Covered Today

- General review of Hematuria in children

- Update on certain common diseases presenting with hematuria in Children
  - IgA
  - Hypercalciuria
  - Thin Membrane disease
Diagnosis

- Diagnosis >5 rbc/HPF
Prevalence Hematuria in Children

- Gross hematuria in children: 0.13%.
  - The most common cause appears to be cystitis (20-25%).

- Asymptomatic microscopic hematuria: 1.5%.

- With repeated evaluations, the prevalence decreases to less than 0.5%.
Red Urine

Centrifuge result
- Sediment red
  - Hematuria
- Supernatant red
  - Dipstick heme

Positive
- Myoglobin
- Hemoglobin

Negative
- Beeturia
- Phenazopyridine
- Porphyria
- Other

Plasma color
- Clear
  - Myoglobinuria
- Red
  - Hemoglobinuria
Site of bleeding

- Glomerular
  - Dysmorphic cells
  - RBC casts
  - Proteinuria
  - Brown, Green

- ExtraGlomerular
  - No proteinuria
  - Neg Dysmorphic Cells
  - Red urine

LABORATORY TESTS

Example Of Phase-contrast Microscopy Test

Non-Glomerular

Glomerular (dysmorphic RBCs)
Glomerular Hematuria
Crenated RBC
Dysmorphic RBC to diagnose Glomerular disease


- 482 subjects with kidney biopsy

- 173 (35.9%) had <25% and 76 (15.8%) had ≥25% urine dRBCs.

- At the dRBC threshold of ≥25%
  - Sensitivity of 20.4%,
  - Specificity of 96.3% observed.

- urine RBCs [>10 versus ≤10/HPF (P < 0.001) independently predicted the presence of GN.

- A scoring system (0–3) based on hematuria and proteinuria level, revealed:
  - Risk for biopsy-proven GN was **15% when the score was “0”**
  - compared with **83% when it was “3”**.
Causes: Glomerular hematuria

• Thin basement membrane disease (benign familial hematuria)
• Alport syndrome
• Hemolytic-uremic syndrome
• Glomerulonephritis
  • Immunoglobulin A (IgA) nephropathy
  • Postinfectious glomerulonephritis
  • Membranoproliferative glomerulonephritis
  • Lupus nephritis
  • Anaphylactoid purpura (Henoch-Schönlein purpura)
  • ANCA + Vasculitis
Nonglomerular hematuria

- Fever, Strenuous exercise
- Mechanical trauma
- Menstruation
- Foreign bodies
- Urinary tract infection
- Hypercalciuria/uroolithiasis
- Sickle cell disease/trait
- Coagulopathy
- Tumors
- Drugs/toxins (nonsteroidal anti-inflammatory drugs [NSAIDs], anticoagulants, cyclophosphamide, ritonavir, indinavir)
- Anatomic abnormalities (hydronephrosis, polycystic kidney disease, vascular malformations)
Classification

• Gross vs Microscopic

• With or Without Proteinuria

• Symptomatic vs Asymptomatic
Gross Hematuria: Diagnostic clues

• **Recent vigorous** exercise or trauma.
• **Dysuria, frequency, or urgency** suggests urinary tract infection (UTI).
• **Unilateral flank pain** that may radiate to the groin suggests nephrolithiasis.
• The timing of hematuria.
  • initial hematuria usually suggests urethral bleeding
  • terminal bleeding is indicative of bladder disease.
• The color of urine may distinguish glomerular from extraglomerular bleeding.
• Evaluation for abdominal discomfort or masses (eg, Wilms tumor).
Gross Hematuria: evaluation

- A history of pharyngitis or impetigo 1-3 weeks prior: PSAGN
- A recent upper respiratory infection (1-3 days prior): immunoglobulin A (IgA) nephropathy
- Known sickle cell disease or trait, or coagulopathy.
- Exposure to medications that can cause
  - hemorrhagic cystitis (such as cyclophosphamide),
  - eosinophilic cystitis (nonsteroidal anti-inflammatory drug or antihistamines)
  - interstitial nephritis
- Physical examination
  - Measurement of blood pressure (BP)
  - Assessment for edema and recent weight gain
  - Skin examination for rash or purpura that suggests systemic condition associated with glomerular disease
  - Genitalia
Further evaluation

- Trauma history – **computed tomography (CT) scan**
- Signs or symptoms of UTI – **urine culture**
- Signs or symptoms of perineal/meatal irritation – Supportive care and reassurance.
- Signs or symptoms of nephrolithiasis
  - **Renal ultrasonography** is the preferred modality in children.
  - **Abdominal plain films**
  - **Spiral CT scan** is the **most sensitive** imaging modality.
- If findings suggestive of Glomerular Pathology – Proteinuria, RBC casts, edema, HTN.
  - Serum creatinine, albumin, CBC, complements C3, C4.
  - Other tests to consider: include ASO titer, ANA and ANCA.
Asymptomatic gross hematuria

• **Thorough evaluation** of children is **warranted** and **generally leads to a diagnosis**.

