Original Article

Simplified Algorithm for Evaluation of Proteinuria in Clinical Practice: How should A Clinician Approach?

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Abstract

Background: Proteinuria is a common laboratory finding among children and adolescents. It can be identified as either a transient or a persistent finding and can represent a benign condition or a serious disease. **Methods:** Pertinent medical literature for asymptomatic proteinuria in children and adolescents published in English was searched between January 1980 and May 2017 using PubMed, MEDLINE, EMBASE, and Google Scholar research databases. Of the 64 reviewed articles, 24 studies were eligible for inclusion. **Results:** Random spot urine protein-to-creatinine (PCR) ratio is widely used to reliably detect proteinuria. The normal value for the spot PCR in children aged 2 years or older is less than 0.3. In children aged below 2 years, the PCR can be as high as 0.5. Orthostatic proteinuria is defined as urine PCR greater than 0.3 detected in a urine specimen during the daytime activity but less than 0.3 on the first morning void specimen. PCR above 3.0 signifies heavy proteinuria as seen in nephrotic syndrome. Orthostatic proteinuria is a frequent cause of proteinuria in asymptomatic children and adolescents, which require no specific therapy except for health maintenance follow-up. Pediatric nephrologist referral is indicated when the proteinuria is constant and persists over 6 months or is associated with hematuria, hypertension, or renal dysfunction. **Conclusions:** We provide a simplified diagnostic algorithm for evaluation of proteinuria in primary care adolescents who appear well and in whom proteinuria is incidentally discovered during a routine examination.

Keywords: *Adolescents, algorithm, asymptomatic proteinuria, children*

Introduction

Proteinuria is a frequent laboratory finding both in the outpatient clinic and inpatient settings. The finding of protein in the urine may reflect either a benign finding or significant renal functional disorders or structural abnormalities.[1-4] This distinction is possible by carefully taking the patient's medical history, performing through physical examination, and ordering appropriate laboratory investigations.

Evaluation of proteinuria should begin with a careful history and thorough physical examination, urine microscopic examination, and determination of the amount of protein excretion rate (PER). The PER has been traditionally measured using 24-h urine collections. However, the collection of 24-h urine is often cumbersome, and spot urinary protein-to-creatinine ratio (PCR), expressed in g/g or mg/mg, has become a simple and attractive yet reliable alternative. A spot urine PCR has been found to have a significant linear correlation with a 24-h urine PCR.[5-9] Furthermore, because the PCR compares urinary protein concentration with urinary creatinine concentration, urinary dilution or concentration does not influence this value.

We present a simple practical diagnostic approach to differentiate benign proteinuria from proteinuria resulting from glomerular disease in children and adolescents who present with asymptomatic isolated proteinuria.

Methods

Pertinent medical literature for proteinuria published in English was searched from January 1980 to May 2017 using PubMed, MEDLINE, EMBASE, and Google Scholar research databases, and then the search was extended as linked citations indicated. The search terms included *asymptomatic proteinuria*, *isolated proteinuria*, *children*, *adolescents*, *evaluation*, and *management*. Of the 64 reviewed articles, 24 studies were eligible for inclusion.

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Results

The initial evaluation of proteinuria should include a complete history, including a family history of renal disease, recent upper respiratory infections, gross hematuria, and changes in urine output. The physical examination should include urinalysis and examination of urine sediment; measurements of height, weight, and blood pressure; identification of edema, ascites, and skin pallor; and palpation of the kidneys.

Orthostatic proteinuria is a benign medical condition with excellent long-term prognosis, and it does not warrant an extensive workup. Patients with constant proteinuria, which persists beyond 6 months, or proteinuria associated with hematuria, hypertension, or abnormal renal function may require referral to a pediatric nephrologist.

Discussion

We aimed to provide an organized practical approach for the primary care adolescents to evaluate a child with proteinuria that emphasizes common conditions and stepwise laboratory and radiologic investigations [Figure 1].

