Hematuria and Proteinuria

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Red Stick Potpourri 2022

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Learning Objectives

- Define microscopic hematuria.
- Distinguish between benign and abnormal proteinuria.
- Determine necessary evaluation for hematuria and proteinuria.
- Identify when referral to pediatric nephrology is indicated.

Hematuria

- Proteinuria and hematuria are the hallmarks of many renal diseases.
- Proteinuria or RBCs are frequently found in the urine of healthy children and adolescents.
- AAP deleted routine urine screening from recommendations for well child visits in 2008.

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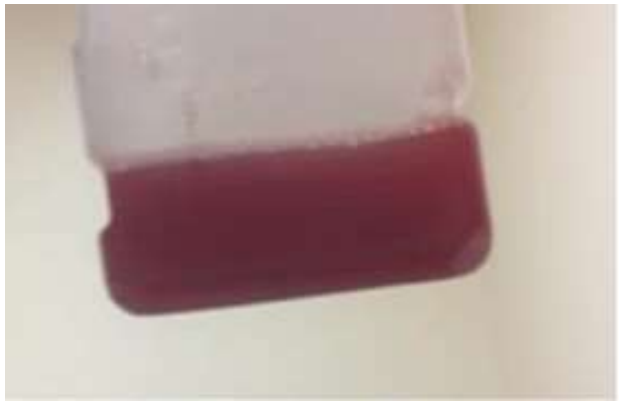
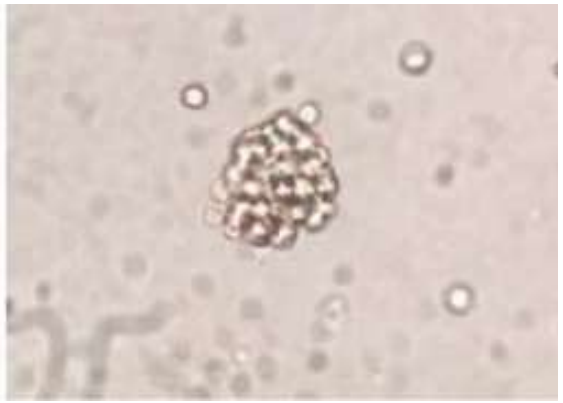
Hematuria

- Gross
  - Defined onset
  - Red or brown discoloration
  - Alarming to patient/parents
  - Symptomatic or asymptomatic
- Microscopic
  - Usually incidental finding, duration unknown
- Must confirm presence of RBCs on microscopy
  - > 3-5 RBCs/HPF





Microscopic Hematuria

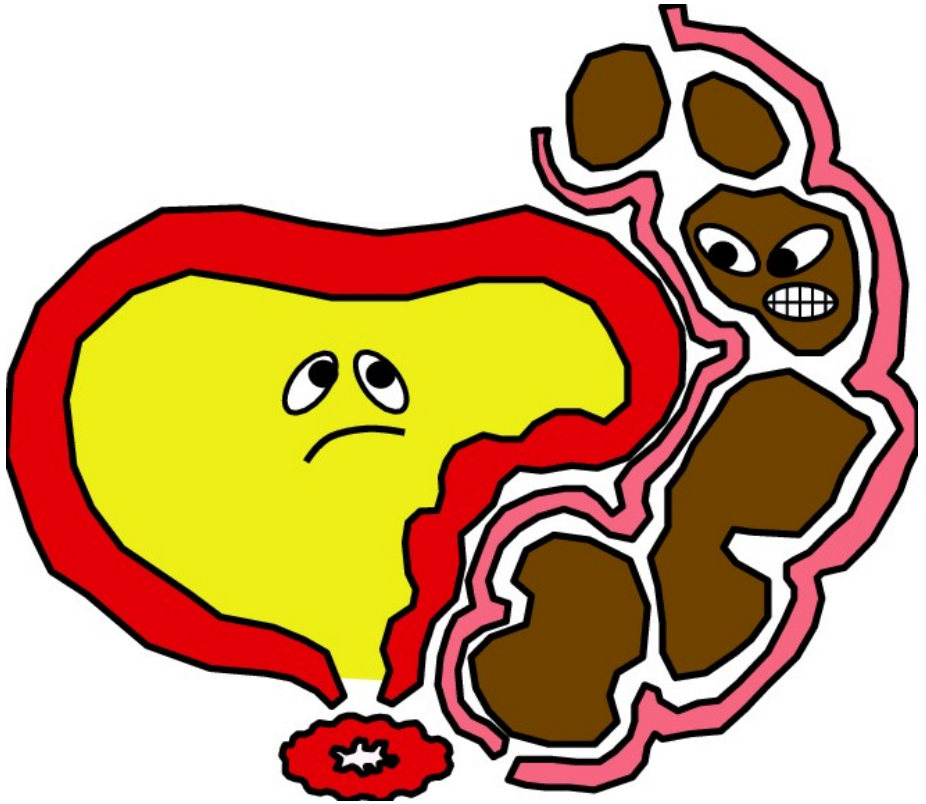
- Transient
  - Fever, exercise, UTI, trauma, perineal irritation
  - Repeat UA with micro every 1-2 weeks x 2
- Persistent
  - Greater than 4-6 weeks of > 5 RBCs/HPF
- Needs to be evaluated independent of trauma, exercise, menstrual cycle, or sexual activity

