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The General Pediatrics Approach to Hematuria and Proteinuria

March 13th, 2024 | Celina Brunson MD MSCE, Nephrology

Disclosures

- None

Learning Objectives

- Learn the definition of hematuria and proteinuria
- Identify the common causes of hematuria and proteinuria
- Understand the initial evaluation of patients with hematuria or proteinuria
- Identify which patients with hematuria or proteinuria need subspecialty referral

History of Preventative Screening

- Hematuria and proteinuria remain a common finding during routine visits done by general pediatricians
- One study of 12,000 school children in 1976 found an incidence of >6% of both hematuria and proteinuria on routine screening but comparatively there was a low annual incidence of death by renal disease
- Studies such as this one and others emphasize the likelihood that most children who screen positive have a low incidence of renal pathology and/or these are transient findings which resolve

History of Preventative Screening

- The low incidence of pathology has likely contributed to urinalyses being removed from AAP recommendations for preventative screening
- However, in other countries including Japan, Taiwan and Korea routine screening of school aged children does occur
- Those patients with persistent urinary abnormalities likely warrant further evaluation and consideration for referral

Who should we consider screening?

Table 1.

Conditions Under Which Children Should Have a Yearly Urinalysis Performed

History of prematurity (<32 weeks' gestational age), very low birthweight, other neonatal complications requiring intensive care, umbilical artery line
Congenital heart disease (repaired or unrepaired)
Recurrent urinary tract infections, hematuria, or proteinuria
Known renal disease or urologic malformations
Solid organ transplant
Malignancy or bone marrow transplant
History of or prolonged treatment with drugs known to be nephrotoxic
History of recurrent episodes of acute kidney injury
Family history of inherited renal disease

Adopted from refs 5 and 6.

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Viteri B, Reid-Adam J. 2018

How do we screen urine samples?

Two options for screening including urine dipstick and urinalysis with microscopy

Urine dipstick

- Can be performed in clinic with fast results
- Needs to be done on a fresh urine sample, no more than 2 hours old
- Contains multiple reagents that react with the urine
- Hematuria: dipstick tests for peroxidase activity of the RBCs, positive indicates heme presence
- Proteinuria: dipstick tests with bromophenol dye which reacts to albumin, varying shades based on concentration

Hematuria

Case 1

10-year-old female presents to pediatrician's office for an annual physical. Parents state that she had two episodes of blood in her urine one month prior to this visit.

Due to this history, the pediatrician decides to check a urine dipstick in the office.

Results show dipstick with 2+ blood.

What should the pediatrician do next?

Definition of Hematuria

Hematuria is defined with urine dipstick positive for blood ***AND*** presence of >5 RBCs/hpf on an uncentrifuged urine sample

ALTERNATIVES INCLUDE

Dipstick positive for blood BUT no RBCs on microscopy

- Dipstick may be positive for hemoglobin or myoglobin
- Associated diagnoses including rhabdomyolysis, hemoglobinuria, menstrual blood, etc.

Dipstick negative but discoloration to the urine

- Medications including rifampin, nitrofurantoin, metronidazole
- Foods including beets, rhubarb, etc