• In a retrospective review of 228 patients. Evaluation: CBC, U/A, U ca+, serum cr., serum C₃, ultrasonography or IVP, and renal biopsy in some cases. Etiologies:

  • No identifiable cause – 36 percent
  • Hypercalciuria – 22 percent
  • IgA nephropathy – 16 percent
  • Poststreptococcal glomerulonephritis – 7 percent
  • Other glomerulopathies including thin basement membrane (TBM) disease – 2 percent
  • Congenital anomalies (eg, UPJ obstruction, renal dysplasia) – 2 percent
  • Sickle cell trait – 1 percent
Nutcracker Syndrome
Asymptomatic Hematuria: Nutcracker Syndrome

- Left renal vein compression between the aorta and superior mesenteric artery
- Usually asymptomatic
- Detected by Doppler ultrasonographic assessment of left renal vein diameter and peak velocity or computed tomography.
- The frequency highest in Asia, with diagnosis rarely entertained in North America.
- Japanese case series of 85 children with hematuria without nephritis, nephrolithiasis, or tumor.
  - Doppler ultrasonographic findings were consistent with a diagnosis of nutcracker syndrome in 21 of 23 children with gross hematuria and 17 of 52 patients with microscopic hematuria and Negative in Normal children without Hematuria.
- Nutcracker syndrome suggested as a cause of orthostatic proteinuria.
Urologic Evaluation

- Cystoscopy is rarely indicated for hematuria in children.
- It should be reserved for the rare child with
  - Bladder mass noted on ultrasound
  - Urethral abnormalities due to trauma
Asymptomatic isolated microscopic hematuria

- most common presentation of microscopic hematuria.
- usually transient and not associated with significant disease.

A landmark 1979 study of an unselected population of 8954 children who were screened for hematuria.
  - 28 patients (0.3 percent) tested positive for blood on two or more urine samples underwent extensive evaluation including renal biopsy and IVP.
  - A cause was found in only 5:
    - #2 IgA nephropathy
    - #1 TBM disease
    - #2 uretero-pelvic stenosis.
Asymptomatic isolated microscopic hematuria

- Retrospective reviews of patients referred to tertiary centers demonstrated standard laboratory and imaging evaluations were unnecessary:

- In a study of 325 children, serum creatinine and electrolyte concentrations were normal in all 254 patients who were tested. Feld LG, Pediatrics. Pediatrics 1998; 102:E42.

  - Renal US with no significant findings in the 283 patients.
  - Hypercalciuria was present in 11 percent of the 263 patients whose urine was tested (U ca/cr)


  - No diagnosis was made in 80 percent of patients.
  - Among those with positive findings, the most common was hypercalciuria in 16%.

- Recommendations for observation of children with asymptomatic microscopic hematuria with normal exam.
Approach to children with asymptomatic isolated microscopic hematuria

- BP measurement and a U/A performed weekly for two weeks.
- Ensure that no exercise prior to obtaining the urine sample.
- If isolated hematuria persists, obtain a urine culture.
- If the patient remains asymptomatic, observe the patient every three to six months.
- If the asymptomatic isolated hematuria persists for one year:
  - Urine calcium/creatinine ratio for hypercalciuria.
  - Test parents and siblings for hematuria to detect possible thin basement membrane disease
  - Perform hemoglobin analysis if there is a clinical suspicion for sickle cell trait.
  - Perform Doppler ultrasonography for the nutcracker syndrome.
Persistent hematuria - most common causes

- IgA nephropathy
- Alport syndrome
- Thin basement membrane disease
- Poststreptococcal glomerulonephritis
- Hypercalciuria
- Nutcracker syndrome
Indications for renal biopsy

• Elevation in S. creatinine, significant proteinuria, or an otherwise unexplained rise in blood pressure.
• Parental worry about the diagnosis and prognosis.
• Family history of kidney failure in early adulthood in a first-order relative.
• Post streptococcal glomerulonephritis, an exception to these recommendations
Value of renal biopsy

• Renal biopsy done on Korean children with an abnormal U/A detected by school screening:
  • 289 patients with persistent isolated microscopic hematuria (≥6 RBCs per HPF, > 6 months)
  • 163 patients with microscopic hematuria and proteinuria.

