Hematuria and Proteinuria

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What is man, when you come to think upon him, but a minutely set, ingenious machine for turning with infinite artfulness, the red wine of Shiraz into urine?

—Izak Dineson

Learning Objectives:
1. Know the current American Academy of Pediatrics recommendations for screening urinalysis
2. Identify the most common causes of hematuria and proteinuria in the pediatric population
3. Describe the diagnostic approaches used to evaluate hematuria and proteinuria

Primary Reference:

CASE ONE:
Norm L. Pea is a 12-year-old boy who is new to your practice and here today for a well child check. His mother says, “Why didn’t you check his urine? Our old pediatrician checked one every year even though they were always normal.”

1. What are current AAP guidelines regarding screening urinalysis in asymptomatic children?
Recommendations for screening urinalysis (UA) have changed over time. In 1974, Kunin proposed a national UA screening program to improve early detection and reduce morbidity from renal disease in children. Over time, formal recommendations for yearly UA in children were adopted. Previously, the AAP recommended checking a UA once at age 5 and then annually in sexually active adolescents. Since 2008, the AAP and Bright Futures no longer call for screening UA in healthy asymptomatic children who are growing and developing normally.

The recommendations have changed, not due to new evidence, but because of lack of evidence of benefit and cost-effectiveness. For example, studies of patients with an abnormal initial screening urinalysis reveal that 84 - 89% had a repeat dipstick UA which was normal. Lack of cost-effectiveness has led the AAP Section on Nephrology to include “don’t order routine screening urinalyses” as its top item in the Choosing Wisely campaign. However, a 2014 study revealed that a substantial number of pediatricians still employed use of screening UA despite the guidelines.

While mass screening is not recommended, targeted and thoughtful screening UA is still important to consider. Notably, the AAP does recommend screening UA for children who have a high risk of kidney disease, including but not limited to those with history of prematurity <32 weeks, very low birthweight, known renal or urologic disease, hypertension, previous acute kidney injury, and family history of genetic renal disease.

In addition to those high-risk patients who still should have screening UAs, the Executive Committee of the AAP’s section on Nephrology has published this list of specific conditions that they believe require a complete urinalysis (including microscopic examination), during well-child care or in the context of a relevant acute evaluation:
- Type 1 or type 2 diabetes mellitus or evidence of the metabolic syndrome
- Sustained hypertension
- Polyuria or inappropriately dilute urine
- Electrolyte, acid-base, or osmolar imbalances
- Systemic inflammatory, metabolic, or infectious disorders (e.g., systemic lupus erythematosus [SLE], Henoch-Schönlein purpura [HSP], endocarditis, sickle cell disease)
- Unexplained growth failure
- Fever or acute illness of undisclosed origin
- Dysfunctional voiding, urinary incontinence, or prolonged enuresis
- Edema
- Macroscopic (gross) hematuria
- History of congenital urinary tract abnormality (e.g., obstructive uropathy, vesicoureteral reflux, multicystic dysplastic kidney, unilateral kidney agenesis)
- Dysuria, urgency, frequency suggestive of urinary tract infection
- Back or flank pain suggesting possible urolithiasis or pyelonephritis.

CASE continued:

| Norm has a history of prematurity (30 weeks gestation) and NICU stay. Therefore, you move forward with screening UA. The urine dipstick shows a specific gravity of 1.015, pH of 6.5, and 2+ protein. The test is otherwise normal. |

2. What are the three main mechanisms of proteinuria and the most common causes in children? What further history and physical exam might help you distinguish among these causes?

Proteinuria may result from alterations in glomerular hemodynamics, from damage to the proximal tubular epithelium, or by the process of overflow proteinuria which occurs when the plasma concentration of small proteins exceeds the resorptive capacity of the tubules. The major causes of proteinuria, which occur from a combination of the three mechanisms listed above, can be divided into the following categories: transient, orthostatic, and persistent.

**Transient proteinuria** is associated with fever, strenuous exercise, extreme cold exposure, epinephrine administration, emotional stress, seizures, and/or hypovolemia. **Orthostatic proteinuria** is a benign condition in which protein excretion is increased when the patient is upright and normalizes when the patient is recumbent. Transient and orthostatic proteinurias occur largely due to alterations in glomerular hemodynamics, although certain transient disorders (e.g., rhabdomyolysis, acute hemolysis) result in temporary overflow proteinuria.