False negative dipstick

- Can be caused by dilute urine, acidic pH or urinary reducing substances

Urine microscopy

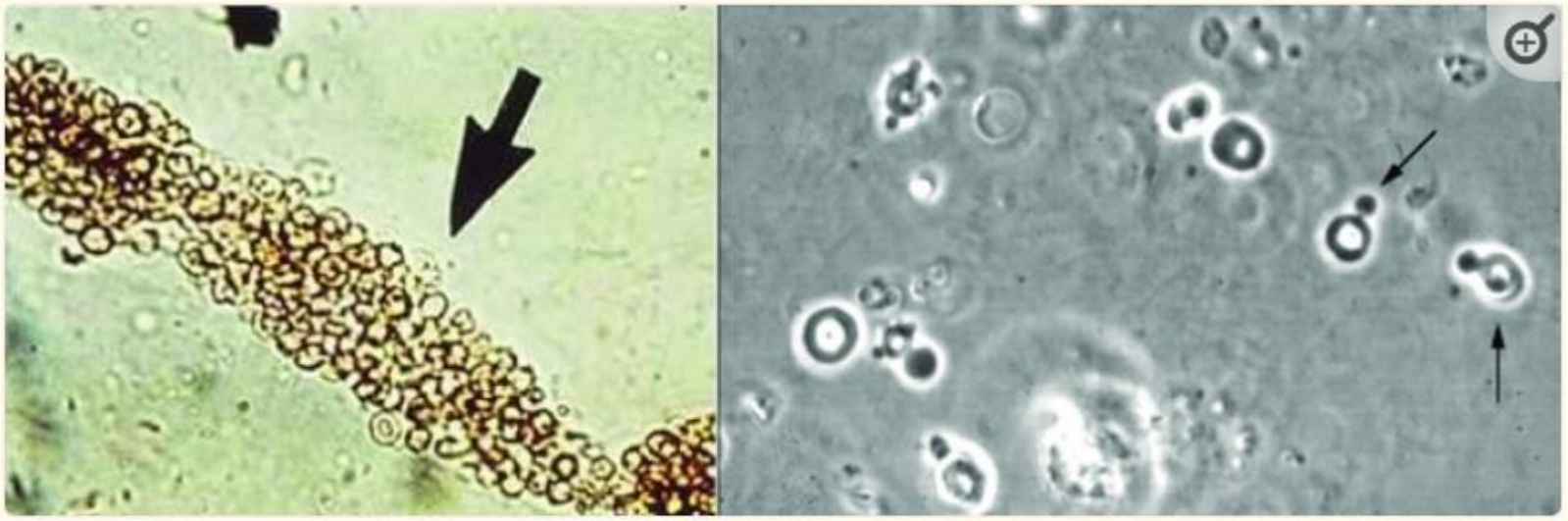

Figure 1.

Urine microscopy of hematuria from a glomerular source demonstrates red blood cell casts and dysmorphic red blood cells. (Left panel) Image shows a red blood cell cast. (Right panel) Image shows deformed red blood cells (arrows). Both findings are consistent with a glomerular source for hematuria.

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Kallash M, Rheault MN. 2020

Definition of Hematuria

Hematuria can be gross (macroscopic) or microscopic

- Gross hematuria can vary in color from red or pink to iced tea or Coca-Cola colored
- 1ml of blood can discolor the urine, can be distressing to families to witness

Hematuria can be transient or persistent

- Transient hematuria has been associated with fever, stress, trauma and infection

Most useful to classify as glomerular vs non-glomerular hematuria

Distinguishing extraglomerular from glomerular hematuria

	Extraglomerular	Glomerular
Color (if macroscopic)	Red or pink	Red, smoky brown, or "Coca-Cola"
Clots	May be present	Absent
Proteinuria	Usually absent	May be present
RBC morphology	Normal	Dysmorphic
RBC casts	Absent	May be present

RBC: red blood cell.

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Prevalence of Hematuria

Large scale population studies give range of ~4% for prevalence of asymptomatic microscopic hematuria in childhood

Studies have shown that the prevalence drops dramatically, one showed prevalence of 0.25% of children with hematuria on 4 consecutive samples

Clinical questions to ask

- Color of the urine?
- When in the urinary stream does the color change happen?
- Is the hematuria transient or persistence? Multiple voids over multiple days?
- Associate symptoms, recent illnesses, etc.

Case 1 continued

Due to the positive urine dipstick the pediatrician gets further history from the family.

They describe her urine in these episodes as iced-tea colored, the urine had an abnormal color for the entire void and it occurred over multiple voids over a two-week period and has since resolved. She had some viral symptoms at the same time as the hematuria.

What should the pediatrician do next?

Classification: Non-glomerular hematuria

Urinary Tract Infection

- Bacterial urinary tract infections remain one of the most common causes of gross hematuria in children
- Symptoms include dysuria, fever, urinary urgency and frequency
- Most caused by E coli however there can be viral causes such as adenovirus that can cause hematuria

Hematuria secondary to localized inflammatory response caused by infection

Classification: Non-glomerular hematuria

Kidney Stones

- History will include gross and/or microscopic hematuria associated with flank/abdominal pain, nausea and vomiting; may also show symptoms of a UTI
- Alternatively, can be an incidental finding on ultrasound/AXR
- Most commonly calcium-based stones including calcium oxalate or calcium phosphate stones

Hematuria caused by crystals forming and irritating the urothelial lining

Classification: Non-glomerular hematuria

Hypercalciuria

- Defined as elevated urine calcium/creatinine ratio >0.2 mg/mg creatinine
- Associated with asymptomatic microscopic hematuria
    - Can see dysuria or abdominal pain
- Patients may have nephrocalcinosis and/or kidney stones

Hematuria caused by elevated calcium irritating the urothelial lining

Classification: Non-glomerular hematuria

Renal/Bladder masses

- Broad differential which can include cystic kidney disease, hydronephrosis, renal or bladder malignancies
- Symptoms will vary based on exact cause i.e. cystic disease can be diagnosed by palpable renal mass, hydronephrosis by associated UTI, etc.

