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PROTEINURIA (UPDATED)

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Case:

You're on call in the pediatric emergency department when you are asked to assess William, a 6-year-old boy with abdominal pain and a rash on his legs and buttocks. His urine dipstick shows 1+ protein. What does this finding mean, and how should you proceed?

Introduction:

This podcast addresses the approach to proteinuria in children. Proteinuria is a common clinical finding and is detected in up to 10% of school-aged children during routine urine testing. This prevalence increases throughout childhood and peaks during adolescence, more often in girls¹. Most children with proteinuria detected in screening tests do not have renal disease, and such abnormal findings are usually transient². In this podcast, we will discuss the causes of proteinuria, identify key elements to look out for in history and physical exam, and explain investigations and management of proteinuria.

By the end of this podcast, listeners should be able to distinguish transient, orthostatic, and persistent proteinuria; identify red flags that suggest kidney disease; and choose appropriate first-line investigations for a child with proteinuria.

Definition and physiology:

First, what is proteinuria? Proteinuria is the presence of excess protein in the urine. Some protein excretion is normal: in children, normal urinary protein excretion is less than 100 mg/m² over 24 hours. This occurs because the glomerular filtration barrier is highly selective and allows only small amounts of protein to pass into the urine. Albumin and the glomerular basement membrane are both negatively charged, which further limits albumin filtration into Bowman's space. Pathologic proteinuria is often described as mild if less than 1 g per 24 hours, moderate if 1 to 3

g per 24 hours, and severe, or nephrotic range, if greater than 3 g per 24 hours or at least 1000 mg/m² per day.

Causes of proteinuria and pathophysiology:

Proteinuria in children can be grouped into three broad patterns: transient, orthostatic, and persistent. This classification is useful because it separates common benign causes from proteinuria that may warrant further investigation.

1- Transient proteinuria

Transient proteinuria is an excess amount of protein in the urine resolving upon repeat testing. It can occur with fever, after exercise or cold exposure, and physical stress¹. Transient proteinuria can be distinguished from persistent proteinuria through repeat urine testing.

2- Orthostatic proteinuria

Orthostatic proteinuria is one of the most common causes of increased protein excretion in adolescents, with a prevalence of 2–5%. It occurs when protein excretion increases in the upright position. The simplest way to diagnose orthostatic proteinuria is to measure the urine protein-to-creatinine ratio in a first-morning urine sample, which should be normal, and compare it with a daytime spot urine sample, which may be elevated. If the result remains unclear, timed day and night urine collections can be used. The patient collects daytime urine after discarding the first-morning urine, then collects overnight urine plus the next first-morning urine in a separate container. Orthostatic proteinuria is supported when the overnight collection shows less than 4 mg/m²/hour of protein, or less than 50 mg in adolescents, and when kidney function is normal and hematuria is absent.

3- Persistent proteinuria

Persistent proteinuria includes glomerular, tubulo-interstitial, and overflow proteinuria.

a. Glomerular

Glomerular proteinuria occurs when there is an increased permeability of the glomerular basement membrane due to structural defects, loss of its negative charges, or damage inflicted by immune complexes¹. It is detected by urine dipstick. It is often associated with hematuria³. Glomerulopathies such as congenital nephrotic syndrome, focal segmental glomerulosclerosis, IgA nephropathy, and minimal change glomerulopathy may be causal. Systemic lupus erythematosus (SLE), diabetes, Alport syndrome and infections such as Streptococcus pyogenes, hepatitis B or C, or infectious mononucleosis are also possible causes of glomerular proteinuria¹.

b. Tubulo-interstitial

Tubulo-interstitial proteinuria is less frequent and occurs when the proximal tubule of the nephron cannot reabsorb low molecular weight proteins. It is not detected by urine dipstick. It is often associated with other tubular defects such as glycosuria and proximal tubular acidosis with phosphaturia. The most frequent causes of tubular proteinuria include acute tubular necrosis, interstitial nephritis caused by medications such as NSAIDs, and obstructive nephropathies. Heavy metal intoxication may also cause tubular proteinuria. Other causes include polycystic kidney disease, cystinosis, Wilson disease, and mitochondrial disorders.

c. *Overflow*

Overflow proteinuria happens when there are too many plasma proteins, exceeding the proximal tubule's capacity to reabsorb filtered proteins¹. It is not detected by urine dipstick. This mechanism is more rare in children and can happen in cases of hemoglobinuria or myoglobinuria³.

