Proteinuria (Protein in Urine) in Children — Symptoms and Treatment
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It is common to detect proteinuria during routine urinalysis in children. Although transient proteinuria and orthostatic proteinuria are common and benign conditions, it is important to differentiate them from clinically significant proteinuria associated with renal pathology or systemic diseases. Such differentiation can be made by considering the clinical presentation and appropriate use of laboratory tests. Treatment of proteinuria usually includes that of the underlying condition along with consideration of proteinuria lowering medications when indicated.

Definition of Proteinuria in Children

Proteinuria can be defined as an excretion of protein in urine more than 100 mg/m$^2$/day or >4 mg/m$^2$/hr. Other definitions are:

<table>
<thead>
<tr>
<th>Definition</th>
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<tbody>
<tr>
<td><strong>Fixed proteinuria</strong></td>
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<td>≥ 1+ proteinuria on urinary dipstick examination or urine protein: creatinine ratio ($U_p/U_c$) &gt; 0.2 in the first-morning urine sample on three consecutive days</td>
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Persistent proteinuria

≥ 1+ proteinuria on urinary dipstick examination (equivalent to ≥ 30 mg/dL) on at least three urine specimens separated by several weeks

Isolated proteinuria

Asymptomatic proteinuria in an otherwise healthy child with normal physical examination, normal blood pressure, and normal laboratory evaluation except for the presence of proteinuria

Heavy proteinuria is marked when wasting of protein is more than 2-3 g per day with a ratio of protein and creatinine 200-300. Low levels of proteinuria occur when protein in urine drops less than 1 g per day or protein/creatinine ratio is less than 100.

Orthostatic proteinuria is a benign condition which is not a kidney disease, protein in urine in 24-hour urine collection become 1000 mg

Epidemiology of Proteinuria in Children

Although 10% of children may have proteinuria in a single void specimen of urine, only 0.1 of children have persistent proteinuria or pathologic proteinuria. Prevalence of proteinuria peaks during adolescence. 60% of school-aged children and adolescents with persistent proteinuria have orthostatic proteinuria; the condition occurs in 3-5% of adolescents.

Etiology of Proteinuria in Children

Benign proteinuria: (High Yield)

- Transient proteinuria: fever, exercise, dehydration, stress, seizure, exposure to a cold, heart failure
- Orthostatic (postural) proteinuria

Glomerular proteinuria:

- Minimal change (idiopathic) nephritic syndrome
- Focal segmental glomerulosclerosis (FSGS)
- Mesangial proliferative glomerulonephritis
- Membranous nephropathy
- Membranoproliferative glomerulonephritis
- IgA nephropathy
- Acute postinfectious glomerulonephritis
- Henoch-Schonlein purpura (HSP)
- Hemolytic-uremic syndrome (HUS)
- Lupus nephritis
- Diabetic nephropathy
- Sickle cell nephropathy
- Amyloidosis
- Alport syndrome
- Bacterial endocarditis
- Hypertensive nephrosclerosis

Tubular proteinuria:

Acute tubular necrosis (ATN) – the most common cause. It can be caused by hypovolemia or hypovolemic shock. ATN can also be caused by some drugs such as NSAIDs,
aminoglycosides, amphotericin, lithium, etc.

- Tubulointerstitial nephritis
- Fanconi syndrome (Cystinosis, galactosemia, Wilson disease, Lowe syndrome)
- X-linked recessive nephropathies (Dent disease)
- Renal dysplasia, polycystic kidney disease
- Reflux nephropathy
- Pyelonephritis
- Mitochondrial disorders
- Heavy metal poisoning

Overflow proteinuria:

- Myoglobinuria in rhabdomyolysis
- Immunoglobulins in multiple myeloma (common in adults)

Pathophysiology of Proteinuria in Children

In children, urinary protein excretion up to 100 mg/m²/day or 150 mg/day is considered normal, while in neonates, it can be as high as up to 300 mg/m²/day. Normally excreted urinary proteins include Tamm-Horsfall protein (uromodulin, ~50%), albumin (~40%), and low-molecular-weight (LMW) proteins (~10%) including β₂-microglobulin and amino acids.

Normally, proteins with molecular weight < 25,000 Da cannot cross glomerular basement membrane (GBM). As GBM is negatively charged due to the presence of heparan sulfate proteoglycans, it also repels anions like albumin. Majority of LMW proteins that are filtered at glomerulus are reabsorbed by the proximal tubule. Proteinuria occurs when any of these mechanisms are disrupted.