Hematuria can be multifactorial including impaired angiogenesis and friable tissue leading to easily ruptured blood vessels and invasion of vascular supply by tumors or cysts

Classification: Glomerular hematuria

IgA Nephropathy

- Characterized by gross hematuria in close association with an upper respiratory viral infection
- Can also present as asymptomatic microscopic hematuria, nephrotic syndrome or RPGN
- Most common cause of chronic glomerulonephritis worldwide
- Caused by deposition of immune complexes within the kidney made up of autoantibodies to abnormal IgA molecules leading to inflammation

HSP Nephritis (IgA Vasculitis)

- Pathognomonic palpable purpuric rash on lower extremities, abdominal pain, arthritis/arthralgia, renal abnormalities
- Primary renal findings include microscopic or gross hematuria
- Same pathogenesis as IgA

Classification: Glomerular hematuria

Post-infectious glomerulonephritis

- Present with symptoms of an acute nephritis (edema, hypertension, gross hematuria, abnormal kidney function) 1-2 weeks after throat or skin infection
- Most commonly secondary to streptococcal infections but has been seen with many other bacteria and viruses
- Laboratory findings include low complement C3 and normal complement C4 levels
- Generally self-limited, around 4-6 weeks

Classification: Glomerular hematuria

Alport syndrome

- Genetic mutation causing abnormal collagen molecules leading to abnormalities in glomerular basement membrane
- Can be inherited X-linked, autosomal dominant or recessive
- Patients can present with microscopic or gross hematuria and have progression to end stage renal disease in 3rd or 4th decade of life
- Associated extra-renal manifestations including sensorineural hearing loss and lens abnormalities

Evaluation of Hematuria

If urine dipstick positive for blood (1+ or greater)

- Repeat urinalysis with microscopy to confirm presence of RBCs and characterization of the RBCs
- Eumorphic RBCs increases likelihood of a non-glomerular cause for the hematuria
- Dysmorphic RBCs and/or RBC casts increased likelihood of glomerular hematuria

Evaluate for other findings including proteinuria, abnormal kidney function and hypertension

Case 1 continued

The pediatrician does further evaluation including urinalysis and renal function panel.

Her urinalysis returned confirming diagnosis of hematuria with 2+ blood and 10-25 RBCs/hpf. Her urinalysis also shows 1+ protein.

Her kidney function and blood pressure are normal.

Should she be referred to nephrology?