**Persistent causes of proteinuria** can be categorized according to the mechanisms described above. Causes of glomerular proteinuria include minimal change disease, focal segmental glomerulosclerosis, IgA nephropathy, membranoproliferative glomerulonephritis, membranous nephropathy, Alport syndrome, acute post-streptococcal glomerulonephritis, diabetes mellitus, SLE, and HSP. Tubular proteinuria is less common and is caused by conditions such as polycystic kidney disease, acute tubular necrosis, Fanconi syndrome, and tubulointerstitial nephritis, among others. Proteinuria is common in children with chronic kidney disease (CKD), and there is an association between severity of proteinuria and CKD progression; thus, its early detection and treatment impacts morbidity.

The history and physical should aim to distinguish whether the proteinuria is likely to be from underlying renal disease, as opposed to a transient process or orthostatic proteinuria. The history should include questions about recent upper respiratory symptoms, hematuria, changes in weight or urine output, presence of swelling, rashes or joint pain, and family history of renal disease or hearing loss. The patient or his parents should also be questioned about causes of false positive results including recent contrast dye exposure or antibiotics. Particularly important aspects of the physical exam include measurements of height, weight, and blood pressure. The clinician should also look for edema, ascites, and skin pallor, and abdominal masses that may herald nephromegaly.

Because of the frequency of false positives or transient proteinuria, the urinalysis should be repeated on a first morning mid-stream clean catch void sample prior to initiating further testing if the history and physical are unremarkable.

CASE continued:

| Physical exam and growth are normal, and history is significant for NICU course of “feeding and growing,” with no known acute kidney injury or umbilical catheterization. Repeat urinalysis one week later again shows 2+ protein. There are no casts or other abnormal features seen on the microscopic examination of the urine. |
3. What tests will you consider at this time?

Orthostatic proteinuria accounts for 60% of cases of proteinuria in asymptomatic children. As such, in patients with a normal history and physical who are older than 6 years of age, especially in the second and third decades of life, the clinician should check a urinalysis in the morning after the patient has been recumbent for 8 hours to evaluate for orthostatic proteinuria. If the first morning urinalysis still contains protein, labs that should be ordered include serum electrolytes, BUN, creatinine, albumin, total protein, C3, complete blood count (CBC), and a spot urine protein to creatinine ratio (UPr/Cr). C4 and ANA should be considered in the adolescent patient in whom autoimmune disease may be suspected. A spot UPr/Cr is a reliable semi-quantitative measurement of proteinuria and is easier to follow than the 24-hour urine protein since it does not require a timed collection. Normal UPr/Cr for children over age 2 years is <0.2 (which predicts roughly 0.2 grams of protein per 24 hours). Infants and younger children have increased protein excretion when corrected for body surface area, and the upper limit of normal UPr/Cr for children aged six months to two years is 0.5.

In young children, renal ultrasound may be helpful as it could detect congenital anomalies such as polycystic kidneys. Depending on the results of the above studies, referral to a pediatric nephrologist and subsequent renal biopsy may be indicated. Renal biopsy is typically not indicated when the clinical picture is consistent with uncomplicated postinfectious glomerulonephritis or minimal change disease. Often, biopsy is recommended with 24-hour collections with persistent proteinuria of >1 gram/day (correlating to a spot UPr/Cr of 1.0) or >4mg/m²/hr.

CASE TWO:

Norm’s little sister, Pink, is 3-years-old and presents to your office with a very hysterical Mrs. Pea who says, “I think my daughter is peeing blood. Is it serious?”

4. Is it serious? What is your differential diagnosis for gross hematuria?

Hematuria is more likely to be associated with serious pathology if it is accompanied by hypertension, edema, oliguria, significant proteinuria, or RBC casts. The most common causes of gross hematuria are urinary tract infections (UTI), irritation of the meatus or perineum, and trauma. Other causes include nephrolithiasis, hypercalciuria (even without stones), sickle cell disease/trait, coagulopathy, glomerular disease (such as postinfectious glomerulonephritis or thin basement membrane disease), cystic disease, ureteropelvic junction (UPJ) obstruction, IgA nephropathy, renal tumors, rhabdomyolysis, and hemorrhagic cystitis. A helpful pneumonic for workup of hematuria is “TICS”:

- T (tumor, trauma, TB, toxins)
- I (inflammation/glomerulonephritis, infection)
- C (cysts, congenital malformations or obstruction, calculi)
- S (stones, sickle cell, “somewhere else” - e.g., vagina, foreskin).

When evaluating the patient with hematuria, history should include questions about symptoms suggesting UTI or nephrolithiasis, such as dysuria, frequency, urgency, or flank or abdominal pain. Providers should also ask about recent trauma, strenuous exercise, menstruation, bladder catheterization, recent sore throat or skin infection, or drug or toxin exposure. As with proteinuria, it is important to ask about family medical history, specifically inquiring about hematuria, kidney disease, nephrolithiasis, hearing loss, and sickle cell disease. The physical exam should have a similar focus as that described for patients with proteinuria.