Microscopic Hematuria

- Urine dipstick detects heme pigment
- Dipstick $\geq$ 1+ (variable sensitivity)
- > 3-5 RBCs/HPF in centrifuged urine on at least 2-3 occasions
- Seen in up to 5% of school-aged children
  - Most often transient and resolves spontaneously
- Persistent MHU in only 1-2% of children
- Girls > boys
- Not age- dependent

Microscopic Hematuria

- Persistent, asymptomatic, and isolated
- Nonglomerular causes
- Glomerular causes
- Family history is important
  - Hereditary nephritis
  - Thin basement membrane disease



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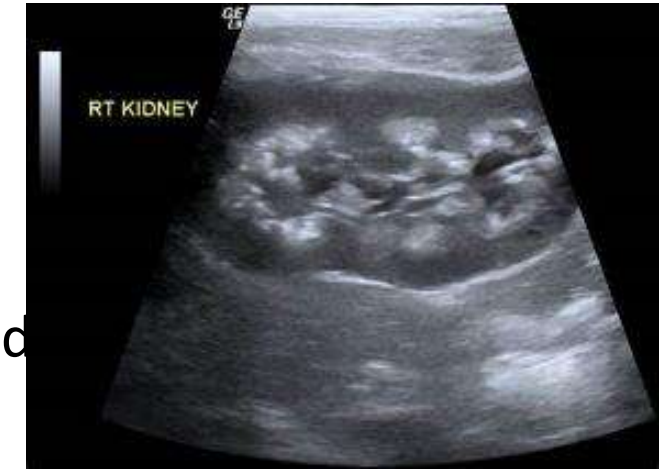
Microscopic Hematuria: DDx

- Idiopathic
- Hypercalciuria
- TBMD (benign familial hematuria)
- IgA nephropathy
- Alport syndrome
- Acute or chronic glomerular disease
  - IgAN
  - PIGN
  - HSP

