OBJECTIVES

- Review definition of hematuria
- Discuss significance of proteinuria
- Review appropriate work up for hematuria and proteinuria
- Determine when a patient with abnormal urinalysis should be referred

Case 1

12 year old girl found to have 2+ blood on dipstick on routine physical. She denies gross hematuria or dysuria. She has not started her menses.
Case 1 (cont.)

Question: Is it necessary to check urine studies on routine physical?

Case 1 (cont.)

Questions: Does she have hematuria?

What is the definition of hematuria?

Case 2

15 year old girl developed cola colored urine with URI symptoms. She had similar findings a year ago. Cola colored urine would resolve once she recovers from URI. No family history of hematuria, hearing loss or renal failure.
Case 2 (cont.)

Questions: What are the differential diagnosis of hematuria associated with URI symptoms?

How would you differentiate between them?

HEMATURIA: CLINICAL PRESENTATION

1. Asymptomatic microscopic hematuria

2. Isolated hematuria

3. Hematuria with other findings, e.g. edema, proteinuria, or UTI symptoms

METHODS TO DETECT HEMATURIA

1. Dipstick/urinalysis

2. Microscopy (expressed as number of RBC/HPF)
DEFINITION OF HEMATURIA

- Microscopic hematuria is defined as the presence of more than five RBCs per high-power field (40x magnification).

- The microscopic examination is the gold standard for the detection of microscopic hematuria.

DEFINITION OF PERSISTENT MICROSCOPIC HEMATURIA

- Persistent microscopic hematuria is defined as the presence of more than five RBCs per high-power field on 3 consecutive occasions, usually 1 week apart or over 6 months period.

FALSE POSITIVES FOR HEMATURIA

- Red urine with negative dipstick:
  - food dyes, foods, drugs, urates

- Positive dipstick but no RBCs:
  - hemoglobinuria, myoglobinuria
HEMATURIA IN CHILDREN

• EPIDEMIOLOGY OF HEMATURIA
• ETIOLOGY OF HEMATURIA
• EVALUATION OF A PATIENT WITH HEMATURIA
• RECURRENT HEMATURIA

HOW COMMON IS ASYMPTOMATIC MICROSCOPIC HEMATURIA?

- Several population-based studies of unselected school-age children have shown that the prevalence rate for microscopic hematuria detected in a single urine sample is 3 to 4 percent, which falls to 1 percent or less for two or more positive samples.


HOW COMMON IS ASYMPTOMATIC MICROSCOPIC HEMATURIA?

- Among the 1 percent of children with two or more positive urines for hematuria, only one-third have persistent hematuria, defined as a positive repeat test after six months.

- The combination of hematuria and proteinuria is less common, with a prevalence rate of less than 0.7 percent in unselected school-age children in a single urine sample.

PREVALENCE OF HEMATURIA DEFINED AS >5 RBC/HPF

NUMBER OF PATIENTS = 12,000
AGE RANGE: 6 TO 12 YEARS

<table>
<thead>
<tr>
<th>URINALYSIS</th>
<th>GIRLS</th>
<th>BOYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>INITIAL URINE +</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>2nd OR 3rd URINE + (2/3 ON RECHECK)</td>
<td>1%</td>
<td>0.5%</td>
</tr>
<tr>
<td>3 OF 3 URINES +</td>
<td>0.3%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

BASED ON DATA OF DODGE, et al

FOLLOWUP OF CHILDREN WITH HEMATURIA

NUMBER OF CHILDREN = 78

PERSISTENCE OF HEMATURIA AT END OF 1 YEAR
> 5 RBC/HPF 29%
> 10 RBC/HPF 37%

15/78 HAD HEMATURIA > 2 YEARS

ONLY 2/15 HAD SIGNIFICANT KIDNEY DISEASE AND BOTH HAD ASSOCIATED PROTEINURIA

CONCLUSIONS FROM SCREENING STUDIES OF HEMATURIA IN CHILDREN

1. Screening for hematuria is of limited benefit in detecting serious underlying renal disease.

2. Routine UA in asymptomatic patients is not cost-effective, which leads to unnecessary and expensive work up.

3. Those with renal disease often have other indicators, such as gross hematuria, proteinuria, positive family history, or hypertension.
AAP RECOMMENDATIONS

Since 2007, the American Academy of Pediatrics (AAP) no longer recommends that children undergo screening dipstick urinalysis. Because multiple large-scale studies of healthy school-aged children have demonstrated the low incidence of chronic kidney disease (CKD) in children, the AAP recommends that a dipstick urinalysis be performed only in patients at higher risk for chronic kidney disease.