History:

Next, let's discuss relevant medical history when investigating proteinuria. For newborns, obtain an extensive obstetrical history, including congenital infections and placental anomalies. For older children, ask about fever, recent *Streptococcus pyogenes* infection such as pharyngitis or scarlet fever, and recent medication use, including NSAIDs and ampicillin. Ask about symptoms of urinary tract infection, foamy urine, changes in voiding patterns, generalized or localized edema such as periorbital or ankle swelling, hematuria, diabetes, hypertension, and recent IgA vasculitis, formerly known as Henoch-Schönlein purpura.

Focused physical exam:

During the physical exam, focus on findings that may suggest systemic disease or kidney involvement. Examine the skin for purpuric lesions, measure blood pressure and temperature carefully, assess growth in younger children, and look for generalized or localized edema, especially around the eyelids, legs, and genitals.

Investigations and management:

But how can proteinuria be detected? The most commonly used screening test for proteinuria is the urine dipstick. The dipstick detects albumin with a sensitivity and specificity beyond 99% if more than 300-500 mg of albumin are excreted per 24 hours. However, this test is much less sensitive for other proteins^{1,3}. The dipstick result gives a ballpark range of how much protein is in the urine, ranging from trace (15 mg per dL), to 1+ (30 mg per dL), 2+ (100 mg per dL), 3+ (300 mg per dL), and 4+ (1000 mg per dL or more). A result of 1+ or more is considered abnormal. The dipstick is an appropriate screening test for patients who are not considered at high risk for kidney disease⁴.

Urine dipstick testing can produce false-positive results in alkaline or concentrated urine and in the presence of gross hematuria, pyuria, or bacteriuria. False-negative results can occur with acidic or dilute urine, or when the urine contains proteins other than albumin. The dipstick also does not detect microalbuminuria in children with diabetes.

The gold standard for proteinuria investigation remains the 24 hour urine collection. However, in young children who are not toilet trained, this technique may not be feasible.

Currently, the urinary protein/creatinine ratio remains the most practical option when investigating proteinuria in children. Not only is this test easy to perform, but it also provides a good correlation with results obtained in 24 hour urine collections. In children aged 6 to 24 months, the normal ratio is less than 0.05 g/mmol of creatinine. In children aged more than 2 years, a normal ratio is less than 0.02 g/mmol of creatinine³.

With all this in mind, the first step in approaching proteinuria in a pediatric patient is to determine whether it is transient or orthostatic. In an asymptomatic child, some authors recommend repeating at least three random urine samples before considering persistent proteinuria. If proteinuria persists, further evaluation may include urine culture, CBC, urinary sediment when available, electrolytes, albumin, total protein, creatinine, urea, lipids, complement levels including C3 and C4, antistreptolysin O titer, and hepatitis B, hepatitis C, and HIV serologies when clinically indicated. A renal ultrasound may also be considered.

Renal biopsy should only be performed if proteinuria is isolated and larger than 1 gram per 24 hours and/or is associated with hematuria, hypertension, hypocomplementemia, decreased glomerular filtration rate or symptoms suggestive of vasculitis^{1,3}.

Treatment of persistent proteinuria should target the underlying cause. For classic nephrotic syndrome, first-line treatment is oral corticosteroids, with close follow-up because of potential adverse effects. Patients should be referred to a pediatric nephrologist if proteinuria is seen in children younger than 1 year of age or in adolescents, and if proteinuria is accompanied by hematuria, hypertension, hypocomplementemia, reduced glomerular filtration rate, or symptoms suggestive of vasculitis.

Returning to our case:

Now that we know more about proteinuria, let's return to William's case. His abdominal pain, rash on the legs and buttocks, and mild proteinuria on urine dipstick should raise concern for IgA vasculitis, formerly known as Henoch-Schönlein purpura. The history of a mild upper respiratory tract infection about 3 weeks earlier further supports this diagnosis. Although William can be diagnosed clinically, he requires serial urinalysis to monitor for proteinuria and hematuria. If there are signs of severe kidney involvement, renal biopsy should be considered before starting oral corticosteroids.

Summary - key learning points:

To conclude our discussion of proteinuria, let's identify some key take-home messages:

1. Proteinuria is commonly encountered in the pediatric population.
2. In most cases, proteinuria is either transient or orthostatic.
3. A complete medical history and physical exam are essential to orient your differential diagnosis. Don't forget to inspect your patient's skin and to take a close look at blood pressure!
4. Although the 24 hour urine collection is considered the gold standard in clinical practice, it has largely been replaced by the more feasible urinary protein/creatinine ratio.
5. If proteinuria is seen in children younger than 1 year of age or in adolescents, and is accompanied by hematuria, hypertension, hypocomplementemia, reduced glomerular filtration rate, or symptoms suggestive of vasculitis, refer the child to a pediatric nephrologist for further assessment and possible renal biopsy.

And that's a wrap! Thank you for listening to this podcast on the approach to proteinuria in children.

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