Urinary PER in the normal child is less than 100 mg/m^2 per day or a total of 150 mg per day. Healthy children excrete small amounts of protein in their urine, which varies with age and the size of the child.[2-4] In neonates, normal urinary protein excretion is higher, up to 300 mg/m^2 per day, because of reduced reabsorption of filtered protein. In children, PER decreases progressively with age until late childhood till it reaches the adult levels of less than 150 mg/m^2 per day [Table 1].[2-4]

The urine dipstick method is widely used in routine office evaluation of proteinuria. The urine protein dipstick is sensitive to the albumin concentration of the urine. It can yield both false-negative and false-positive results in the presence of dilute (specific gravity less than 10.10) or alkaline urine (pH greater than 7.0), respectively.[7]

The 24-h urine collection is traditionally used for the urinary protein quantitation. The 24-h urine collection can be done as a single collection or two split collections during the daytime activity and overnight recumbent positions.[6,7] However, the 24-h timed urine collections, particularly, in small children, cumbersome and often are flawed with collection errors.

Furthermore, PER can vary significantly from day to day and is also influenced by diet, posture, exercise, and body size. Does a 10-kg patient seem as "nephrotic" at 0.5 g per day protein excretion compared with the 80-kg patient at 4.0 g per day? Does the 80-kg patient have eight times worse glomerular disease and is this person eight times as nephrotic [Table 2].

The answer is "NO!" These value by themselves, while each a eightfold difference, are similar in each of the two patients and have the same clinical significance as their PCR values are similar, 2.5 mg/mg [Table 2]. The ease and simplicity of obtaining first morning spot urine PCR value allows one to exactly estimate the 24-h PER and automatically adjust values for patient size.[10]

Table 1: Normal urinary protein excretion in infants and children 90

	Total protein mg per day	Total protein mg/m^2 per day	Range mg per day
Premature <1 month	29	182	88-377
Full term <1 month	32	145	68-309
1-12 months	38	109	48-244
1-4 years	49	91	7-223
4-10 years	71	85	1-234
10-16 years	83	63	2-181

Table 2: Comparison of creatinine excretion, protein excretion, and protein-to-creatinine ratio in relation to increasing weight*

	Timed (24-h) urine collection		
Weight	CrE, mg per day	PE, mg per day	Spot P/Cr, mg/mg
10 kg	200	500	2.5
20 kg	400	1000	2.5
40 kg	800	2000	2.5
80 kg	1600	4000	2.5

*Assuming that the patient excretes 20 mg/kg of creatinine a day. CrE=Creatinine excretion, PE=Protein excretion, P/Cr=Protein-creatinine ratio

A random spot PCR is a good representative of 24-h urine PCR, and is now widely used in children in lieu of a 24-h urine collection because of its convenience and simplicity.[5-9] One of the advantages of measuring the spot untimed urine PCR over a 24-h urine protein measurement is that the urinary concentration or dilution does not affect its values as the PCR compares urinary protein concentration with urinary creatinine concentration, and as a result, the urinary concentration or dilution does not affect its value.[9,11]

The KDIGO guidelines (Kidney Disease: Improving Global Outcomes) reports that there are insufficient data to recommend 24-h or spot urine for PER.[12]

More recent studies have compared the first morning void PCR and random single void PCR with the PCR of a timed urine collection ranging from 4 to 24 h to determine collection accuracy in PER, documenting the accuracy and reliability of random single void for determination of PER.[10,13,14] Because a false-positive result may occur if urine in highly diluted, the PCR should be performed on a first-voided morning specimen rather than the one collected randomly later in the day.[9,10,12]

The normal PCR in children and adolescents is less than 0.3. In infants and younger children, the PCR is higher

with the upper normal limit of 0.5. PCR above 3.0 is found in patients with nephrotic syndrome.[9] The daily PER can be determined from spot urine PCR, based on sex, age, and weight using the following equations.[9,10,13-15]

PER (g/m^2 per day) =0.63 × (PCR)

Many clinical disorders are associated with proteinuria [Table 3]. Transient proteinuria is benign and non-pathologic and is usually after infantile febrile seizure, exposure to rigid cold, and strenuous exercise.[16,17] These conditions require no specific therapy and need only health maintenance follow-up.