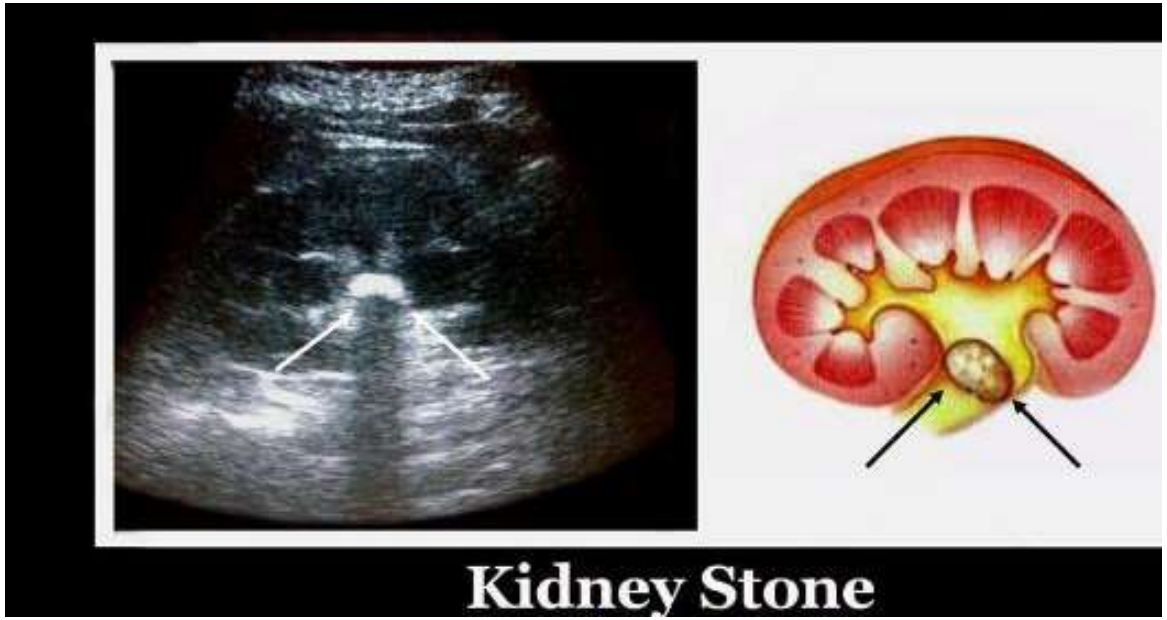
Microscopic Hematuria: Evaluation

- UA with microscopy
- Urine calcium/creatinine
- **Urine protein/creatinine**
- Imaging not indicated for MHU
  - Consider RUS in infants
- Urology evaluation not indicated
- Follow-up is important

Hypercalciuria



- Urine Ca/Cr >0.2 mg/mg in >2 years old
  - Urine Ca/Cr > 0.6 mg/mg in 6-12 mo old
  - Urine Ca/Cr > 0.8 mg/mg in < 6 mo old
- Confirm with 24hour urine
  - > 4 mg/kg/day
- Isolated finding
- Nephrocalcinosis
  - Asymptomatic
- Stones



Glomerular Hematuria

- Thin Basement Membrane Nephropathy
- IgA Nephropathy
  - Gross hematuria simultaneous with viral illness
  - Often have persistent MHU between episodes
- HSP (IgA systemic vasculitis)
- Alport syndrome
  - Gross and microscopic HU
  - 80% X-linked, also AR and AD
  - Abnormal collagen (type 4)in the glomerular basement membranes
  - Eye and ear abnormalities
  - ESRD, particularly in males
  - Female carriers with hematuria
  - Affected females

Thin Basement Membrane Disease

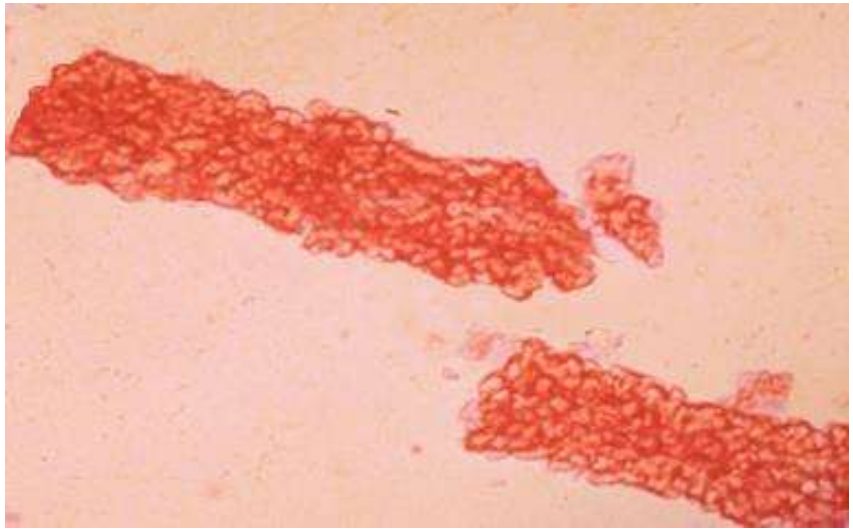
- Benign familial hematuria
- Hereditary nephritis without deafness
- Autosomal dominant
- Persistent MHU or episodic gross hematuria
- In general, no CKD progression- benign course
- Also associated with various genetic mutations (type 4 collagen mutation in basement membrane) and other rare glomerulopathies leading to CKD
- Benign, but a subset of patients with TBMN develop progressive proteinuria and renal failure.