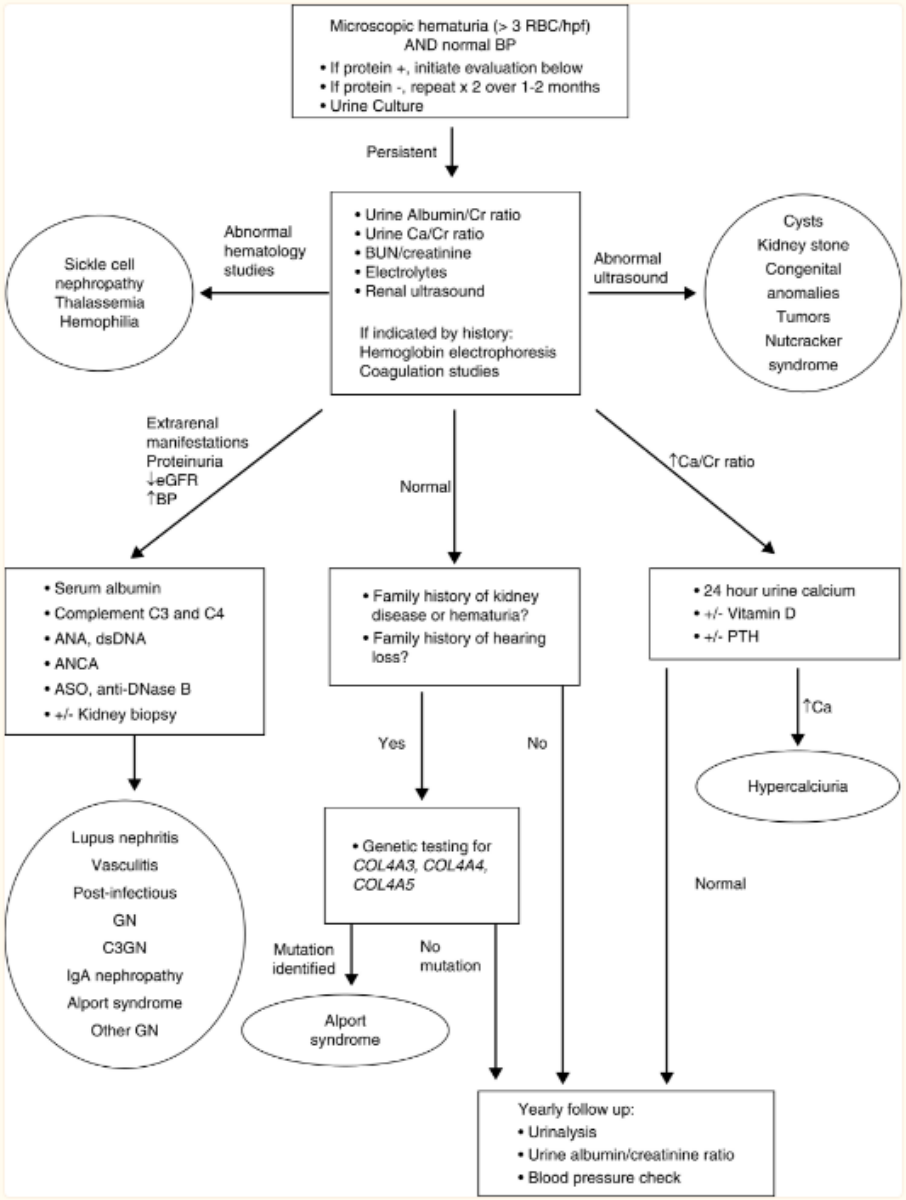


Figure 2.

Algorithm for evaluation of a child with microscopic hematuria. ANA, antinuclear antibody; ASO, antistreptolysin O antibody; Ca, calcium; Cr, creatinine; C3GN, complement factor 3 glomerulopathy; dsDNA, antidouble-stranded DNA antibody; hpf, high-powered field; PTH, parathyroid hormone; RBC, red blood cell.

Referral to Nephrology

Persistent hematuria

- Urine dipstick > 1+ and >5 RBCs/hpf

Alone OR with ANY of the FOLLOWING

Elevated serum creatinine
Associated proteinuria, especially nephrotic-range proteinuria
Hypertension

Generally isolated microscopic hematuria with good prognosis and patients usually monitored annually due to lifetime risk of CKD

Referral to Urology

Can consider if

- Strong evidence of non-glomerular cause for hematuria
- The intervention is likely to be surgical i.e. kidney stones* or renal mass
- Consideration for further evaluation including cystoscopy

Case 1 Conclusion

Possible diagnoses include IgA nephropathy and Alport's syndrome.

Patient warrants nephrology referral due to persistent hematuria and proteinuria.

Tips and Opportunities for collaboration

- If the repeat urine dipstick is negative, decreased concern for serious renal pathology
- Blood in the urine may not always be blood in the urine
- Asymptomatic microscopic hematuria
    - Could these kids be followed by their PCP with close collaboration with nephrology?

Proteinuria

Case 2

A 4-year-old male presents to the pediatrician's office for a sick visit. His parents state that he had a recent viral illness, along with multiple other children in his daycare. Since the illness, they have noted that his eyelids are swollen especially first thing in the morning and his abdomen has been more full appearing.

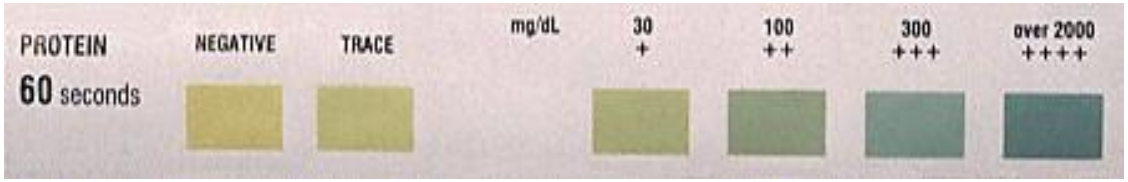
The pediatrician does a urine dipstick which shows 2+ protein.

What should the pediatrician do next?

