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Evaluation of the Urine

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Disclosures

I have no financial disclosures or other conflicts of interest to report

Today's Agenda:

- **Hematuria:**
  - How is Hematuria Defined?
  - How Common is Hematuria?
  - What are the Main Causes of Gross and Microscopic Hematuria?
  - What is the Evaluation for Gross and Microscopic Hematuria?
  - When Should I Refer my Patient to Nephrology?

Hematuria

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First Patient of Your Very Busy Day…

9-year-old female presents to your office for routine physical examination. She denies any recent illnesses or injuries. She has no complaints.

Birth history: Full-term, NSVD, no complications in the postnatal period

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Past surgical history: None

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Medications: Albuterol as needed

Allergies: Seasonal allergies

Review of systems: Negative

Physical examination:

Vitals: 97.3F, 110/60mmHg, 83bpm, 16/min, 100% on room air
Height: 135cm (73rd percentile)
Weight: 30kg (50th percentile)

Remarkable findings on physical examination: None

You check a urine sample given her strong family history of Chronic Kidney Disease:

Urinalysis: pH 5.5, spec grav 1.015, **2+ blood**, negative protein, negative glucose, negative ketones, negative leukocyte esterase, negative nitrites

Urine microscopy: 5-10 RBCs/hpf

What do you do next?

1. Repeat the urinalysis in 1 week
2. Repeat the urinalysis in 1 year
3. Send a urine calcium and urine creatinine for ratio
4. Send for a renal ultrasound and basic metabolic panel
5. Refer to Nephrology
6. None of the above

How is Hematuria Defined?

- 5 or more red blood cells per high power field

- Requires three consecutive fresh, centrifuged specimens obtained over the span of several weeks for diagnosis

What Should be Done Next?

Evaluate the dipstick carefully!

- Reddish urine with dipstick positive for heme but negative for RBCs:
  - Myoglobinuria and hemoglobinuria: excessive exertion (rhabdomyolysis), crush injuries, anesthetic exposure, thermal burns

- Reddish urine with dipstick negative for heme:
  - Drug exposure: sulfonamides, nitrofurantoin, salicylates, phenazopyridine, phenolphthalein
  - Toxin exposure: lead, benzene
  - Food exposure: food coloring, beets, blackberries, rhubarb, paprika
  - Porphyria

How Common is Hematuria?

- 3%-6% of school-aged children have asymptomatic microscopic hematuria on single urine check
- This declines to 0.5% to 1% with repeated urinary screenings
- Slightly higher prevalence in females
- No ethnicity or socioeconomic prevalence
- 1.3/1000 children have gross hematuria

How Does Gross Hematuria Present?

Lower Urinary Tract Bleeding	Glomerular Bleeding
Bright red blood	Coca-cola or tea-colored urine
+/- clots	No clots present
Normal RBCs under microscopy	Dysmorphic RBCs +/- red cell casts under microscopy