Microscopic Hematuria

- Persistent asymptomatic isolated MHU
- Generally good outcome
- Annual follow-up
  - Monitor for the development of proteinuria
  - Proteinuria signals CKD
- If associated gross hematuria/proteinuria/HTN, needs referral and more frequent f/u
- If family history of hematuria/CKD consider genetic testing

Gross Hematuria

- Incidence: 1.3/1000 outpatient visits
- Color
  - Red: lower urinary tract, clots
  - Brown/Tea: upper urinary tract
- Symptomatic
  - UTI, stones, trauma, cysts, urethritis
- Asymptomatic
  - Glomerular
  - Urethrorrhagia in prepubertal males (terminal HU)



Gross Hematuria

- Voiding onset
  - Urethral bleeding
- Terminal hematuria
  - Bladder or urethral bleeding
- Duration: single void to weeks
- Often recurrent with MHU in between episodes

Gross hematuria

- No RBCs on microscopy
  - Myoglobinuria
    - Rhabdomyolysis, extreme exercise, myopathy
  - Hemoglobinuria
    - Rapid hemolysis
- Red/Pink/Brown urine, negative dipstick
  - Beets, blackberries, paprika
  - Sulfonamides, nitrofurantoin, salicylates, Pyridium
  - Uric acid crystals in diaper

Gross Hematuria

- Most common causes
  - UTI (not if asymptomatic)
  - Trauma
  - Perineal irritation
- Less common causes
  - Sickle cell disease/trait
  - Benign familial hematuria (TBMD/hereditary nephritis) and Alport syndrome
  - Hypercalciuria
  - Nephrolithiasis
  - Glomerulonephritis: PIGN, IgA nephropathy
  - Urologic structural abnormalities (UPJO): hydronephrosis, cysts, ureterocele, bladder polyp
  - Coagulopathies
  - Drug-induced cystitis
  - Malignancy: Wilms tumor

No diagnosis found in up to 35%

Causes of Hematuria:

A) Glomerular hematuria

Isolated renal disease	Multisystem disease
-Postinfectious GN (Post streptococcal) - IgA nephropathy(Berger ds) - Alport syndrome(hereditary) - Thin Glomerular Basement membrane disease - Membranoproliferative GN - Membranous nephropathy - Focal segmental glomerulosclerosis - Antiglomerular basement membrane ds	-HSP nephritis -SLE nephritis -HUS -Wegener granulomatosis -Polyarteritis nodosa -Goodpasture syndrome -HIV nephropathy -Sickle cell glomerulopathy

Gross Hematuria: Evaluation

- Assess severity
  - BMP
  - Urine Pr/Cr
- Diagnostic
  - C3, anti-Strep titers
  - Urine Ca/Cr
  - Urine culture
  - Renal ultrasound
  - Doppler to evaluate for renal arterial or venous thrombosis
  - RVT: gross hematuria in a nephrotic newborn or child

Further Evaluation

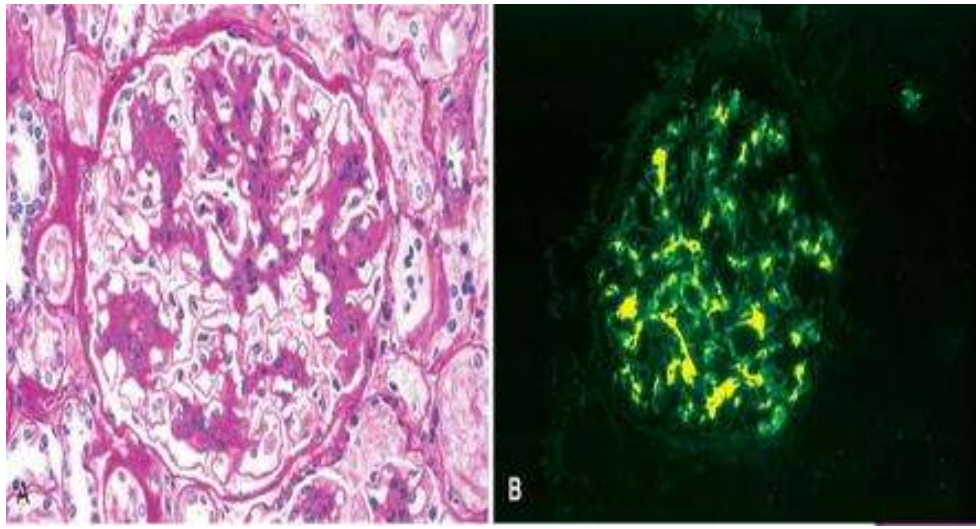
- ANA, C3, C4
- ANCA
- Sickle cell screen
- Hearing evaluation if positive FH
- VCUG/cystoscopy (if lower tract symptoms)