• In children with **isolated microscopic hematuria**
  • normal biopsy 47%
  • TBM disease 34%
  • IgA nephropathy 16%

• In children with **microscopic hematuria and proteinuria**
  • normal findings, 25%
  • TBM disease, 18%
  • IgA nephropathy in 46%.
  • Other: mesangial proliferative glomerulonephritis (3 percent), poststreptococcal glomerulonephritis (3 percent), Alport syndrome (2 percent), and focal segmental glomerulosclerosis (FSGS)
Hypercalciuria: Presentation

• Approximately 30% of children with isolated hematuria
  • Hematuria gross or microscopic,
  • +/- dysuria, a history of "sandy urine".

• A spot U ca++/cr > 0.2 mg/mg is considered abnormal. (low specificity)
  • The ratio varies with age and averages 0.86 in infants younger than 7 months,
    • 0.6 in children aged 7-18 months
    • 0.42 in children aged 19 months to 6 years.

• An excretion rate of more than 4 mg/kg/24 hours is diagnostic.
Intestinal Calcium Absorption

- Two major mechanisms for Ca absorption:
  1. Between cells (paracellular):
     - Passive
     - Quantitatively significant when intake is high
  2. Through cells:
     - Active
     - Influenced by calcitriol
     - Calbindin: acts as an intracellular sink to reduce the microvilli [Ca]

**Proximal reabsorption**: 60-70% (80% of which is paracellular)

**TAL**: minimal Ca+ absorption (Calcitonin) in mTAL.

In cTAL 20% of total filtered Ca+ reabsorption (Passive mostly, due to electrochemical gradient, some active due to PTH and Calcitriol)

**DCT**: Active transport (PTH, Vit D) (10% of total filtered)
Pathophysiology

• Both genetic and environmental factors can affect these mechanisms

• Genetic factors with genes affecting:
  
  • calcium channels in the intestine and kidney
  • vitamin D receptor
  • renal and bone resorption
  • renal excretion of calcium, oxalate, and citrate
Monogenic disorders that impair renal tubular calcium reabsorption:

- Dent disease, also referred to as X-linked recessive nephrolithiasis
- Bartter syndrome
- Wilson disease
- Distal renal tubular acidosis (RTA)
- Familial hypomagnesemia with hypercalciuria and nephrocalcinosis
- HHRH: hereditary Hypophosphatemic rickets
- ADHH: Hypocalcemia with Hypercalciuria
Environmental factors

- Immobilization with increased bone resorption.
- Medications such as
  - loop diuretics, which increase calcium renal excretion
  - glucocorticoids, which increase bone resorption
- Excessive amounts of vitamin D.
- Diet (ca and Na rich affect calciuria)
Idiopathic Hypercalciuria (IH): Causes

• Three mechanisms contribute to higher urinary calcium excretion:

  • **Absorptive hypercalciuria:**
    - Increases intestinal calcium absorption.
    - Type 1 and Type 2 (latter is Vitamin D mediated)
  
  • **Renal hypercalciuria**
    - defect in renal tubular calcium reabsorption.

  • **Resorptive hypercalciuria:**
    - Increased bone resorption ("").
Idiopathic Hypercalciuria workup/management

- R/O secondary causes and monogenic causes
- Check Vit D (25 OH and 1-25 OH), K, CO₂, cl, Phos, PTH, Mg, Urinary citrate
- Limit Ca intake to RDA, look for response
- NaCl restriction
- Thiazide diuretics
IgA nephropathy

Auto-immune GN

- most common cause of chronic glomerulonephritis in the world.
- The disease appears to be less common in black individuals.
- A slight male preponderance is observed.
- Progression to chronic renal failure
- End-stage renal disease has been reported to occur in 20-50% of patients
IgA Nephropathy: presentation

- Hematuria: gross (1-3 days post Infectious illness),
- Hematuria microscopic
- +/- proteinuria
- Nephrotic Syndrome
- Acute Renal Failure
- Crescentic GN
- BP / fluid overload with severe involvement
- Colicky abdominal or loin pain may occur in some patients who develop clots in the genitourinary tract.
IgA: Pathophysiology

Increased secretory IgA Conc (associated with disease severity)

The serum IgA level is elevated in 30-40% of patients (not sufficient for diagnosis).