Classically painful
Presents with dysuria, urgency, and frequency

Classically painless
Absence of dysuria, urgency, and frequency

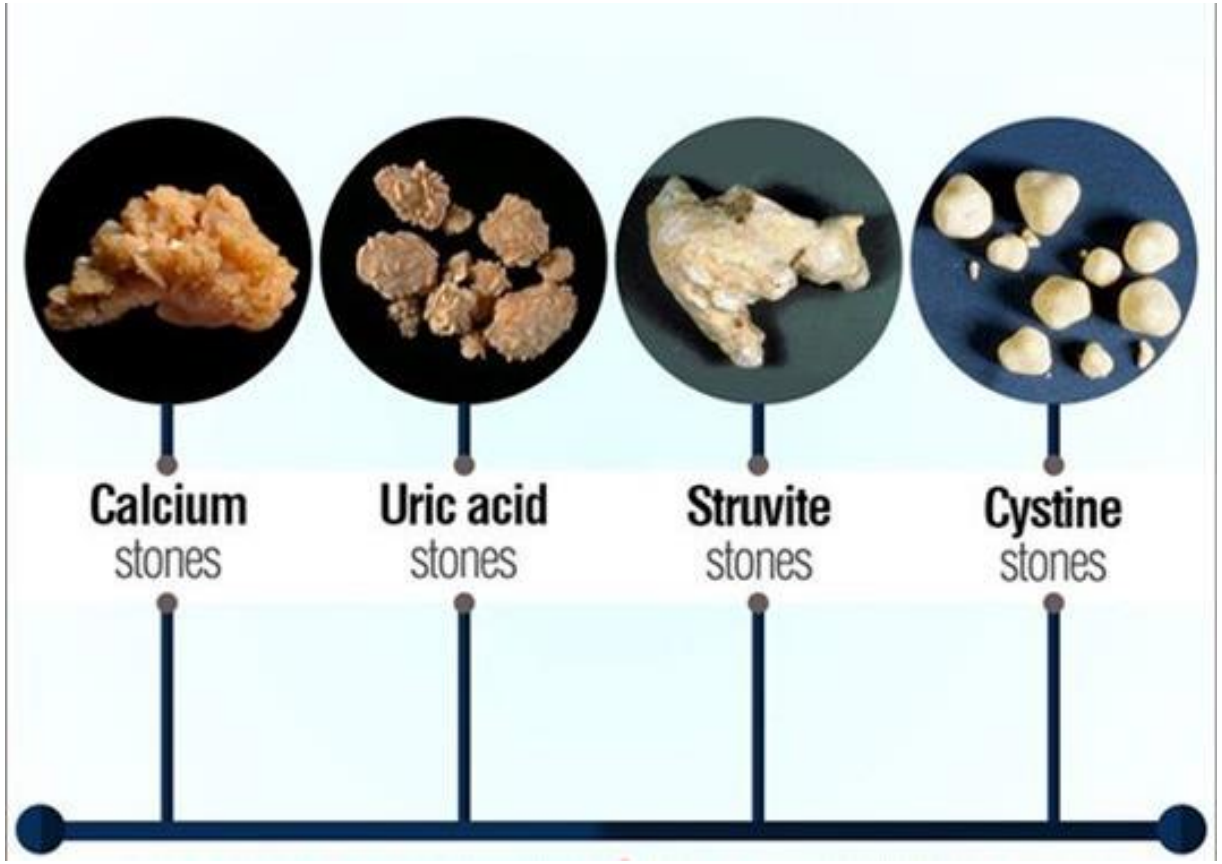
Causes of Lower Urinary Tract Bleeding

- **Urinary tract infection:**
  - Dysuria, urgency, frequency, +/- fever, emesis, diarrhea, abdominal/flank pain
  - UA positive for leukocyte esterase, bacteria, +/- nitrites
  - Urine culture positive

- **Kidney stones:**
  - Flank pain, abdominal pain, nausea, vomiting, dysuria
  - History of passing stone(s) and/or sediment
  - Family history may be helpful
  - Renal ultrasound and/or CT without contrast may be helpful in diagnosis
  - Litholink used to determine etiology

- **Cystitis:**
  - Dysuria, urgency, frequency
  - Not common, ?adenovirus

Types of Kidney Stones

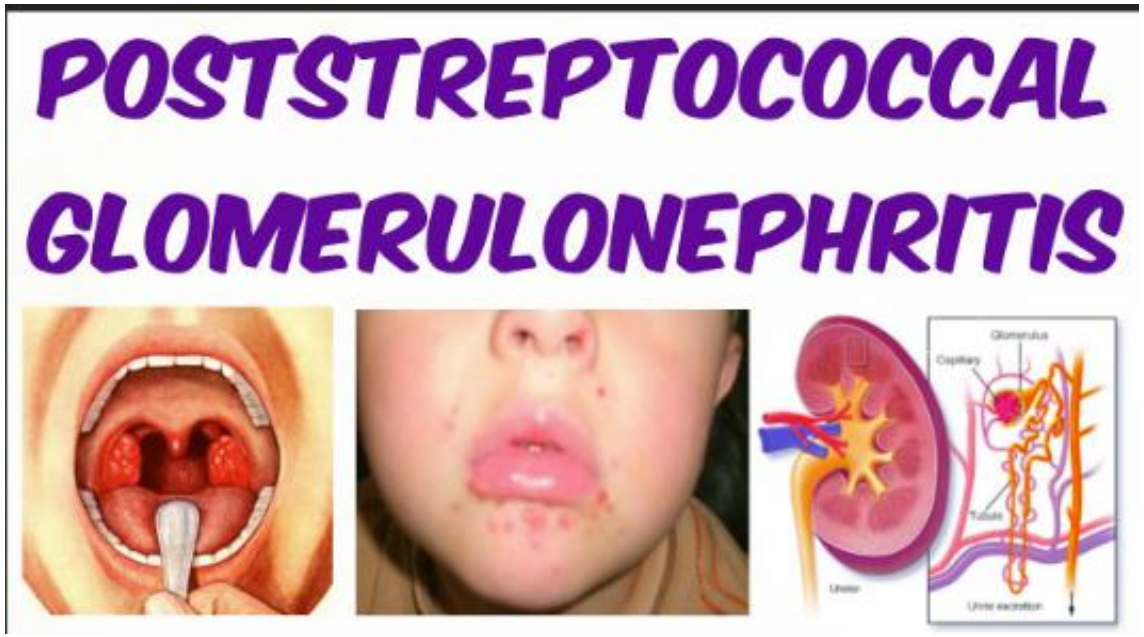


https://ar.inspiredpencil.com/pictures-2023/uric-acid-stone

Causes of Glomerular Bleeding

- **Post-infectious/Post-streptococcal glomerulonephritis:**
  - Preceding streptococcal pharyngitis (1-2 weeks) or skin infection (2-3 weeks)
  - 85% of children have edema and hypertension
  - Positive streptococcal throat swab, elevated ASO titers, positive anti-DNAse B, streptozyme, low C3 with normal C4
  - Microscopic hematuria can continue for another 6-12 months

- **Henoch-Schonlein Purpura:**
  - Abdominal pain, joint pain, rash, bloody stools
  - Renal involvement can happen weeks to months later
  - Microscopic hematuria can persist