Postinfectious Glomerulonephritis

- Variable presentation
- Classic presentation
  - Red-brown or cola colored urine (70%)
  - Nephritic syndrome: HTN, edema from salt and water retention
- Microscopic hematuria (100%)
- Antecedent GAS throat infection (1-2 weeks earlier) or GAS skin infection (2-6 weeks) earlier
- Numerous other infectious agents can cause PIGN
- Low C3, normal C4

IgA Nephropathy

- Recurrent gross hematuria
  - 40-55%
- Persistent microscopic hematuria
  - 30-40%
- Triggered by URI or GI infection
- Occurs within days of infection



Gross Hematuria: Yield of evaluation

Acute GN	25%
Hypercalciuria	15%
IgA Nephropathy	15%
Other	5%
Unknown (TBMD?)	40%

Indications for Renal Biopsy

- Evidence of nephritis and APSGN ruled out
  - HTN, edema
  - Proteinuria
  - Renal insufficiency
- Positive ANA with low C3
- Gross hematuria greater than 2 weeks
- Frequent episodes

Remember

- Asymptomatic MHU detected on screening UA
  - Repeat UA with micro q 1-2 weeks x 2 weeks to confirm RBCs in urine
  - Persistent asymptomatic MHU: most are idiopathic
  - If a diagnosis is made: TBMN, IgAN, HCU
- Lots of overlap between causes of gross and microscopic hematuria
- Other signs/symptoms should guide the initial workup
- Microscopic hematuria with proteinuria is renal disease until proven otherwise and needs a renal biopsy.
- Persistent proteinuria is more concerning for renal disease.

Proteinuria

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Proteinuria

Udip ≥ 1+
Obtain first am UA and UPC ratio

False Positives
High SG
High urine pH

Neg/ Trace	**<30 mg/dL**	**May be abnormal in dilute urine**
1+	**30-100 mg/dL**	**May be normal in concentrated urine**
2+	**100-300 mg/dL**	**Abnormal**
3+	**300-1000 mg/dL**	**Abnormal**

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Quantification

- Timed urine collection
  - Adolescents and adults: >200 mg/d
  - Children >100 mg/m2/d
  - Neonates and infants >300 mg/m2/d
  - Children: <4 mg/m^2/hr
  - >40 mg/m^2/hr or > 1000 mg/m2/day: Nephrotic Range
- Obtain urine creatinine to evaluate adequacy of collection
- Spot urine protein/creatinine (mg/mg)
  - <0.2 mg/mg: normal
  - <0.5 mg/mg: 6-24 months
  - >2-3 mg/mg: nephrotic range

Urine protein/creatinine ratio

	Antidiuresis	Diuresis
24-h protein	200 mg	200 mg
Urine volume	0.5 L	5 L
Protein conc.	40 mg/dl	4 mg/dl
Dipstick	1+	Negative
24-h Cr	1000 mg	1000 mg
Cr conc.	200 mg/dl	20 mg/dl
Prot/Cr	0.2	0.2