Orthostatic proteinuria is diagnosed when the PCR is greater than 0.3 in a urine specimen tested during the daytime activity but less than 0.3 when the urine is collected after the nighttime recumbent position [Table 3].[16,17]

Isolated persistent proteinuria lasting more than 6 months or proteinuria complicated with hematuria, hypertension, or abnormal renal function usually associated with glomerular lesions or congenital kidney and urinary tract anomalies such as unilateral kidney agenesis, obstructive hydronephrosis, and reflux nephropathy, which often require further evaluations including renal ultrasonography and voiding cystourethrogram (VCUG) [Table 4].[18-23] If proteinuria is associated glomerulonephritis, then referral to a pediatric nephrologist is warranted for possible renal biopsy indication [Figure 1].[22,23] Further therapeutic regimen with immunosuppressive medications, inhibition of angiotensin converting enzyme (ACE) or angiotensin receptor blockade (ARB), may be indicated to slowing the progression of glomerular disease.[24]

Table 3: Etiologic classification of proteinuria among children and adolescents

Transient proteinuria
Fever
Strenuous exercise
Extreme cold exposure
Epinephrine administration
Emotional stress
Congestive heart failure
Seizures
Abdominal surgery
Isolated asymptomatic proteinuria
Orthostatic proteinuria
Persistent fixed proteinuria
Proteinuria secondary to renal disease
Minimal change nephrotic syndrome
Focal segmental glomerulosclerosis (FSGS)
Acute postinfectious glomerulonephritis
Membranoproliferative glomerulonephritis
Membranous glomerulonephritis
Lupus nephritis
Henoch-Schönlein purpura (HSP)
Human immunodeficiency virus (HIV)-associated nephropathy
Hemolytic uremic syndrome
Vasculitis
Chronic interstitial nephritis
Renal structural abnormalities
Hydronephrosis
Cystic kidney disease
Reflux nephropathy
Renal dysplasia
Unilateral kidney agenesis

Conclusions

We have developed a simple and yet cost-effective diagnostic algorithm that is based on determinations of random urine PCR to differentiate the multiple causes of proteinuria in children and adolescents, in a step-by-step fashion [Figure 1]. The ease and simplicity of obtaining first morning spot urine PCR value allows one to exactly estimate the 24-h PER. Utilization of this approach brings

Table 4: Clinical correlations in proteinuria

Likely diagnosis	History/physical examination	Cr[a]	Blood Albumin	C3[b]	Pr/Cr[c]	Other
Orthostatic proteinuria	>10 years of age	Normal	Normal	Normal	<1.0	-
Nephrotic syndrome MCD[d]	Edema <6 years of age	Normal	Low	Normal	>3.0	High cholestrol
Acute GN[e]	Edema, gross hematuria	High or low	Normal or low	Low	<3.0	High ASO[f] titer, HTN[g]
FSGS[h], MGN[i]	Hematuria,HTN	High or low	Normal or low	Normal	>1.0	High cholesterol
MPGN[j]	Hematuria, HTN	High or low	Normal or low	Low	>1.0	
Lupus nephritis	Rash, arthritis	Normal or low	Normal or low	Low	>1.0	High ANA[k]
HSP[l]	Hematuria	Normal	Normal	Normal	>1.0	-
Tubulointerstitial disease	Polyuria	Normal	Normal	Normal	<1.0	-

[a]creatinine, [b]complement-3, [c]protein/creatinine ratio, [d]minimal change disease, [e]glomerulonephritis, [f]antistreptolysin-O, [g]hypertension, [h]focal and segmental glomerulosclerosis, [i]membranous glomerulonephritis, [j]membranoproliferative glomerulonephritis, [k]antinuclear antibody, [l]Henoch-Schönlein purpura