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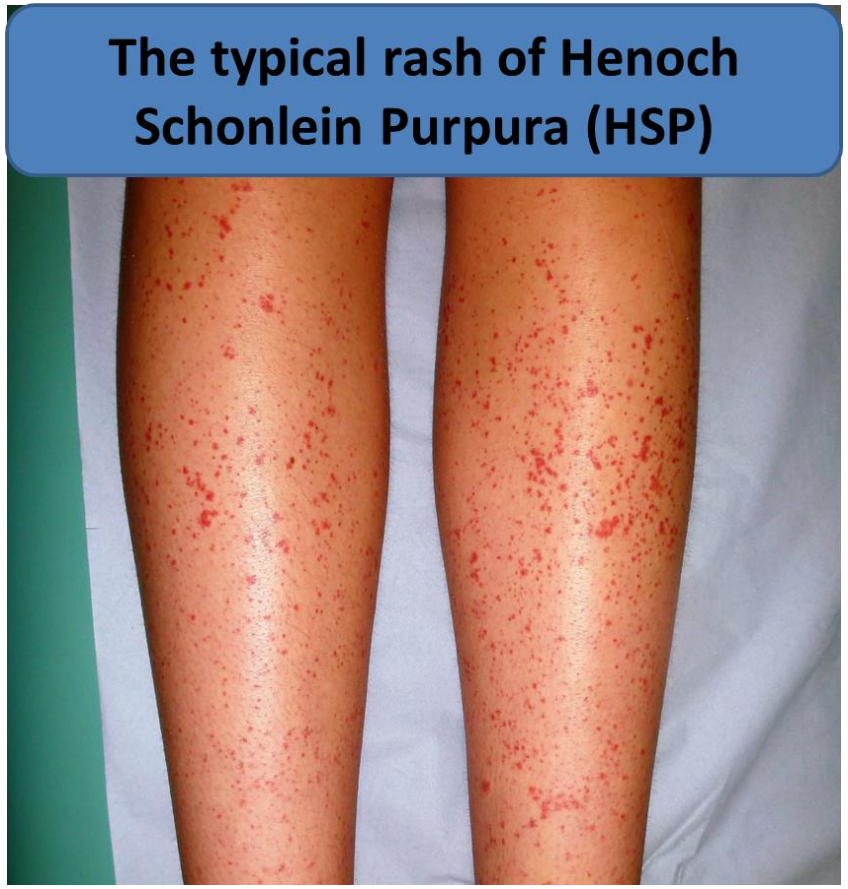


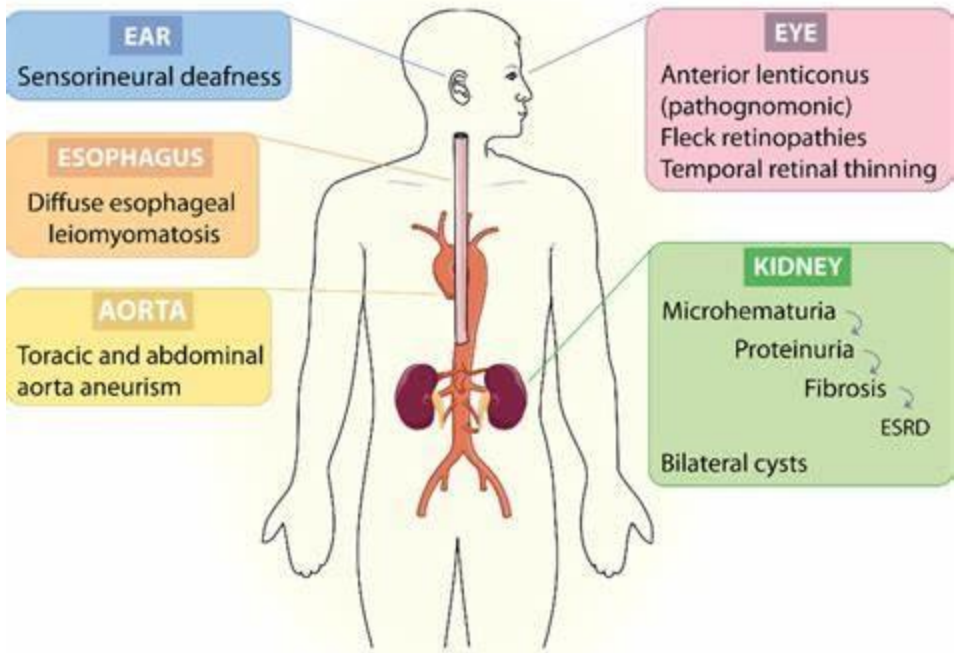
https://ar.inspiredpencil.com/pictures-2023/henoch-schonlein-purpura-symptoms

Causes of Glomerular Bleeding

- **Alport syndrome:**
  - Can be x-linked recessive or autosomal dominant or recessive
  - Family history of hearing loss in males and renal failure in 20s-30s
  - Females can have microscopic hematuria

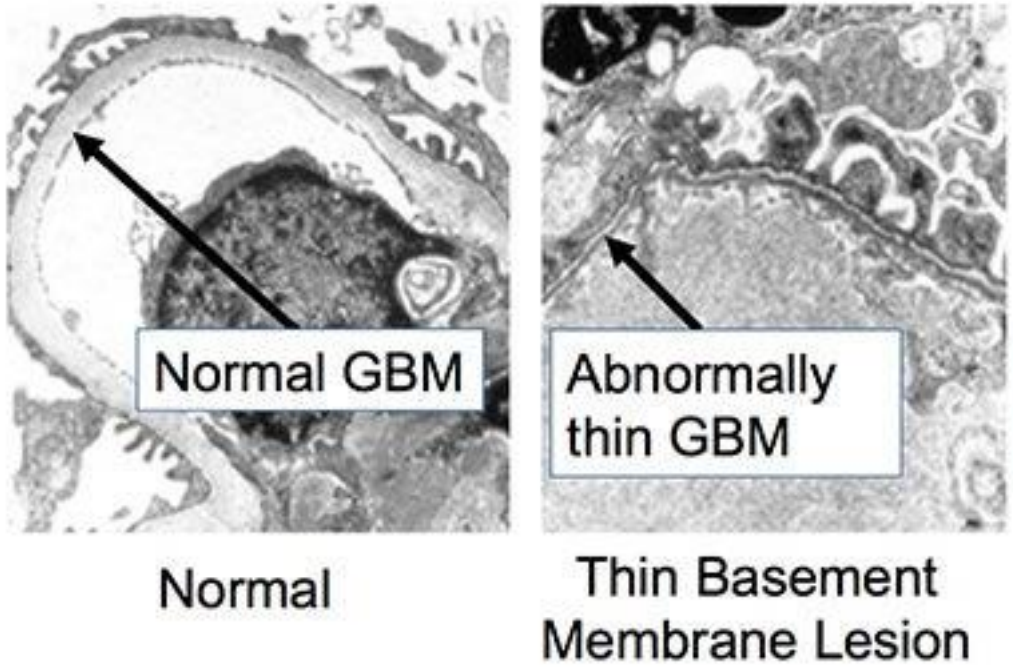
- **Thin basement membrane disease:**
  - Autosomal dominant
  - Microscopic hematuria with potential episodes for gross hematuria (<10%)
  - Proteinuria and hypertension are rare