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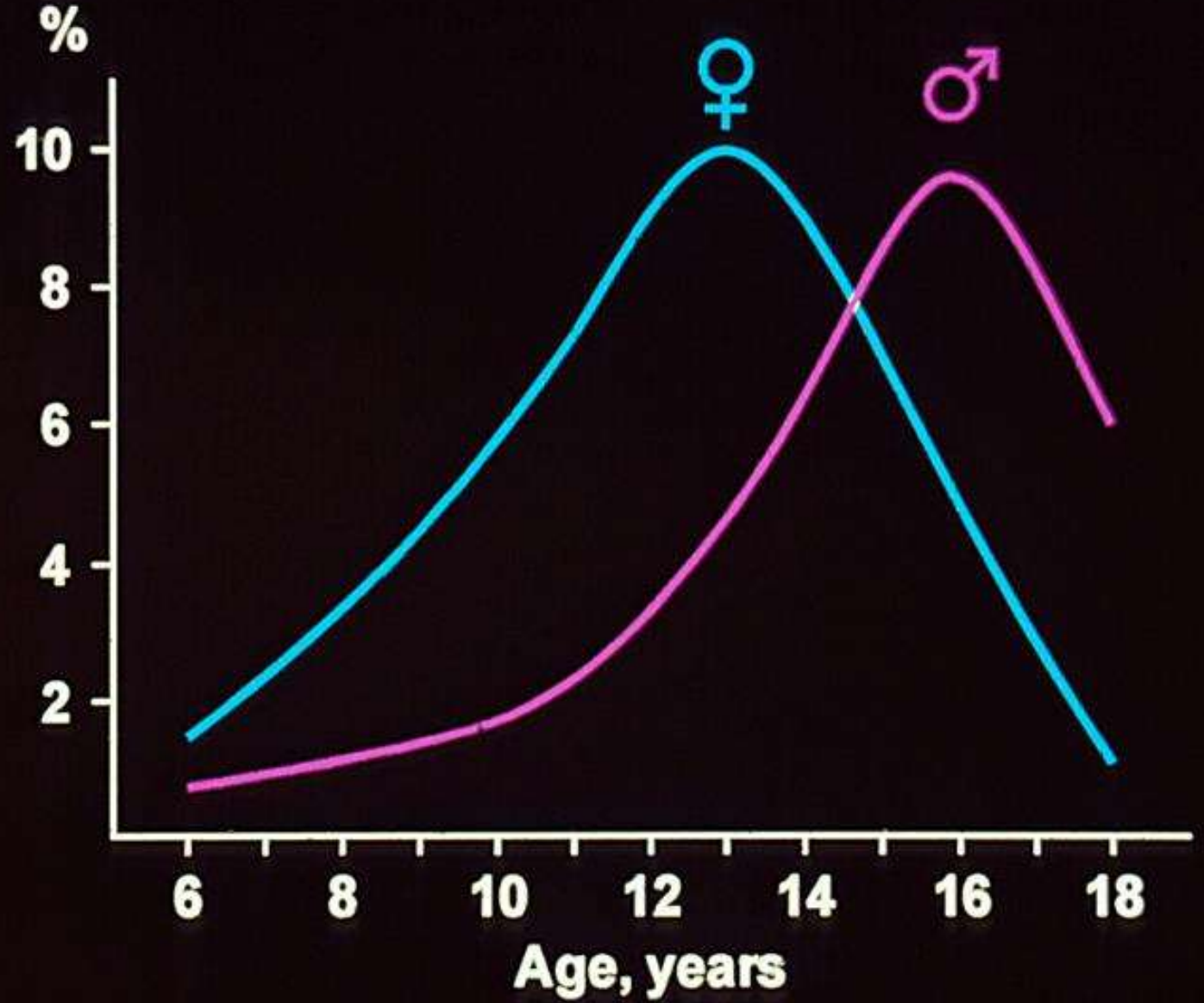
Asymptomatic Proteinuria

- False positive on the dipstick
    - High spec gravity, alkaline urine
- Transient
    - Fever, acute illness, exercise, stress, dehydration, cold exposure
- Orthostatic
- Persistent
    - Glomerular: Glomerular disease
    - Tubular: Tubulointerstitial disease or injury
- Benign in >90% of cases
- Silent renal disease in 10% of cases