Abnormal Glycosylation in IgA1

in vitro: increased HMC binding + induction of cell proliferation plus increased Matrix formation

Composition of IgA1 relates to pathological Phenotypes

alpha 2,6 linked Sialic acid level associated progressive disease

deS/deGall IgA1 associated with sclerosing phenotype
IgA: Diagnosis

- A kidney biopsy with the characteristic deposition of IgA in the glomerular mesangium is diagnostic.
IgA: Treatment

- Children with proteinuria (>0.5-1 g/d/1.73 m²) should be treated with ACE inhibitors or angiotensin II receptor blockers (ARBS).
- Corticosteroids have been suggested in children with persistent proteinuria despite 3-6 months of optimized care.
- Fish oil is another treatment modality suggested in this subgroup of children.
- Other treatments like Mycophenolate Mofetil, azathioprine, danazol, dipyridamole, and antioxidants (eg, vitamin E) have been used with inconclusive results.
TBMD – Benign Familial Hematuria or:

- Thin basement membrane nephropathy (TBMN)
  - considered a relatively common disorder causing hematuria.

- By EM: Diffuse thinning of the glomerular basement membranes (GBM).

- Historically, these patients were often described as having benign familial hematuria.
TBMD: Collagen Gene story

- Family history of hematuria noted in 30 to 50 percent of cases.
- Mutations of the type IV collagen genes (COL4A3 and COL4A4)
- Such mutations are not present in all families.
- Use of the term "hematuria with thin glomerular basement membranes" for patients in whom mutations in collagen IV genes cannot be identified.
CLINICAL CHARACTERISTICS

- Incidentally discovered on routine urinalysis. Persistent or Intermittent
- Proposed that red cells move through localized, ruptures in the GBM
- Gross hematuria and flank pain — At times post URI
- Association with hypercalciuria and a + Fam Hx of lithiasis
DIAGNOSIS : TMD

- Renal biopsy is generally not performed
  - Unless presence of proteinuria.

- Renal biopsy: GBM width usually between 150 and 225 nm, versus 300 to 400 nm in normal subjects

- Renal biopsy may reveal thin GBM as **only abnormality** in **children** and **women** with X-linked Alport syndrome or autosomal recessive Alport syndrome

- Immunostaining

- Genetic testing
• The long-term **prognosis is good** in most patients.

• Presence of a heterozygous COL4A3/COL4A4 mutation in a patient with hematuria and thin GBM should be considered a risk factor for CKD.

• A study of 116 patients with TBMN from 13 Greek-Cypriot families identified 20 with biopsy-proven FSGS.

• A study of 70 families with a diagnosis of hereditary FSGS found that 7 families had heterozygous COL4A3/COL4A4 mutations.

• Collagen IV mutations were identified in 38 percent of families with "familial FSGS" and in 3 percent of adults with sporadic FSGS.

• Proteinuria or a family history of CKD may portend a less benign prognosis.
Distinction from Alport syndrome

- X-linked pattern, (70% of cases)
  - mutations in the COL4A5 gene.
  - In males, who have only one X chromosome, one altered copy of the COL4A5 gene is sufficient to cause severe Alport syndrome. Hearing loss, Ocular abnormalities (later in life) and progressive renal failure.
  - In females, one copy of the COL4A5 gene usually results in blood in the urine, but most affected females do not develop kidney failure.

- Alport syndrome can also be inherited in an autosomal recessive (15%) if both copies of the COL4A3 or COL4A4 gene, located on chromosome 2, have been mutated.

- Autosomal dominant pattern (20%) with mutations of COL4A3 or COL4A4 gene
Distinction from Alport syndrome

- TBMN may be difficult to distinguish from Alport syndrome in many cases.
- Screening first-degree relatives for hematuria
- Father-to-son transmission may be present, a finding that is not seen in X-linked Alport syndrome but may occur in autosomal dominant Alport syndrome.
- Patients with TBMN rarely have hearing loss, ocular abnormalities, or a family history of renal failure.
  - The absence of hearing loss and ocular abnormalities does not exclude a diagnosis of Alport syndrome.
- Incubation of kidney tissue with antibodies against the alpha-3, -4, and -5 chains of type IV collagen
  - Abnormal staining in the majority of patients with Alport (but shows normal staining in TBMN).
  - Normal immunostaining of GBM does not exclude a diagnosis of Alport syndrome.
- Molecular testing for COL4A3, COL4A4, and COL4A5 mutations by next-generation sequencing is a valuable addition to the diagnostic menu for familial hematuria’s (in some centers, replacing kidney biopsy) in the evaluation of possible familial hematuria.
Hematuria in Children