Definition of Proteinuria

Proteinuria is defined as urine dipstick positive for protein at 1+ or greater

Urine dipstick is 99% sensitive and specific for albumin but not for low molecular weight proteins



ALTERNATIVES

False negative protein: Acidic urine, dilute urine, other proteins
False positive: Concentrated urine, alkaline urine, hematuria, pyuria, presence of substances (Pyridium, chlorhexidine, iodinated contrast)

Definition of Proteinuria

Quantitative measurement of proteinuria

24hr Urine protein: More accurate than urine dipstick but hard to obtain

- Abnormal is a value greater than 100mg per m2 per day
- Nephrotic range proteinuria is defined as greater than 1000mg per m2 per day

Spot urine protein/creatinine ratio: Easier to obtain

- Abnormal is value greater than 0.2mg/mg creatinine
- Nephrotic range proteinuria is defined as greater than 2 mg/mg creatinine

Prevalence of Proteinuria

Large scale population studies give range of 5-15% for prevalence of proteinuria in childhood

However, one study showed that prevalence of proteinuria went from 10% on the first sample and then dropped to 0.1% after repeating 4 urine samples for the patient

Case 2 continued

On further history the parents state that he has seemed to gain weight over a short period of time and isn't urinating as often as his baseline. On exam his pediatrician notes periorbital and abdominal edema.

What should the pediatrician do next?

Classification: Transient proteinuria

Defined as proteinuria on 1-2 tests but not on repeat testing

Temporary change in glomerular hemodynamics causes the protein loss

Causes include

- Fever, seizure, exercise, stress, dehydration or cold weather

Generally benign and self-limited and doesn't require nephrology referral

Classification: Orthostatic proteinuria

Defined as increased protein excretion when patient is upright that normalizes when patient is supine

Diagnosed when the random urine sample shows UPC > 0.2 while the first morning urine sample is < 0.2

One of the most common causes of proteinuria in adolescents

Etiology unclear but understood to be benign

Classification: Persistent proteinuria

Differs based on mechanism

Glomerular proteinuria caused by increased filtration of albumin

- Caused by increased permeability of glomerular basement membrane due to structural defects, loss of negative charge or damage by immune complexes
- Reduced functioning nephrons in chronic kidney disease

Tubular proteinuria caused by increased excretion of low molecular weight proteins

- Caused by impaired reabsorption by proximal tubules

Less commonly secretory and overflow proteinuria

Table 2. Clinical Clues to the Cause of Persistent Proteinuria in Children

Cause of proteinuria	*Clinical features*	*Laboratory findings**
Glomerular		
Adaptation to nephron loss	History of vesicoureteric reflux or recurrent urinary tract infection	Elevated serum creatinine or blood urea nitrogen levels
Alport syndrome	Hearing loss, decreased vision, gross hematuria, family history of the condition	RBCs on urinalysis
Collagen vascular disease or vasculitis		
Henoch-Schönlein purpura	Nonblanchable, palpable, purpura in gravity-dependent area, arthritis, abdominal pain, hematuria	WBCs, RBCs, cellular casts on urinalysis
Systemic lupus erythematosus	Recurrent fever, butterfly facial rash, arthritis, hematuria, growth failure, multisystem involvement	Positive antinuclear antibody findings, pancytopenia, decreased C3 and C4 levels
Diabetes mellitus	Polyuria, polydipsia, weight loss	Elevated fasting blood glucose and A1C levels, glycosuria
Glomerulopathy		
Congenital nephrotic syndrome	Age younger than three months, prematurity, low birth weight, placentomegaly, edema at birth or during first week of life	Elevated α-fetoprotein level in amniotic fluid, nephrotic-range proteinuria, hypoalbuminemia, hyperlipidemia
Focal segmental glomerulosclerosis	Nephrotic or nephritic features, history of human immunodeficiency virus infection	Proteinuria of varying degree, including nephrotic-range proteinuria; hypoalbuminemia; hyperlipidemia; thrombocytosis; normal complement; serology positive for human immunodeficiency virus
Immunoglobulin A nephropathy	Usually age older than 10 years, nephritic features, recent upper respiratory tract infection, microscopic hematuria interspersed with episodes of macroscopic hematuria	Hematuria, elevated serum immunoglobulin A level, normal C3 and C4 levels
Membranoproliferative glomerulonephritis	Nephrotic or nephritic features; history of chronic hepatitis B or C; may be associated with infections, rheumatologic disease, and malignancies	Hematuria, decreased C3 level, usually normal C4 level, serology positive for hepatitis, possibly nephrotic laboratory findings
Mesangial proliferation	Nephrotic features, hematuria	Nephrotic-range proteinuria, hypoalbuminemia, hyperlipidemia, thrombocytosis, normal complement levels
Minimal change glomerulopathy	Most common form of nephrotic syndrome, usually age younger than six years, may be associated with recent viral infection or allergy	Nephrotic-range proteinuria, hypoalbuminemia, hyperlipidemia, thrombocytosis, normal complement levels
Infection		
Poststreptococcal glomerulonephritis	Recent pharyngitis or skin infection, nephritic features	Positive throat swab findings, elevated antistreptolysin titer result, decreased C3 and C4 levels, dysmorphic RBCs or RBC casts on urinalysis
Malignancies	Weight loss, cachexia	Abnormal laboratory findings depending on underlying cause