INDICATORS OF KIDNEY DISEASE

- Hematuria and proteinuria together
- Persistently large heme on dipstick and/or > 20 RBC/HPF
- Previous episode(s) of gross hematuria
- Family history of hematuria, stones, renal disease or renal failure
- Increased serum creatinine and BUN
HEMATURIA IN CHILDREN

- EPIDEMIOLOGY OF HEMATURIA
- ETIOLOGY OF HEMATURIA
- EVALUATION OF A PATIENT WITH HEMATURIA
- RECURRENT HEMATURIA

SITE OF HEMATURIA

1. Lower urinary tract (post renal)
   Bladder or urethra

2. Upper urinary tract (renal)
   Kidney, pelvis or ureter
   Glomerular
   Non-glomerular

3. Bleeding & clotting disorders
   Site uncertain (prerenal)

HEMATURIA: BLEEDING & CLOTTING DISORDERS

1. Bleeding disorders
   Hemophilia, ITP, hemorrhagic disease

2. Coagulation disorders
   DIC, renal vessel thrombosis
POST RENAL CAUSES OF HEMATURIA
(BLADDER OR URETHRAL SITE)

1. Exclude menstrual period
2. UTI/hemorrhagic cystitis, bacterial, viral, parasites, drugs
3. Perineal irritation, meatal ulcer
4. Trauma to bladder or urethra
5. Miscellaneous: stones, vesicoureteral reflux tumor, hemangioma, urethrorrhagia, urethral prolapse, factitious

RENAI NONGLOMERULAR CAUSES OF HEMATURIA

Urinary tract infection
Sickle cell trait or disease
Trauma
Congenital renal anomaly (hydronephrosis, polycystic kidneys)
Idiopathic hypercalciuria, stones
Neoplasms: Wilms tumor
Interstitial nephritis, acute renal failure

GLOMERULAR CAUSES OF HEMATURIA: I

- Recurrent hematuria syndrome
  - Benign familial or sporadic
    (Thin GBM disease)
  - Alport syndrome
    (Hereditary progressive nephritis)
  - Iga NEPHROPATHY (Berger’s disease)

- Acute glomerulonephritis
  Poststreptococcal, others
GLOMERULAR CAUSES OF HEMATURIA: II

Membranoproliferative GN
Rapidly progressive GN (crescentic GN)
Anti-GBM GN
Henoch-Schonlein Purpura
Lupus nephritis
Hemolytic uremic syndrome

METHODS TO DIFFERENTIATE GLOMERULAR FROM NONGLOMERULAR HEMATURIA

1. Presence of red cell casts
2. Proteinuria > ++
3. Phase contrast microscopy or electron microscopy of sediment

RBC Cast
EXERCISE OR SPORTS RELATED TO HEMATURIA

1. Long distance running

2. Direct trauma to kidneys or bladder with boxing, wrestling, or football.

3. Rowing, swimming, cycling
HEMURIA IN CHILDREN

- EPIDEMIOLOGY OF HEMATURIA
- ETIOLOGY OF HEMATURIA
- EVALUATION OF A PATIENT WITH HEMATURIA
- RECURRENT HEMATURIA

EVALUATION OF HEMATURIA: HISTORY

1. Painless hematuria or with dysuria, passage of clots or gravel
2. UNIFORM red color vs. TERMINAL hematuria
3. Preceding respiratory or skin infection
   latent period 1 or 2 days vs. 1 or 2 weeks
4. History of fever, rash, joint pains
5. Recent trauma or vigorous exercise
6. History of hematuria in the past
7. Family history of hematuria, stones, deafness, renal failure