Alport syndrome



https://www.researchgate.net/figure/Main-defining-phenotypic-characteristics-of-Alport-syndrome_fig1_355220203

Thin Basement Membrane Disease



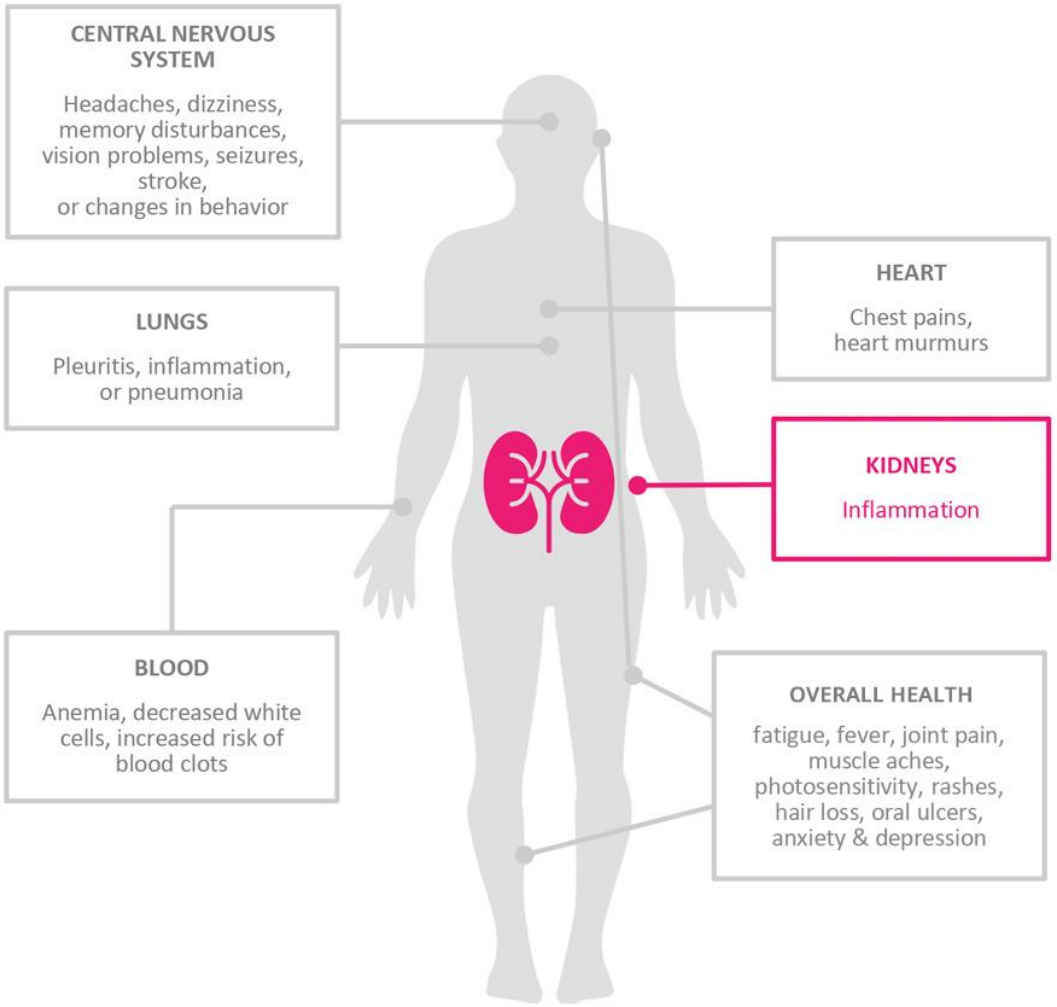
https://www.midotrust.com/

Causes of Glomerular Bleeding

- **Lupus nephritis:**
  - Gross or microscopic hematuria
  - Proteinuria, edema, hypertension
  - Low C3 and C4
  - Other systemic symptoms: rash, joint pain, joint swelling, fatigue, low-grade fevers, lymphadenopathy