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Tubulointerstitial		
Acute tubular necrosis	Medication history includes aminoglycosides, cisplatin, amphotericin B, or nonsteroidal anti-inflammatory drugs; history of radiocontrast media use	Elevated serum creatinine or blood urea nitrogen levels; granular casts, epithelial cell casts, renal tubular epithelial cell casts on urinalysis
Acute tubulointerstitial nephritis	Medication history includes nonsteroidal anti-inflammatory drugs, penicillin, cephalosporins, quinolones, sulfonamides, cimetidine (Tagamet), allopurinol; nonspecific malaise, fever, rash	Acute rise in serum creatinine level, eosinophilia, WBC casts on urinalysis
Polycystic kidney disease	Hematuria, hypertension, renal insufficiency, nephromegaly, family history of the condition	RBCs on urinalysis, elevated serum creatinine or blood urea nitrogen levels
Proximal renal tubular acidosis	Cystinosis: visual impairment, Fanconi syndrome, thyroid disorder, hepatosplenomegaly, delayed puberty Fanconi syndrome: growth failure, polyuria, polydipsia Lowe syndrome: cataracts, Fanconi syndrome, hypotonia Wilson disease: Kayser-Fleischer rings (slit lamp), liver dysfunction or cirrhosis	Cystinosis: elevated leukocyte cystine level Fanconi syndrome and Lowe syndrome: acidic urine, glycosuria, aminoaciduria Wilson disease: decreased serum ceruloplasmin level, elevated liver enzymes
Pyelonephritis	Fever, chills, flank and costovertebral tenderness, hematuria, irritative urinary symptoms	Leukocytes on urinalysis, positive urine culture results
Toxins	Copper: history of exposure (e.g., food containers) Lead: history of exposure, constipation, lead line along gum margin, cognitive or behavioral impairment Mercury: history of exposure (e.g., dental amalgam filling; diet, such as consumption of contaminated seafood), may have cognitive impairment or nephrotic-type syndrome	Elevated level of the toxin

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Causes of Proteinuria: Nephrotic syndrome

One of the most common causes of glomerular proteinuria

Characterized by edema, hypoalbuminemia, nephrotic range proteinuria and hyperlipidemia

Common presentation is children between 3 and 9 years of age

Diagnoses can include

- Minimal change disease, FSGS, etc

Causes of proteinuria: Inflammatory conditions

Variety of acute causes of nephritis can present with proteinuria

IgA and HSP can present with nephrotic syndrome

Systemic lupus erythematosus

- Chronic autoimmune condition that affects multiple organs in the body
- Can present with lupus nephritis with glomerular disease that varies in severity based on Class I-V on renal biopsy
- Clinical symptoms can include proteinuria, hematuria, abnormal kidney function

Evaluation of Proteinuria

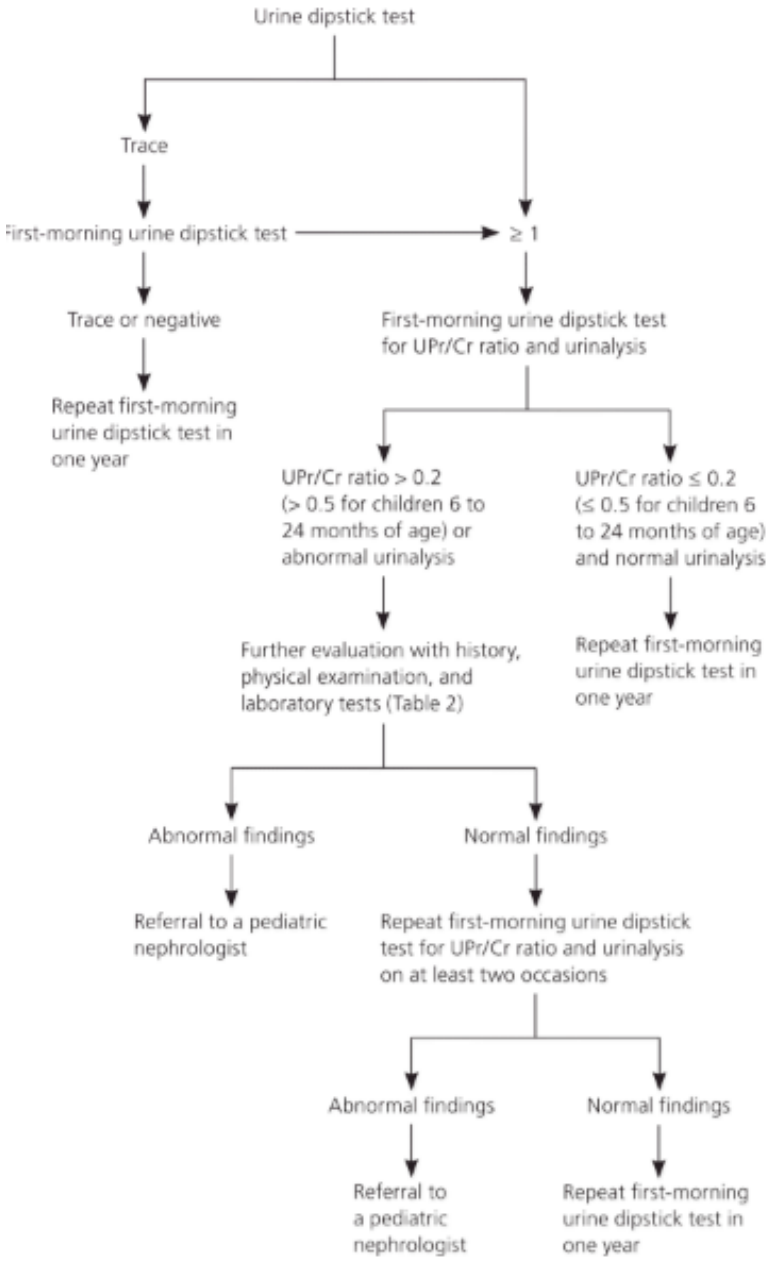
If urine dipstick is positive for protein (>1+)