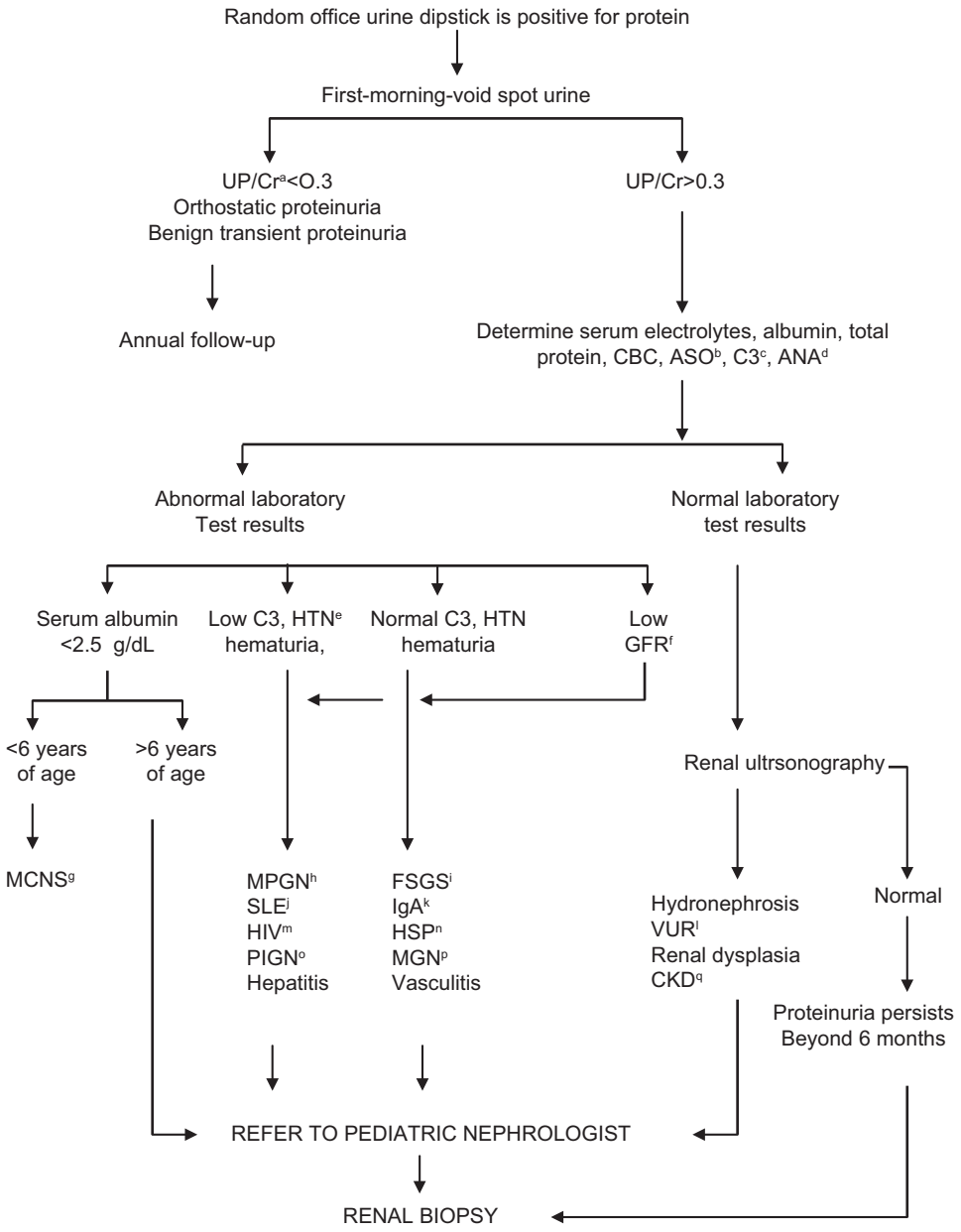

Figure 1: Simplified algorithm for the evaluation of proteinuria. [a]Protein/creatinine ratio, [b]antistrepolysin O, [c]hypertension, [d]antinuclear antibody, [e]hypertension, [f]glomerular filtration rate, [g]minimal change nephrotic syndrome, [h]membranoproliferative glomerulonephritis, [i]focal segmental glomerulosclerosis, [j]systemic lupus erythematosus, [k]immunoglobulin-A glomerulonephritis, [l]vesicoureteral reflux, [m]human immunodeficiency virus, [n]Henoch–Schönlein Purpura, [o]post-infectious glomerulonephritis, [p]membranous glomerulonephritis, [q]cystic kidney disease

a greater clarity and simplicity for evaluation of patients with asymptomatic isolated proteinuria.

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Conflicts of interest

There are no conflicts of interest.

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