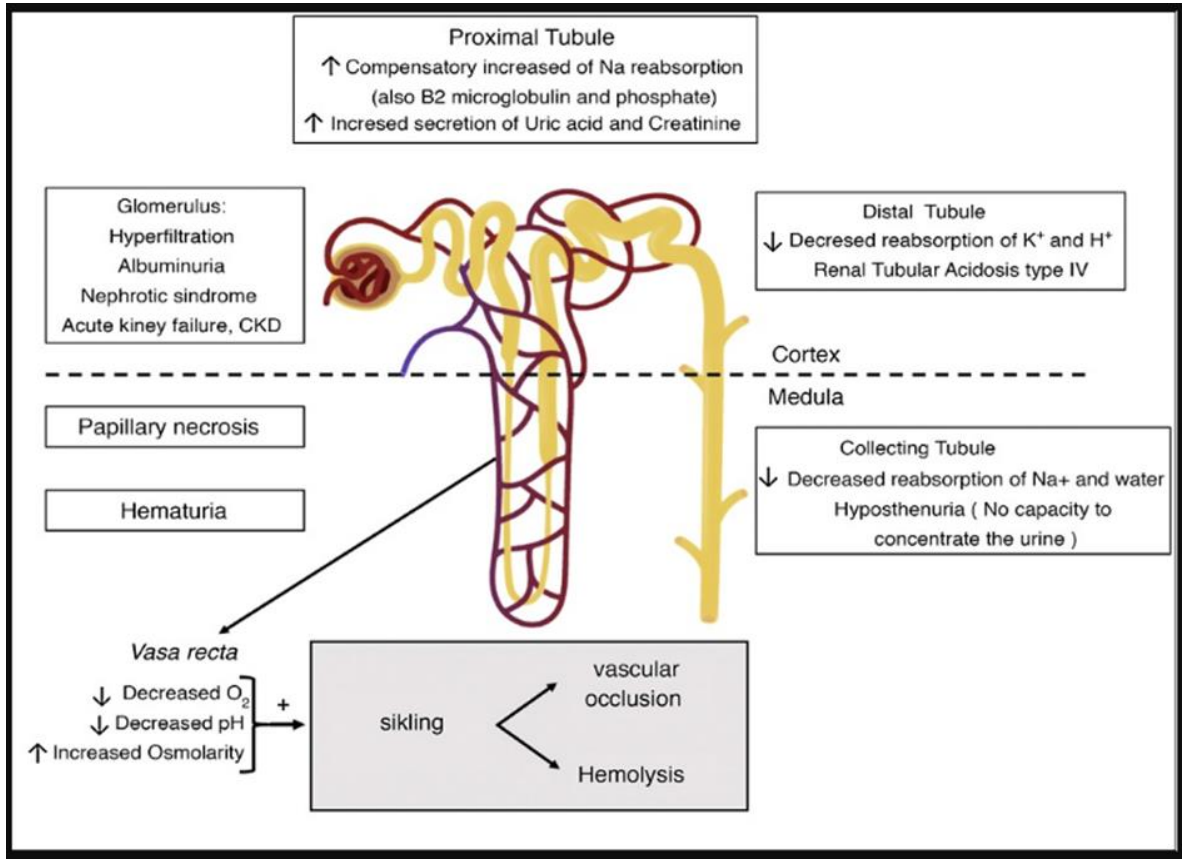
- **Sickle cell trait/disease:**
  - Typically, in African-American patients
  - Ask about newborn screen!
  - Need to consider evaluation of medullary renal carcinoma

Systemic Lupus Erythematosus



https://www.auriniapharma.com/patients#lupus-nephritis

Sickle Cell Disorder



https://auctoresonline.org/article/renal-manifestations-in-patients-with-sickle-cell-disorder

Causes of Microscopic Hematuria

- Renal calculi and/or sediment
- Glomerular causes (e.g. Thin Basement Membrane Disease, Lupus Nephritis)
- Menstruation
- Recent urological procedure
- Malignancy
- Extreme exercise
- Unknown

What is the Evaluation for Gross Hematuria?

- BMP, CBC, and urine microscopy for all patients
- Additional bloodwork and urine tests based on history and physical exam:
  - ASO titer, anti-DNAaseB, streptozyme, C3, C4, ANA, dsDNA, MPO, PR3, sickle cell screen, urine calcium/urine creatinine
- Renal/bladder ultrasound always for gross hematuria:
  - Stones (all stones except uric acid), cysts, tumors
  - CT without contrast if you suspect stones and renal ultrasound is negative

Always think about Wilms tumor in young children!

When to Consider Invasive Testing

- Renal biopsy:
  - Multiple episodes of gross hematuria
  - Nephrotic syndrome
  - Hypertension with nephritic syndrome
  - Elevated creatinine
  - Co-existing systemic symptoms (e.g. SLE)

- Cystoscopy
  - Not often performed in children

What is the Evaluation for Microscopic Hematuria?

- For asymptomatic microscopic hematuria no further evaluation is required other than evaluating urine microscopy for RBCs and RBC casts, and for proteinuria
  - These children should be followed yearly by a Pediatric Nephrologist to monitor blood pressure, proteinuria, and for red cell casts
  - Proteinuria typically does not exceed 2+ if present from hematuria alone
  - At yearly visits additional family history should be obtained, if possible, especially any new information on renal failure or hearing loss
  - ? yield of sending urine calcium/urine creatinine to assess for hypercalciuria

- For asymptomatic microscopic hematuria with proteinuria, obtain a first morning urine protein/urine creatinine and refer to a Pediatric Nephrologist

Referrals to Nephrology

- Persistent asymptomatic microscopic hematuria
- Persistent symptomatic microscopic hematuria
- Red flags:
  - Gross hematuria, edema, hypertension, proteinuria, oliguria

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Proteinuria

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Today's Agenda:

- **Proteinuria:**
  - What is Normal Protein Excretion?
  - How is Proteinuria Evaluated?
  - What are the Main Causes of Proteinuria?
  - When Should I Refer my Patient to Nephrology?

The Second Patient of Your Very Busy Day…

An 11-year-old male presents to your clinic for a routine physical examination. He has no complaints. He has not been ill recently. Of note, he has been told by a previous provider that he has had protein in his urine before, but no further evaluation was done.

Vitals: 115/65mmHg, 78bpm, 37.6C, 18/min, 100% on room air

Medications: None

Allergies: None

Physical examination: No pertinent positive findings

UA: 1.020, pH 6.0, Protein: **Trace**, Blood: Negative, Leukocyte esterase: Negative, Ketones: Negative, Bilirubin: Negative

What is Your Next Step?