- Repeat urinalysis with urine protein/creatinine ratio on first morning urine sample
- If UPC <0.2, no further evaluation is needed*
- If UPC >0.2, further evaluation needed which can be determined by clinical findings including renal function, complements, autoantibodies, etc.

There are various algorithms which can be referenced to help with evaluation

FIGURE 1

Evaluating Asymptomatic Proteinuria in Children



Algorithm for evaluating asymptomatic proteinuria in children. (UPr/Cr = urine protein-to-creatinine.)

Information from references 1 through 3.

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From: **Hematuria and Proteinuria in Children**

Pediatr Rev. 2018;39(12):573-587. doi:10.1542/pir.2017-0300

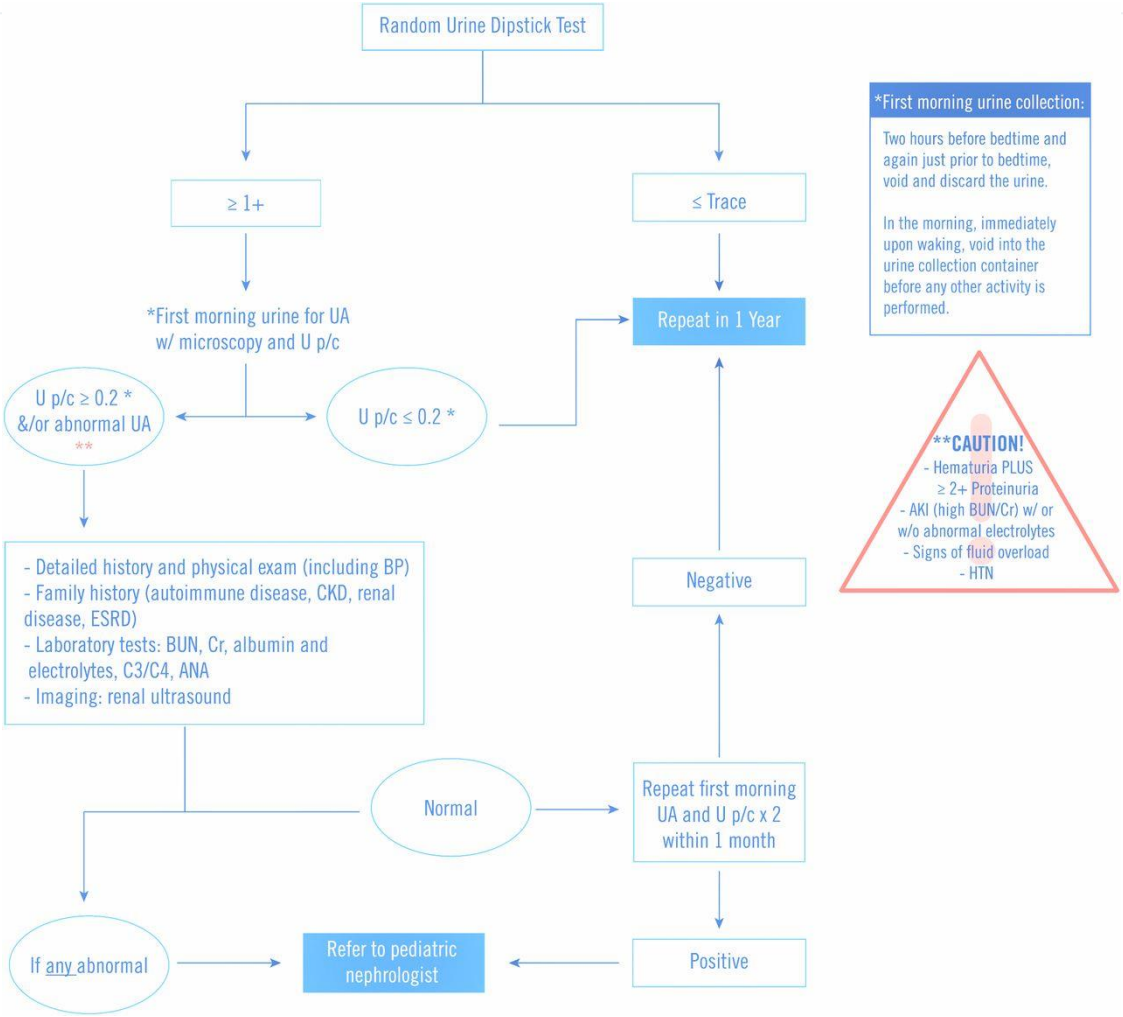

Figure Legend:

Approach to a child with asymptomatic proteinuria. Caution items warrant urgent consultation with a nephrologist. ANA=antinudear antibody; AKI=acute kidney injury; BP=blood pressure; BUN=blood urea nitrogen; C3=complement component 3; C4=complement component 4; Ca/Cr=calcium/creatinine; CKD=chronic kidney disease; ESRD=end-stage renal disease; HPF=high-power field; HTN=hypertension; RBC=red blood cell; UA=urinalysis; U p/c=urine protein/creatinine ratio. (Adapted from refs 14, 41, 48, and 49.)

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Case 2 continued

The pediatrician sends a urinalysis and urine protein/creatinine ratio which show 2+ protein and a urine protein/creatinine ratio of 2.5.

His lab work shows albumin of 1.8 and a normal creatinine.

Should this patient be referred to nephrology?

Referral to Nephrology

Persistent proteinuria

- Urine dipstick > 1+ or urine protein/creatinine ratio >0.2 mg/mg

Alone OR with ANY of the FOLLOWING