EVALUATION OF HEMATURIA: PHYSICAL EXAM

1. Blood pressure measurement
2. General exam for fever, edema, rash
3. Abdominal exam for mass or tenderness
4. Examination of genitalia
5. (Prostate exam in adults)
EVALUATION OF HEMATURIA: I
1. Urinalysis: presence of hemoglobin, proteinuria, and/or pyuria
2. Urine microscopy: confirm presence of >5 RBC (3 consecutive samples if asymptomatic)

EVALUATION OF HEMATURIA: II
1. Screen family members for hematuria
2. CBC
3. Bun, creatinine, electrolytes, serum protein
4. C3, C4, ANA, ANCA
5. Urine calcium / creatinine ratio (normal < 0.2)
6. Renal & bladder ultrasound

EVALUATION OF HEMATURIA: III
- Voiding cystourethrogram
- Cystoscopy
- Renal biopsy
- Audiogram
INDICATIONS FOR CYSTOSCOPY

1. Persistent lower tract symptom with hematuria & sterile urine

2. In some patients with terminal or initial hematuria

INDICATIONS FOR KIDNEY BIOPSY

1. Recurrent episodes of gross hematuria

2. Persistent microscopic hematuria with:
   A. Reduced kidney function
   B. Proteinuria
   C. Hypertension
   D. Symptoms of vasculitis

REFERAL GUIDELINES (MICROSCOPIC HEMATURIA)

Criteria for Referral: If isolated hematuria on a clean catch specimen is noted, please have patient repeat urine analysis 2 more times for total of 3 samples (at least one week apart between specimen collections). If > 5 RBC still persistent after 3 samples please obtain the screening labs listed and refer.
REFERAL GUIDELINES
(MICROSCOPIC HEMATUARIA)

- **Tests to be done at time of referral:**
  - CBC, serum electrolytes, BUN, Cr, C3, C4, ANA and ASO
  - First morning void urine for UA, microscopy, urine calcium/creatinine + urine protein/creatinine (these are **spot specimens** not a 24 hour urine collection – but must be done as a first morning void)
  - Renal and bladder ultrasound
  - Hearing test

REFERAL GUIDELINES
(GROSS HEMATURIA)

- Please evaluate for urinary tract infections. Please refer only in the absence of an infection.
- Please examine patient for any local causes such as rash/discharge/trauma that would account for local causes for hematuria

REFERAL GUIDELINES
(GROSS HEMATURIA)

**Criteria for Referral:**
- Refer to **Pediatric Nephrology** for gross hematuria in the absence of trauma.
- Refer to **Pediatric Urology** if there is gross hematuria with trauma
REFERAL GUIDELINES (GROSS HEMATURIA)

- Urine culture (should be negative)
- First morning void urine for UA, microscopy, urine calcium/creatinine + urine protein/creatinine (these are spot specimens not 24 hour urine collections – but must be done as a first morning void)
- Renal and bladder ultrasound
- CBC, serum electrolytes, BUN, Cr, C3, C4, ANA, ASO, ANCA.

PROTEINURIA AND NEPHROTIC SYNDROME

SIGNIFICANCE OF PROTEINURIA

- Early sign of kidney injury
- Protein loss accelerates renal failure
- Independent risk factor for CV disease
PRESENTATION OF PROTEINURIA

- Dipstick positive, no symptoms (asymptomatic proteinuria)
- Isolated proteinuria and edema (nephrotic syndrome)
- Proteinuria, hematuria, hypertension, edema, fever, rash... (nephritis)

PROTEINURIA

- Glomerular
- Tubular
- Overload
- Benign
GLOMERULAR FILTRATION

- Capillary loop with basement membrane which allows passage of specific molecules into the nephron.
GLOMERULAR PROTEIN

- Size of protein
- Shape of protein
- Charge of protein

GLOMERULAR PROTEIN

- Hemodynamic Alterations
  - Postural Proteinuria, Fever, CHF
  - GBM more porous due to damage or loss of GBM charge
  - Epithelial cell or slit membrane damage and/or denuding (detachment) of cells
  - Over production proteinuria due to light & kappa chains: Monoclonal gammopathies
URINARY PROTEIN EXCRETION

