloma

Mixed

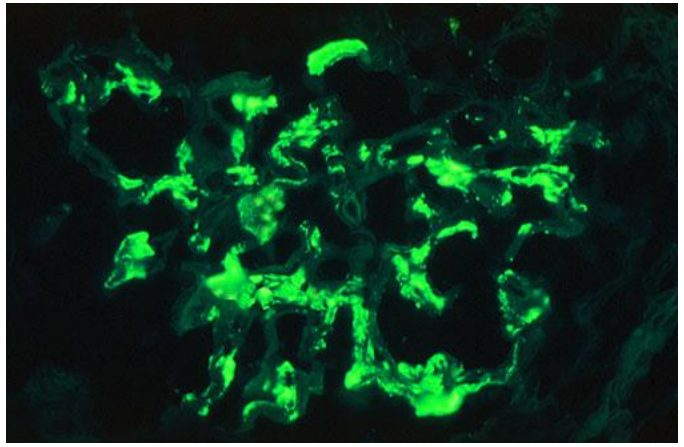
- Membranoproliferative GN (MPGN)
- IgA

GN WORKUP

- You can have primary GN or it can be related to an underlying cause such as ***malignancy, autoimmune disease, infection, or drugs***

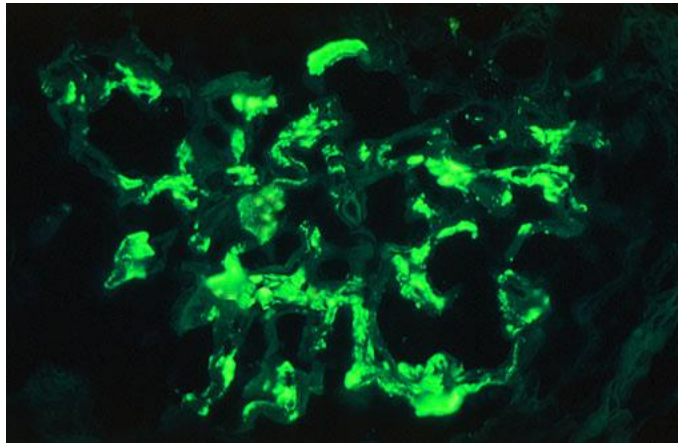
- HIV, Hepatitis B and C, Syphilis
- ANA, complements
- SPEP and UPEP
- ANCA and anti-GBM serology
- Cryoglobulins
- Blood cultures and ASOT

IGA NEPHROPATHY



- ”Berger’s diease”
- Most common primary glomerulonephritis in Western and Asian countries
- Characterized by deposits of IgA in glomerulus, causing inflammation
- Clinically
  - Episodic hematuria in 40-50%
  - Asymptomatic hematuria and proteinuria
  - Nephrotic syndrome or nephritic syndrome (rare, < 5%)
  - Acute kidney injury
  - CKD (25%)
- Episodes of macroscopic hematuria are often preceded by infection

IGA NEPHROPATHY

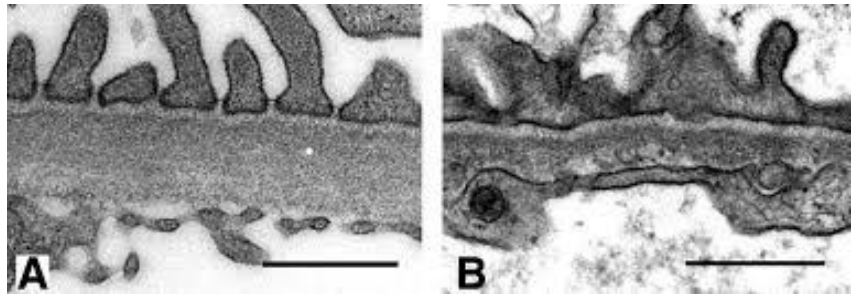


- Prognosis
  - Markers of poor prognosis: Hypertension, renal impairment, severity of proteinuria, renal biopsy findings
  - Good prognosis: Recurrent episodes of macroscopic hematuria

- Treatment
  - Blood pressure control (< 130/80)
  - RAS blockage (Urine ACR < 100 mg/mmol)
  - Fish Oil
  - Immunosuppressive agents for more severe cases
  - Transplant

THIN BASEMENT MEMBRANE DISEASE

- Familial or sporadic
  - Typically autosomal dominant
- Male = female
- Onset of hematuria typically in childhood/adolescence
- Can get gross hematuria, often in association with URTI
- Common cause of isolated glomerular hematuria
  - 20-25% of patients referred to nephrology for persistent hematuria
- GBM thinning seen on renal biopsy
- Hypertension, proteinuria, and progression to ESRD are rare
- Should be monitored over time as small risk of CKD (<5%)