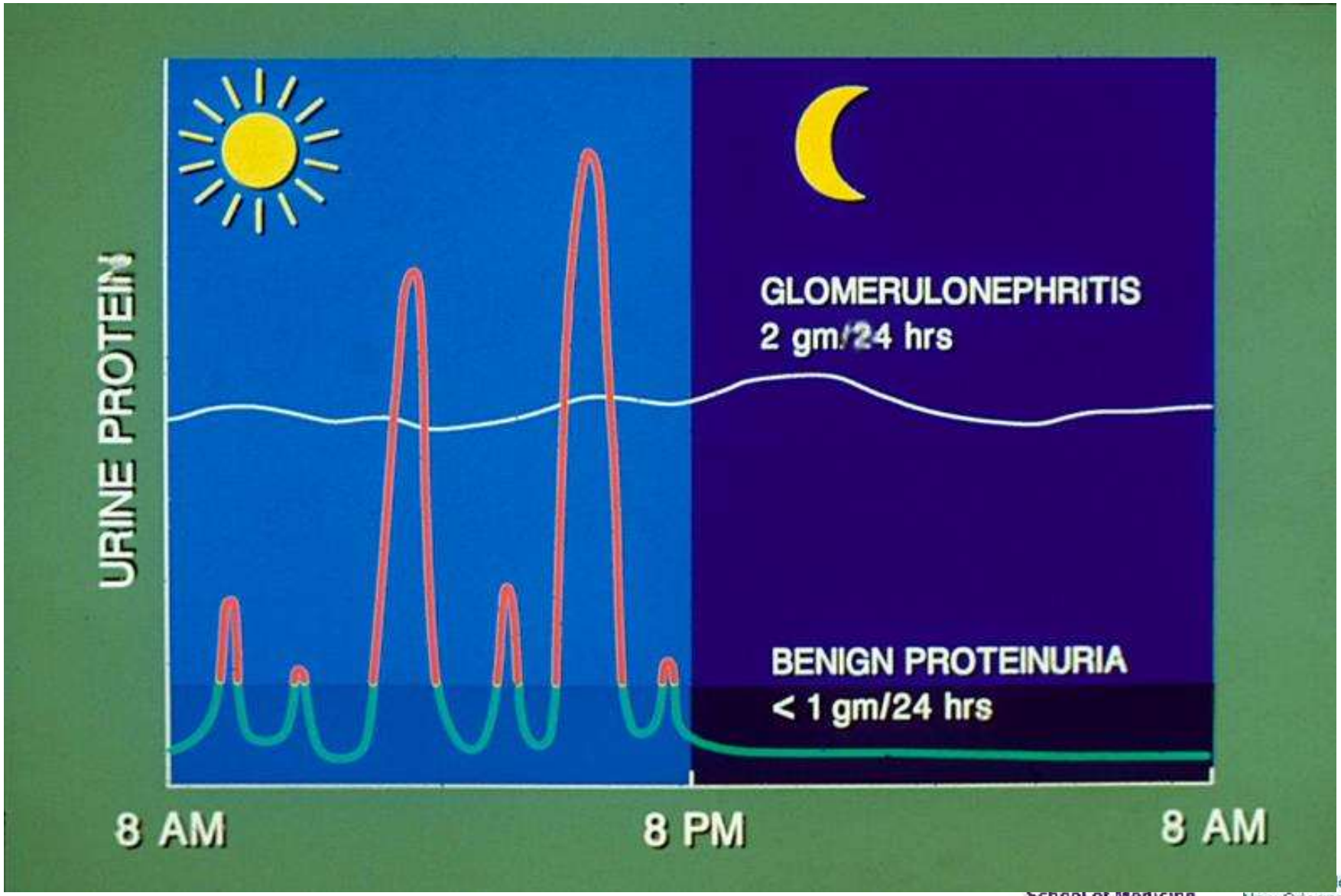
Benign Orthostatic Proteinuria

- Characterized by increased protein excretion when upright, but normal excretion when recumbent
- On average less than 1 gram/24h upright
- Most common during adolescence
- Benign condition, no increase in renal morbidity during 50 year follow-up

Prevalence of Proteinuria



Benign Proteinuria: Diurnal Pattern



Proteinuria: Evaluation

- Positive urine dipstick (≥1+)
  - Laboratory UA: hematuria, infection, SG
  - Spot urine Pr/Cr
    - **First am urine Pr/Cr**
  - H and P, family history
- **Rule: if proteinuria is isolated and intermittent (orthostatic), it is not a sign of renal disease.**