Adults: < 150 mg/24 hours (Average: 50 mg/24 hrs)

Children: < 100 mg/M^2/24 hours

Protein/Creatinine (on a spot urine) < 0.2

Microalbuminuria < 30 mg/day (Albumin:creatinine ratio)

METHODS TO MEASURE PROTEINURIA

Dipstick: fairly sensitive

Sulphosalicylic Acid

DIPSTICK
FALSE-POSITIVE

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dipstick</th>
<th>Sulfosalicylic Acid</th>
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<tbody>
<tr>
<td>Macroscopic hematuria</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Urine pH &gt; 8</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Phenazopyridine</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Radiocontrast media</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>High levels of penicillin</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>or cephalosporin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Tolmetin</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Sulfonamide</td>
<td>–</td>
<td>+</td>
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</tbody>
</table>

TRANSIENT PROTEINURIA

- Orthostatic proteinuria
- Exercise
- Fever
- Congestive heart failure
- Following abdominal operation
- Pyuria and UTI

BEST TEST TO ASSESS PROTEINURIA

- First morning protein/creatinine ratio
- Normal ratio < 0.2
- Only the ratio is informative, not the absolute urine protein value
Nephrotic syndrome

- Proteinuria > 2 g/m²/day
- Serum Albumin < 3 g/dl
- Edema
- Cholesterol > 250 mg/dl
NEPHROTIC SYNDROME IN CHILDREN

Incidence: 2-5/100,000 children
Prevalence: 15/100,000 children

NEPHROTIC SYNDROME IN CHILDREN

- Minimal Change disease
- Focal segmental glomerulosclerosis
- Congenital nephrotic syndrome
- Membranous nephropathy
- Secondary nephrotic syndrome (infection, malignancy, vasculitis, drugs)

MINIMAL CHANGE DISEASE
MINIMAL CHANGE DISEASE

MANAGEMENT OF NEPHROTIC SYNDROME

1. General Care: Education of Family
2. Diet and Fluid Alterations
3. Diuretics
4. Albumin Infusion
5. Steroids
6. Immunosuppressive Agents
7. Miscellaneous: Immunization, TB test prior to starting prednisone, Pneumovax

MANAGEMENT OF EDEMA

1. Low sodium diet, < 2 grams/day
2. Fluid restriction in severe cases
3. Lasix 1 mg/kg/dose P.O. 2-4 times/day
4. Albumin 25%: ½-1 gram/kg followed by intravenous Lasix
**PREDNISONE - SCHEDULE**

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Dosage</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Initially</td>
<td>60mg/m² daily</td>
<td>for 4-6 weeks or until urine protein free for 3 days</td>
</tr>
<tr>
<td>Thereafter</td>
<td>40mg/m² on alternate days</td>
<td>for 4-6 weeks</td>
</tr>
<tr>
<td>Thereafter</td>
<td>taper to zero</td>
<td>over 6-8 weeks</td>
</tr>
</tbody>
</table>

**MINIMAL CHANGE DISEASE**

- **100% STEROID TREATMENT**
  - **95% RESPONSE**
  - **5% NO-RESPONSE**
- **75-80% RELAPSE**
- **30-40% INFREQUENT RELAPSER**
- **15-20% NO-RELAPSE**
- **MOST OUTGROW DISEASE BY LATE ADOLESCENCE**
- **OUTGROW DISEASE**
- **CONTINUED PROTEINURIA**
- **RENAL FAILURE**

**COMPLICATIONS OF STEROID THERAPY**

1. Growth failure
2. Cushingoid appearance
3. Increased incidence of infection
4. Hypertension
5. Cataracts
6. Striae, hirsutism
7. Osteoporosis
8. Behavioral changes, depression
COMPLICATIONS OF NEPHROTIC SYNDROME

Increased incidence of infection
Increased incidence thromboembolism
Long-term effects of persistent hyperlipidemia
Long-term effects steroid use
CASE 1
- 13 year old male found to have 2+ proteinuria on routine physical. No history of edema. Urine specific gravity=1.025. Urine was done at 2pm.
- BP 115/60.
- First morning urine protein/creatinine ratio 0.1.
Is the proteinuria concerning?