When evaluating macroscopic hematuria, the pattern and color of the urine may indicate the source - brown, tea-colored, or cola-colored urine is usually of glomerular origin while red or pink urine is typically from the lower urinary tract. Terminal hematuria suggests urethrorrhagia. Urine microscopy should be performed; the absence of RBCs suggests hemoglobinuria or myoglobinuria, while presence of cellular casts indicates glomerulonephritis.

If the patient has any of the markers of serious glomerular pathology mentioned above, a basic metabolic panel, albumin, CBC, C3, C4, ANA, anti-streptolysin (ASO) and anti-DNAse B titers can be helpful. Spot urinary calcium to creatinine ratio may also be obtained. Unless results are consistent with UTI, stones, or uncomplicated postinfectious glomerulonephritis (i.e., macro- or microscopic
hematuria, group A streptococcal infection 7-21 days prior, positive ASO, antiDNAse B, or streptozyme, decreased C3, RBC casts, and proteinuria) the patient should be referred to a pediatric nephrologist. If there are signs or symptoms of urinary tract infection, a urine culture and appropriate imaging tests should be ordered. Any history of trauma, family history of stones, or other pertinent findings on history or physical exam should trigger the appropriate work-up.

Hematuria with proteinuria, especially in the context of hypertension, or with edema, is highly suggestive of intrinsic renal disease and requires thorough evaluation and consideration of consultation with a pediatric nephrologist.

5. How does microscopic hematuria differ from macroscopic? How would your evaluation of microscopic hematuria differ from that of gross hematuria?

Microscopic hematuria, by its nature, is hematuria that is not visible to the eye, but is rather found on urinalysis, with >5 cells per high powered field. The history obtained should focus on the same areas as for macroscopic hematuria, and the family history may further include questions about hearing loss or renal cystic diseases. The presence of hematuria among family members in the absence of progressive renal disease may point to benign familial hematuria. Points which should not be missed on physical examination include any costovertebral angle tenderness or fever, which could indicate infection, and any rashes which could raise suspicion for HSP or SLE.

Microscopic hematuria is often transient. Studies of asymptomatic school-age children have shown a prevalence of 3 to 4 percent for microscopic hematuria. The rate for two positive samples is around 1 percent, and of that, only one-third will have persistent hematuria in six months. Because transient hematuria is so common, it is important to repeat the urinalysis weekly for two weeks in otherwise asymptomatic patients prior to further workup. Repeat urinalysis should be performed after the child has refrained from strenuous physical activity.

If the hematuria is persistent, further evaluation is indicated. This typically includes a urinary calcium to creatinine ratio, microscopic urinalysis, serum creatinine, C3, C4, ANA, and ASO/anti-DNAse B. Many nephrologists will also order a renal ultrasound for persistent microscopic hematuria, looking for stones, tumors, hydronephrosis with possible UPJ obstruction, structural anomalies, renal parenchymal dysplasia, medical renal disease, inflammation of the bladder, or evidence of posterior urethral valves. A high urine calcium/creatinine ratio can indicate hypercalciuria, a common cause of asymptomatic hematuria which should be followed by a nephrologist who may recommend increased fluid intake, decreased sodium intake, or a thiazide diuretic. Additional testing may include hearing evaluation for patients with a family history of renal disease and hemoglobin electrophoresis if sickle cell disease is suspected. When cases of isolated microscopic hematuria are investigated by renal biopsy, results may reveal thin basement membrane disease, Alport's syndrome, IgA nephropathy, or normal histology. A suggested algorithm for the evaluation of hematuria is presented in Figure 2 in the article by Brown and Reidy.

In summary:

• Although screening urinalysis should NOT be universally performed in healthy asymptomatic children, those with risk factors for kidney disease or with specific related complaints that could herald kidney pathology still require evaluation in the well-child setting
• Asymptomatic proteinuria should be evaluated with first morning urine specimen to rule out orthostatic proteinuria, before embarking on a larger workup
• Hematuria can be caused by a variety of mechanisms and TICS help guides differential diagnosis
• Again, hematuria with proteinuria, especially in the context of hypertension, or with edema, is highly suggestive of intrinsic renal disease and requires thorough evaluation and consideration of consultation with a pediatric nephrologist

Additional References:

2. Bock GH. Screening UA should be based on specific conditions. AAP News. 2006;27(12): 18.
17. Primack W. AAP does not recommend routine urinalysis for asymptomatic youths. AAP News. 2010;31: 16.

Resources:
2. Information on hematuria for patients and families from University of Michigan Health System. http://www.med.umich.edu/1libr/pa/pa_hematuri_hhg.htm

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