Persistent Proteinuria: Further Evaluation

- CBC, CMP
- C3, C4 (SLE, MPGN, APSGN)
- ANA
- Hep B, Hep C, HIV
- Consider renal biopsy

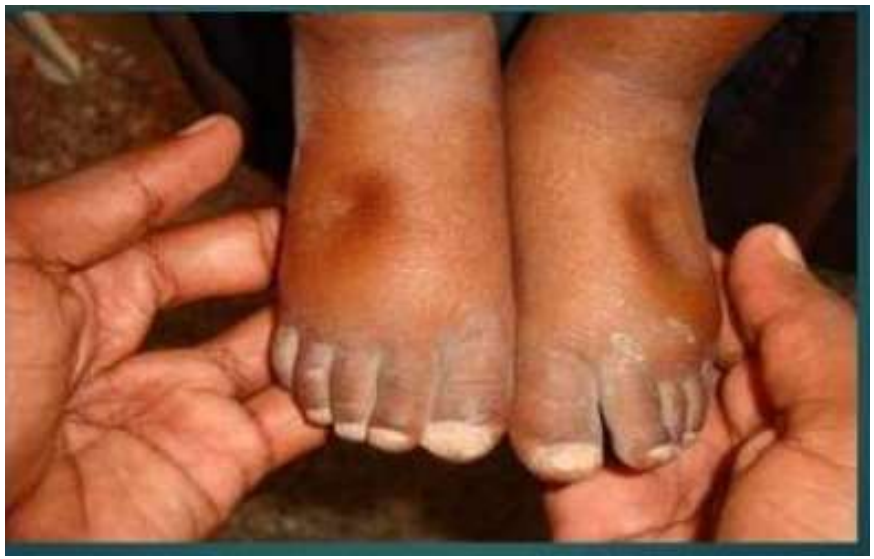
- Minimal change disease
- FSGS
- Membranous nephropathy
- CKD/adaption due to nephron loss
- Immune-complex mediated MPGN
- C3 glomerulopathy
- Congenital nephrotic syndrome
- Diabetes mellitus
- SLE

Microalbumin

- Highly sensitive test to detect very small quantities of albumin in the urine
- MA/Cr
- Obesity
- Diabetes
- Sickle cell disease
- Alport syndrome

Nephrotic Syndrome

- Nephrotic range proteinuria
- Hypoalbuminemia
  - sAlb < 2.5 g/dL
- Edema
- Hyperlipidemia



Remember

- Hematuria and proteinuria together is renal disease until proven otherwise and requires renal biopsy.
- Proteinuria is more concerning for underlying kidney disease than isolated MHU.
- Most adolescents with proteinuria on a screening UA do not have renal disease and proteinuria will resolve on repeat testing.
- Urine Pr/Cr is a very valuable test- ideally should be a first morning urine sample.
- Positive urine dipstick ≥ 1+ protein needs UA with micro and UPC ratio on a properly collected first morning urine sample.
- As always, let your history and PE guide evaluation.

When to Refer

- Gross hematuria without a clear cause (UTI, PIGN)
- Symptomatic microscopic hematuria
- Asymptomatic microscopic hematuria
  - Annual follow up to monitor for co-existing symptoms, development of proteinuria, revisit family history
- Persistent asymptomatic hematuria with ≥ 1+ proteinuria
- Coexistent HTN, edema, or AKI
- Repeat urine samples before referring.
- Repeat BPs manually and repeatedly over time before referring.

Annual UA

- History of prematurity (<32 wga), VLBW, significant NICU course, UAC
- Congenital heart disease
- Recurrent UTI, HU, or PU
- Known renal disease or urologic malformations
- Solid organ transplant, BMT, or malignancy
- History of prolonged treatment with nephrotoxic drugs
- History of recurrent episodes of AKI
- Family history of inherited renal disease

How to Change your Practice

- Repeat all abnormal urine testing x 2.
- Understand the value and how to order a urine protein to creatinine ratio.
- Instruct your patients on how to properly collect a first morning urine sample.
- Know which patients need annual screening urinalysis.

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