1. Have him return to clinic next week for a repeat UA
2. Order a BMP to assess his kidney function
3. Order a BMP and renal ultrasound
4. Send for a first morning UA within the next 1-2 weeks
5. Send him for a first morning UA next year at his yearly physical examination

What is Normal Protein Excretion?

- Less than 100 mg/m^2 per day or a total of 150 mg per day in children
- Urinary protein excretion more than 100 mg/m^2 per day or 4 mg/m^2 per hour is abnormal
- Nephrotic range proteinuria is defined as ≥1000 mg/m^2 per day or 40 mg/m^2 per hour

How Common is Proteinuria?

- 5-15% of normal school-age children and adolescents will have a positive urine dipstick (defined as ≥1+)
- In a study of 9000 children, 10.7% had proteinuria in 1/4 urine samples
- Only 0.1% of children had proteinuria in all 4 samples

How Should you Approach a Patient with Proteinuria?

Ask Questions

- Symptoms of swelling, headaches, hematuria, joint pains, rashes, elevated blood pressure, urinary tract infections, recent throat or skin infections, loss of appetite, decreased energy, weight loss

- Medications/ingestions

- Family history of cystic kidney disease, deafness, visual disturbances, or renal disease/renal failure/dialysis

Physical Examination

- Growth
- Blood pressure
- Flank pain, fluid overload, edema, organomegaly, rashes, joint swelling, or pallor suggesting anemia

How is Proteinuria Evaluated?

- The urinary dipstick measures albumin concentration via a colorimetric reaction between albumin and tetrabromophenol blue

●Negative

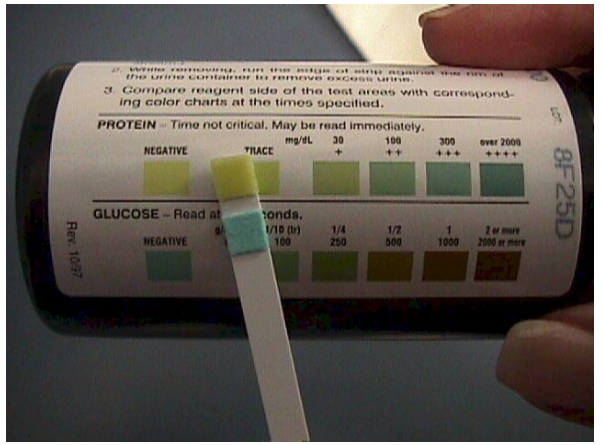
●Trace – between 15 and 30 mg/dL

●1+ – between 30 and 100 mg/dL

●2+ – between 100 and 300 mg/dL

●3+ – between 300 and 1000 mg/dL

●4+ – >1000 mg/dL



http://www.brooksidepress.org/Products/Military_OBGYN/Textbook/PregnancyProblems/hypertensive_issues_during_pregn.htm

- Dipstick testing will **not** detect low molecular weight proteins

The Pitfalls of the Dipstick

- Beware of the specific gravity:
  - A dilute urine will underestimate the degree of proteinuria
  - A highly concentrated urine may overestimate the degree of proteinuria

- False positives:
  - Fever
  - Intensive exercise
  - Orthostatic (or postural) proteinuria
  - Alkaline urine samples (pH >8)
  - Samples contaminated by antiseptic agents (such as chlorhexidine or benzalkonium chloride) or iodinated radiocontrast agents
  - Stress
  - Hypovolemia
  - Seizures

Evaluating the Spot Ratio

- Persistent proteinuria requires a spot urine protein/urine creatinine ratio
- Normal ratios:
  - <0.2 mg protein/mg creatinine in children >2 years of age
  - <0.5 mg protein/mg creatinine in infants and toddlers from 6 to 24 months
- First morning sample should be obtained when orthostatic proteinuria is suspected

- If the spot ratio is normal:
  - Most likely from transient or orthostatic proteinuria and no further evaluation is required
- If the spot ratio is abnormal:
  - Pursue further evaluation

24 Hour Urine Collections

- Difficult to perform especially with young, non-toilet trained patients
- Correlation with spot urine protein/urine creatinine ratios is relatively good
- Still a useful tool for patients who have fixed proteinuria with elevated first morning urine protein/urine creatinine ratios (>0.2-2mg/mg)
- Total urine volume and urine creatinine will be reported which is helpful

What are the Main Causes of Proteinuria?

Orthostatic Proteinuria:

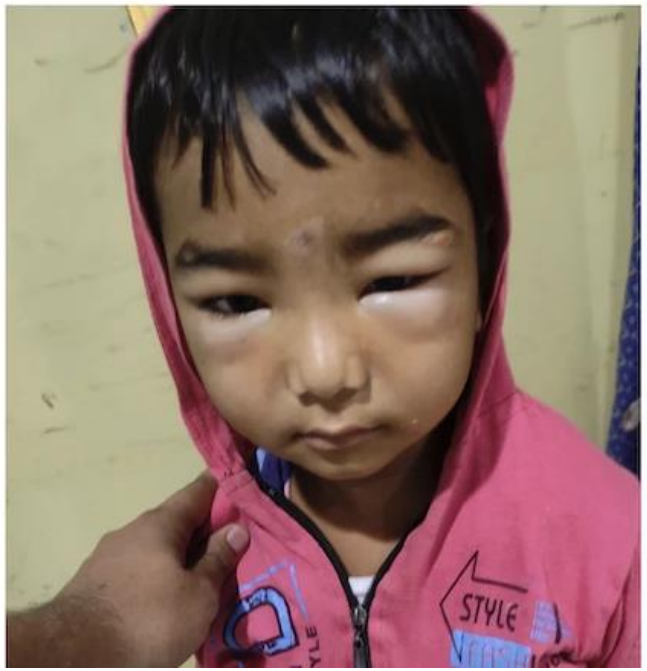
- Orthostatic proteinuria is common in older children and adolescents with a prevalence of 2–5%
- Orthostatic proteinuria is the most common cause of proteinuria in adolescents (75%)
- Due to changes in glomerular hemodynamics from postural changes
- Rarely exceeds 1 gm/day
- Yearly follow-up is recommended