Tryggvason et al, JASN 2006

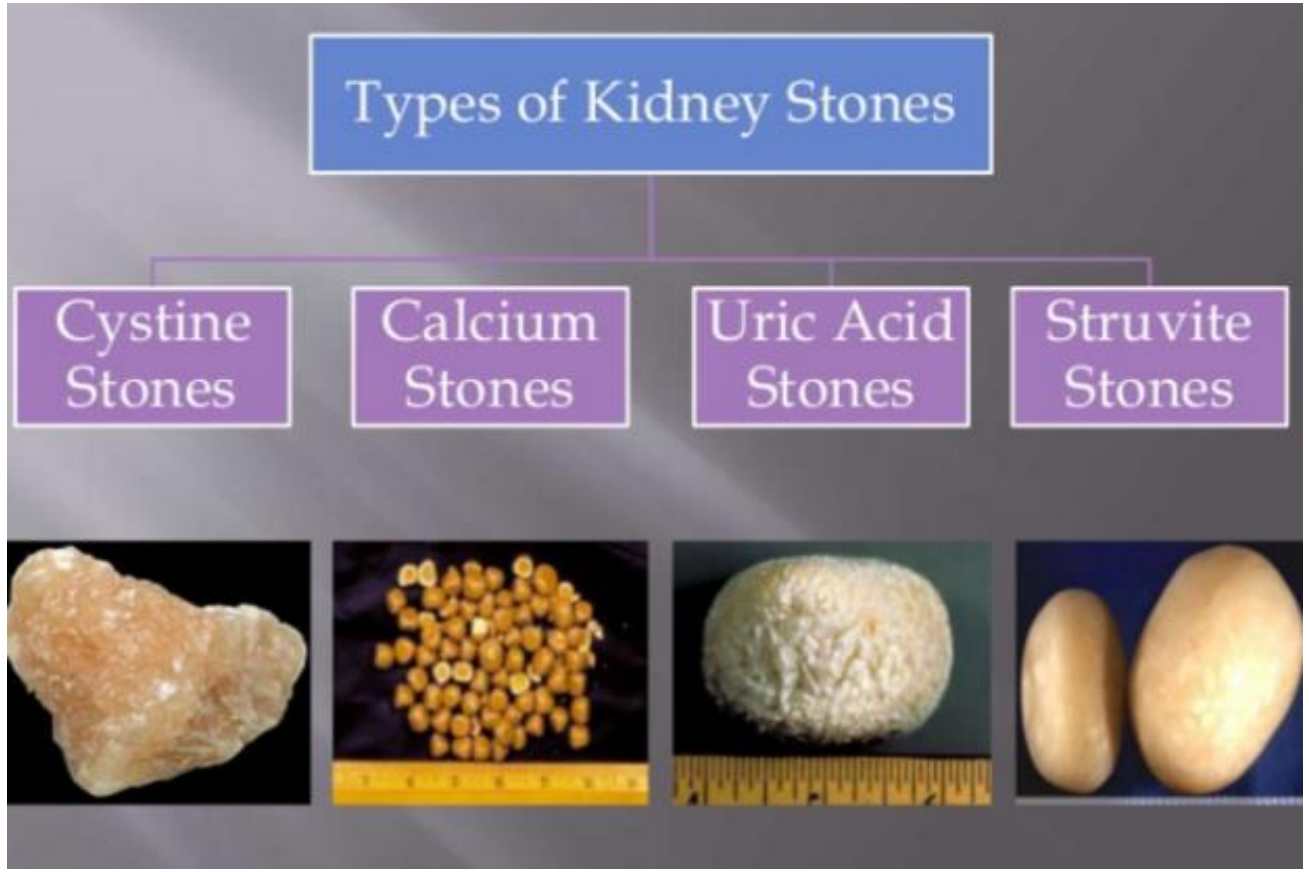
ALPORT SYNDROME

- Generalized inherited disorder of basement membranes
- Mutation affecting type IV collagen
- Clinical presentation
  - Hematuria, proteinuria, progressive nephritis
  - Sensorineural deafness
  - Ocular abnormalities
- Three forms
  - X-linked: 80% of patients, male patients progress to ESRD
  - Autosomal recessive: Typically no family history, likely form in females with severe disease
  - Autosomal dominant

ALPORT SYNDROME

- Diagnosis:
  - Kidney biopsy and genetic testing
- Treatment:
  - Early RAS blockade
  - Kidney transplantation

NEPHROLITHIASIS



-12% lifetime risk
-50% recurrence in 10 years

TYPES OF STONES

- **Calcium oxalate**: 75-80%
- Calcium phosphate 5%
- Struvite 15%
  - More common in females, associated with UTI
- Cystine: Rare, genetic
- Uric acid:
  - Often uric acid nidus, but mixed
  - higher risk if high uric acid levels/gout
- Meds (indinavir)
- Mixed

RISK FACTORS FOR STONES

- Risk factors
  - Urine pH: Uric acid stones only form in low pH, so that is why we alkalinize the urine
  - Hypocitruria
    - Citrate inhibits stone formation
    - Causes: chronic acidosis, high sodium intake
  - UTI and instrumentation risk factors for struvite
  - Family history
  - High sucrose and fructose
  - Vitamin D and C intake
  - Other diseases: Inflammatory bowel disease, hyperparathyroidism, sarcoidosis, idiopathic hypercalciuria, renal tubular acidosis, polycystic kidney disease, medullary sponge kidney

KIDNEY STONES: TREATMENT

- Treatment: Calcium oxalate stones
  - INCREASE WATER INTAKE (day and night)
  - Add some lemon to water (citrate)
  - Avoid high oxalate food
    - Tea, chocolate, lots of coffee, rhubarb, cranberry juice
  - High dietary calcium is protective
  - Reduce sodium intake
  - Reduce sucrose/fructose intake
  - Medications
    - K-citrate
    - Thiazide
  - Surgery

SUMMARY

- Significant microscopic hematuria is defined as **≥ 3 RBC per high power field** on urine microscopy
- Urine testing
  - Dipstick as screening/initial test
  - Urine microscopy as confirmatory test
- Rule out reversible causes such as UTI and re-test
- If persistent disease, image with Renal-Bladder Ultrasound
- Urology referral in high risk patients (anyone over 40 or with risk factors)
- Nephrology referral if reduced renal function, proteinuria, or active urine

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