# PEDIATRIC URINALYSIS INTERPRETATION : PROTEINURIA AND HEMATURIA EVALUATION

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# 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



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?



Questions: Does she have hematuria?

What is the definition of hematuria?



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.

Dodge WF, J Pediatric 1976; Vehaskari VM, J pediatrics 1979, Iitaka K, Ped Neph 1994

### HOW COMMON IS ASYMPTOMATIC MICROSCOPIC HEMATURIA?

- Among the 1 percent of children with two or more positive urines for hematuria, only onethird 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.

Dodge WF, J Pediatric 1976; Vehaskari VM, J pediatrics 1979, Iitaka K, Ped Neph 1994

#### PREVALENCE OF HEMATURIA DEFINED AS >5 RBC/HPF

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

| <b>URINALYSIS</b>                      | <u>GIRLS</u> | BOYS |
|--|--------------|------|
| INITIAL URINE +                        | 2%           | 1%   |
| 2nd OR 3rd URINE +<br>(2/3 ON RECHECK) | 1%           | 0.5% |
| 3 OF 3 URINES +                        | 0.3%         | 0.2% |
| BASED ON DATA OF DO                    | DCF of al    |      |

BASED ON DATA OF DODGE, et al



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

- 1. Screening for hematuria is of limited benefit in detecting serious underlying renal disease.
- Routine UA in asymptomatic patients is not costeffective, which leads to unnecessary and expensive work up.
- 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.



#### Forum On Subspecialties

#### AAP does not recommend routine urinalysis for asymptomatic youths

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### 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



- 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)



- 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

### RENAL 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

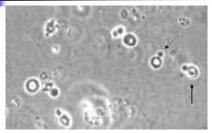
Membranoproliferative GN Rapidly progressive GN (crescentic GN) Anti-GBM GN Henoch-Schonlein Purpura Lupus nephritis Hemolytic uremic syndrome

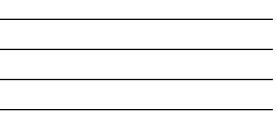
### METHODS TO DIFFERENTIATE GLOMERULAR FROM NONGLOMERULAR HEMATURIA

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

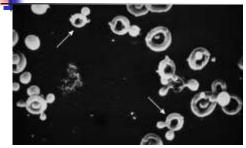












### EXERCISE OR SPORTS RELATED TO HEMATURIA

- 1. Long distance running
- 2. Direct trauma to kidneys or bladder with boxing, wrestling, or football.
- 3. Rowing, swimming, cycling

## HEMATURIA 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

- 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 HEMATUARIA)

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 > 5RBC 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

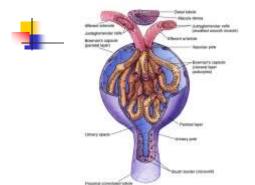
- Early sign of kidney injury
- Protein loss accelerates renal failure
- Independent risk factor for CV disease

# PRESENTATION OF PROTEINURIA

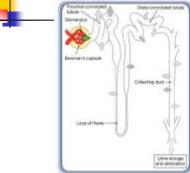
- Dipstick positive, no symptoms (*asymptomatic proteinuria*)
- Isolated proteinuria and edema (nephrotic syndrome)
- Proteinuria, hematuria, hypertension, edema, fever, rash...(*nephritis*)

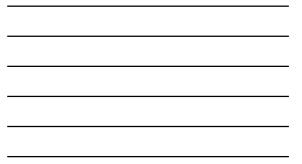
# PROTEINURIA

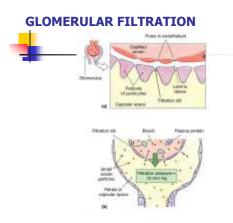
- Glomerular
- Tubular
- Overload
- Benign



# **GLOMERULAR FILTRATION**







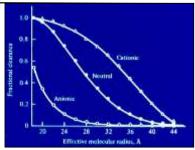


 capillary loop with basement membrane which allows passage of specific molecules into the nephron

# **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<sup>2</sup>/24 hours

Protein/Creatinine < 0.2 (on a spot urine)

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



Dipstick: fairly sensitive

Sulphosalicylic Acid



# FALSE-POSITIVE

| Condition                                     | Dipstick | Sulfosalicylic Acid |
|---|----------|---------------------|
| Macroscopic hematuria                         | +        | +                   |
| Urine pH > 8                                  | +        | -                   |
| Phenazopyridine                               | +        | -                   |
| Radiocontrast media                           | -        | +                   |
| High levels of penicillin<br>or cephalosporin | -        | +                   |
| Tolbutamide                                   | -        | +                   |
| Tolmetin                                      | -        | +                   |
| Sulfonamide                                   | -        | +                   |

# 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</p>
- Only the ratio is informative, not the absolute urine protein value

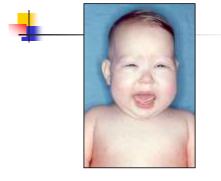
# Nephrotic syndrome

Proteinuria > 2 g/m<sup>2</sup>/day

Serum Albumin < 3 g/dl

Edema

Cholesterol > 250 mg/dl





# NEPHROTIC SYNDROME IN CHILDREN

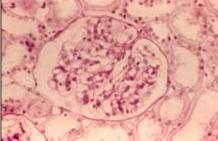
| Incidence | : | 2-5/100,000 children |
|-----------|---|----------------------|
|           |   |                      |

Prevalence : 15/100,000 children

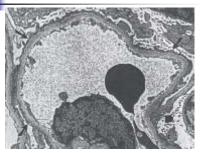
### NEPHROTIC SYNDROME IN CHILDREN

- 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

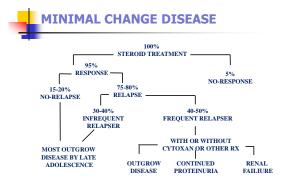
- 1. General Care: Education of Family
- 2. Diet and Fluid Alterations
- 3. Diuretics
- 4. Albumin Infusion
- 5. Steroids
- 6. Immunosuppressive Agents

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%: <sup>1</sup>/<sub>2</sub>-1 gram/kg followed by intravenous Lasix

| PREDNISONE - SCHEDULE |                                       |  |  |
|-----------------------|---------------------------------------|--|--|
| Initially             | 60mg/m <sup>2</sup><br>daily          | for 4-6 weeks or<br>until urine protein<br>free for 3 days |  |
| Thereafter            | 40mg/m <sup>2</sup> on alternate days | for 4-6 weeks  |  |
| Thereafter            | taper to zero                         | over 6-8 weeks   |  |

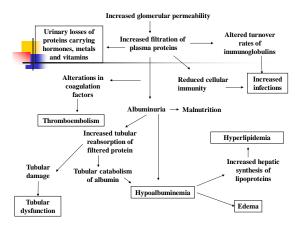


# **COMPLICATIONS OF STEROID THERAPY**

- 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



CASES

# 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.



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BP 115/60.

# 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.



- 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.



- 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.

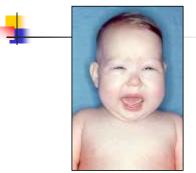
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- 3 year old with generalized swelling and scrotal edema. Urine specific gravity 1.015, 4+ proteinuria, no RBC.
- Blood pressure 90%ile.



- 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.







- 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



# **THANK YOU!**