- 13 year old male found to have 2+ proteinuria on routine physical. No history of edema. Urine specific gravity=1.025. Urine was done at 2pm.

- BP 115/60.

- First morning urine protein/creatinine ratio 0.1.

No. He has orthostatic proteinuria.

- 13 year old male found to have 2+ proteinuria on routine physical. No history of edema. Urine specific gravity=1.025. Urine was done at 2pm.

- BP 115/60.

- First morning urine protein/creatinine ratio 0.1.

CASE 2

- 5 year old girl with dysuria, urgency and gross hematuria. Urine showed spec gravity 1.010, > 25-50 RBC, 10-25 WBC, 2+ proteinuria, urine culture pending.

- Normal blood pressure.
CASE 2

- 5 year old girl with dysuria, urgency and gross hematuria. Urine showed spec gravity 1.010, > 25-50 RBC, 10-25 WBC, 2+ proteinuria, urine culture pending.

- Normal blood pressure.
- First morning urine protein/creatinine ratio 0.1 in 1 month.

Is the proteinuria concerning?

- 5 year old girl with dysuria, urgency and gross hematuria. Urine showed spec gravity 1.010, > 25-50 RBC, 10-25 WBC, 2+ proteinuria, urine culture pending.

- Normal blood pressure.
- First morning urine protein/creatinine ratio 0.1 in 1 month.

No, she has UTI. No proteinuria on repeat urine.

- 5 year old girl with dysuria, urgency and gross hematuria. Urine showed spec gravity 1.010, > 25-50 RBC, 10-25 WBC, 2+ proteinuria, urine culture pending.

- Normal blood pressure.
- First morning urine protein/creatinine ratio 0.1 in 1 month.
CASE 3

- 14 year old girl with fatigue, joint pain and facial rash for 2 weeks. She noticed dark and foamy urine for 2 days. Urine spec grav 1.015, 3+ proteinuria, no WBC, 25-50 RBC.

- BP 140/90.
- First morning urine protein/creatinine ratio 3.5. Creatinine 1.5.

Is the proteinuria concerning?

- 14 year old girl with fatigue, joint pain and facial rash for 2 weeks. She noticed dark and foamy urine for 2 days. Urine spec grav 1.015, 3+ proteinuria, no WBC, 25-50 RBC.

- BP 140/90.
- First morning urine protein/creatinine ratio 3.5. Creatinine 1.5.
Yes. She has glomerulonephritis and acute kidney injury, likely lupus. She needs renal biopsy and treatment.

- 14 year old girl with fatigue, joint pain and facial rash for 2 weeks. She noticed dark and foamy urine for 2 days. Urine spec grav 1.015, 3+ proteinuria, no WBC, 25-50 RBC.

- BP 140/90.
- First morning urine protein/creatinine ratio 3.5. Creatinine 1.5.

CASE 4

- 3 year old with generalized swelling and scrotal edema. Urine specific gravity 1.015, 4+ proteinuria, no RBC.

- Blood pressure 90%ile.

CASE 4

- 3 year old with generalized swelling and scrotal edema. Urine specific gravity 1.015, 4+ proteinuria, no RBC.

- Blood pressure 90%ile.
- First morning urine protein/creatinine ratio=17.
Is the proteinuria concerning?

- 3 year old with generalized swelling and scrotal edema. Urine specific gravity 1.015, 4+ proteinuria, no RBC.
- Blood pressure 90%ile.
- First morning urine protein/creatinine ratio=17.
Yes, he has nephrotic syndrome, likely minimal change disease.

- 3 year old with generalized swelling and scrotal edema. Urine specific gravity 1.015, 4+ proteinuria, no RBC.

- Blood pressure 90%ile.
- First morning urine protein/creatinine ratio=17.

PROTEINURIA: WHEN TO REFER

- After ruling out orthostatic proteinuria.
- After ruling out transient proteinuria.
- When suspecting underlying kidney disease, such as glomerulonephritis, nephrotic syndrome, etc.
- If hypertensive emergency, elevated creatinine, severe edema, contact peds nephrology immediately

Questions?
THANK YOU!