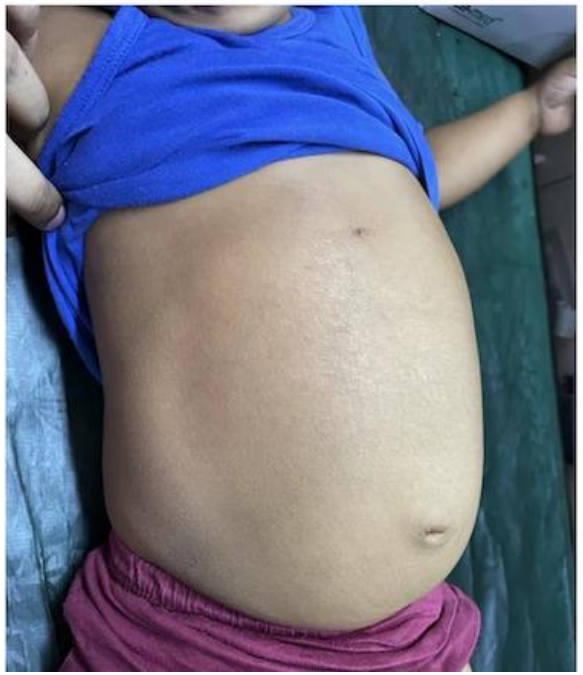
What are the Main Causes of Proteinuria?

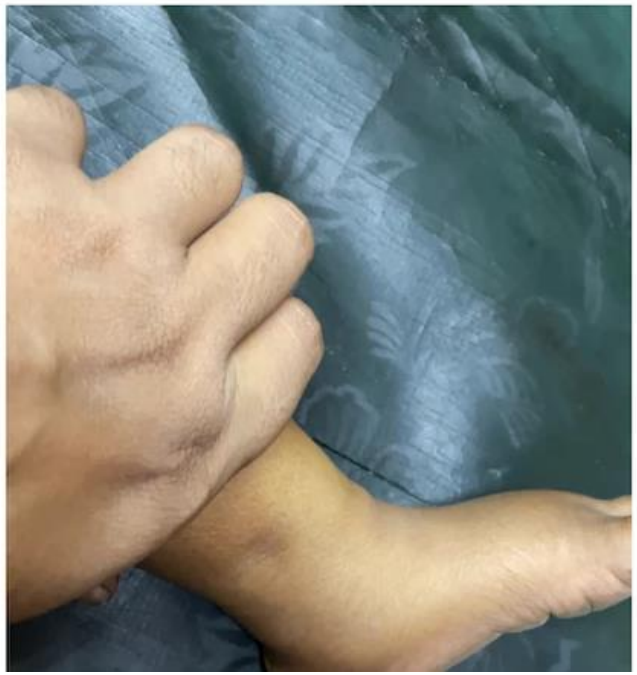
Minimal Change Disease:

- Typically affects children 2-8 years of age
- Affects approximately 2 to 3 cases per 100 000 children
- Classically children present with bilateral eye swelling thought to be secondary to allergies
- Nephrotic syndrome (requires all 4 for diagnosis):
    - 1. Nephrotic range proteinuria
    - 2. Edema
    - 3. Hypoalbuminemia
    - 4. Hypercholesterolemia

Minimal Change Disease







https://medigac.com/nephrotic-syndrome-causes-clinical-features-diagnosis-and-treatment/

Minimal Change Disease Continued

- Lab values:
  - CMP: Hyponatremia, hypoalbuminemia, hypocalcemia
  - CBC: Thrombocytosis, hemoconcentration
  - Lipid panel: Hypercholesterolemia
  - UA: 25% of children can have microscopic hematuria

  - **Elevated creatinine is not typical for nephrotic syndrome!**

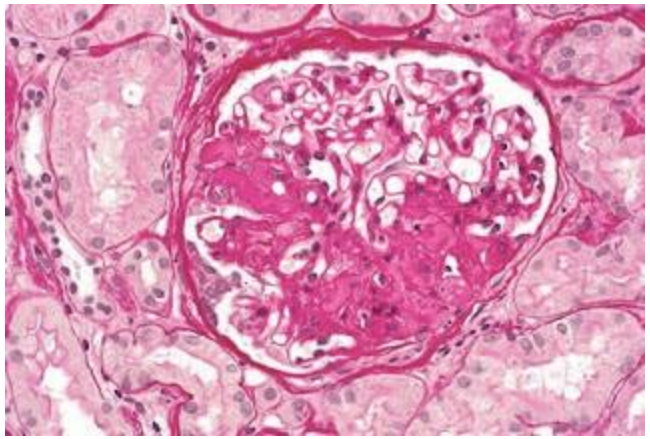
What to do in the Office?