Elevated serum creatinine
Associated gross or microscopic hematuria
Hypertension
Concerning clinical findings including rash, edema, joint pain, etc

Case 2 conclusion

Most likely diagnosis nephrotic syndrome and warrants referral to nephrology for further evaluation.

Tips and Opportunities for collaboration

- Urine dipsticks are very sensitive to the patient environment and false negatives and positives are common
- A first morning urine protein can prevent need for referral especially in adolescents
- Persistent proteinuria remains both an indicator of renal disease and can cause further progression and shouldn't hesitate to evaluate and refer

References

Dodge WF, West EF, Smith EH, et al. Proteinuria and hematuria in schoolchildren: Epidemiology and early natural history. Pediatr. 1976; 88(2): 327-347. https://doi.org/10.1016/S0022-3476(76)81012-8.

Bignall ONR 2nd, Dixon BP. Management of Hematuria in Children. Curr Treat Options Pediatr. 2018 Sep;4(3):333-349. doi: 10.1007/s40746-018-0134-z. Epub 2018 Jun 14.

Kallash M, Rheault MN. Approach to Persistent Microscopic Hematuria in Children. Kidney360. 2020 Jul 10;1(9):1014-1020. doi: 10.34067/KID.0003222020. PMID: 35369549; PMCID: PMC8815596.

Leung AK, Wong AH, Barg SS. Proteinuria in Children: Evaluation and Differential Diagnosis. Am Fam Physician. 2017 Feb 15;95(4):248-254. PMID: 28290633.

Simerville JA, Maxted WC, Pahira JJ. Urinalysis: a comprehensive review. Am Fam Physician. 2005 Mar 15;71(6):1153-62. Erratum in: Am Fam Physician. 2006 Oct 1;74(7):1096. PMID: 15791892.

Viteri B, Reid-Adam J. Hematuria and Proteinuria in Children. *Pediatr Rev* December 2018; 39 (12): 573–587. https://doi.org/10.1542/pir.2017-0300

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