- Children with new-onset nephrotic syndrome should be referred to a Nephrologist as soon as possible
- Initial clinic visit is highly detailed and includes information on infections, immunizations, risk of thrombosis, dietary changes (including meeting with our dietician), natural progression of the disease, etc
- Prior to referral:
  - If you suspect a child has minimal change disease, please send them for a BMP, lipid panel, and CBC (non-fasting)
  - A renal/bladder ultrasound is not necessary
  - If it will take several days to see a Nephrologist, please start prednisolone or prednisone 2mg/kg (max 60mg daily)
  - Please advise to the best of your ability on a low sodium diet

What are the Main Causes of Proteinuria?

Focal Segmental Glomerulonephritis:

- Should be suspected in any child that fails to respond to the initial course of steroids
- Requires a kidney biopsy +/- genetic testing
- Treated with additional immunosuppressive medications (e.g. tacrolimus)



http://renalfellow.blogspot.com/2011/08/fsgs-basics.html

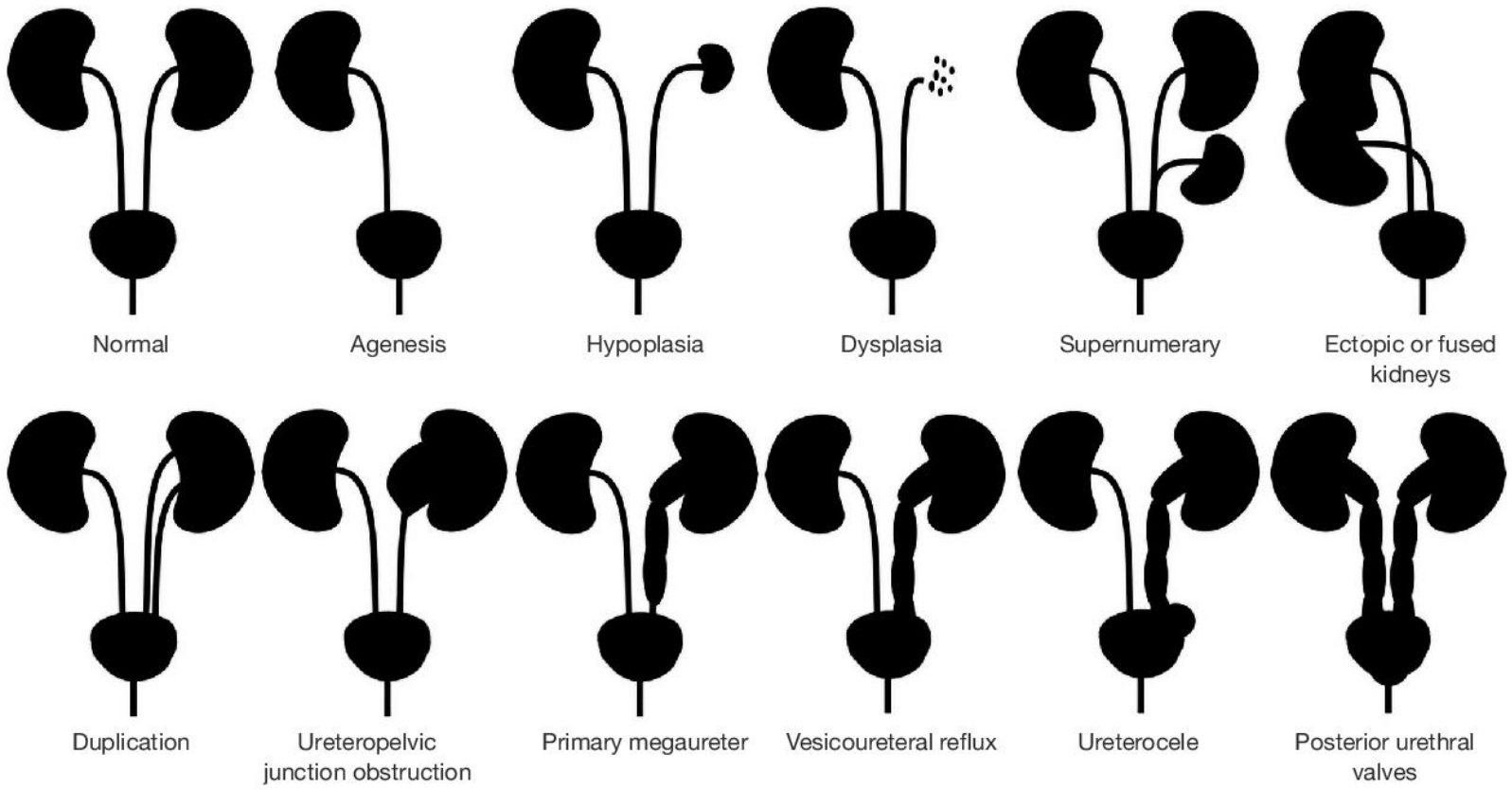
What are the Main Causes of Proteinuria?

Membranoproliferative glomerulonephritis:

- More common in females
- Affects older children and young adults
- 50% present with nephrotic syndrome and 25% with nephritic syndrome
- Low C3 level beyond 6-8 week period

- **Membranous nephropathy:**
  - Typically affects older adolescents
  - Can present with nephrotic syndrome
  - High rate of spontaneous remission

CAKUT (Congenital Anomalies of the Kidney and Urinary Tract)



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When Should I Refer my Patient to Nephrology?

- When a patient has an elevated first morning urine protein/urine creatinine ratio
- When the patient has any degree of proteinuria accompanied by hematuria, elevated creatinine, swelling, elevated blood pressure, or abnormal labs/renal imaging
- Any degree of proteinuria with additional systemic symptoms
- Any new diagnosis of nephrotic syndrome

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Thank you!

Questions?