Proteinuria can cause damage in the epithelium of glomeruli leading to the loss of podocyte and production of chemokines and cytokines that can cause an inflammatory response in it. Albumin gets filtered in proximal tubules which can go 250 g of albumin per day that may result in nephrotic syndrome.

**Glomerular proteinuria** occurs due to increased permeability of glomeruli, while tubular proteinuria occurs due to decreased reabsorption of LMW proteins by renal tubules. Glomerular proteinuria is usually dominant in albumin and can be of high degree, while tubular proteinuria is usually dominant in LMW proteins and is usually low grade (Uₚ/Ur < 1.0).

**Overflow proteinuria** occurs where proteins cannot be effectively reabsorbed by the proximal tubule, due to overproduction of proteins.

Children with transient proteinuria do not have an underlying renal parenchymal disease. A possible explanation for transient proteinuria is hemodynamic changes in glomerular blood flow causing increased protein diffusion into the urine.

Possible mechanisms that explain orthostatic proteinuria include renal hemodynamic changes associated with postural change, partial renal vein occlusion, increased glomerular capillary wall permeability, or the role of circulating immune complexes. In renal diseases with persistent proteinuria, it is believed that proteinuria itself can cause injury to renal tubular cells with fibrosis and sclerosis, possibly by a generation of reactive oxygen species.
Symptoms of Proteinuria in Children

Proteinuria is mostly asymptomatic and may be detected during routine screening urinalysis or during diagnostic evaluation. In transient proteinuria, proteinuria is present during a fever (temperature > 101 °F), dehydration, stress or heart failure, or following exercise, seizure or exposure to cold. Dipstick test shows 2+ or lower proteinuria, which resolves after the resolution of the condition. Sometimes, exercise-induced proteinuria may last for as long as 48 hours following exercise.

In orthostatic proteinuria, increased protein excretion (up to 1000 mg/day) is seen in an upright position, while is normal protein excretion is seen in the supine position. The child does not have hypertension, edema, hematuria, hypoalbuminemia, or renal dysfunction. It is seen in tall and thin young adults less than 30 years. Children with isolated proteinuria are otherwise healthy, asymptomatic children with a normal physical examination, normal blood pressure, and normal other laboratory findings. Proteinuria is usually < 2 g/day.

When proteinuria is due to a specific disease, symptoms of the disease are the presenting symptoms of the child. Nephrotic syndrome is characterized by nephrotic range proteinuria, hypoalbuminemia, hyperlipidemia, and edema.

The child may present with:

- Periorbital or pedal edema
- Ascites
- Anasarca or abdominal pain
- Hematuria or hypertension
- The frothy appearance of urine

Patients with systemic renal diseases usually have hematuria or hypertension in addition to proteinuria. Patients with post-infectious glomerulonephritis usually have a history of pharyngitis or impetigo before 2-4 weeks and present with an acute nephritic syndrome, hematuria, proteinuria, hypertension, and acute renal failure.

IgA nephropathy is characterized by episodes of macroscopic hematuria, proteinuria, abdominal or flank pain, and fever within 72 hours of a respiratory infection. HSP is characterized by purpuric lesions, especially over buttocks and lower extremities, abdominal pain, edema, and arthralgia. HUS may present with a history of bloody
diarrhea, vomiting, abdominal pain, anemia, and renal failure.

Children with interstitial nephritis may have a history of recent exposure to antibiotics or other medications and may have allergic symptoms like skin rash.

Diagnosis of Proteinuria in Children

**Collection of 24-hour urine is a gold standard** for urinary protein quantization but is often impractical or not possible in children. 24-hour urine protein > 100-150 mg/m²/day usually suggests proteinuria, but preterm infants and neonates may have even higher protein excretion normally. Urinary protein excretion >1000-2000 mg/day is usually pathologic in children, except in cases of orthostatic proteinuria.

Urinary protein excretion ≤ 4 mg/m²/h is considered normal; 4-40 mg/m²/h is considered as proteinuria and > 40 mg/m²/h is considered is nephrotic-range proteinuria.

Urine protein: creatinine ratio (Uₚ/Ur) is widely used to diagnose proteinuria. Uₚ/Ur > 0.5 (in children aged < 2 years) or > 0.2 (in children aged > 2 years) suggests proteinuria. However, in children < 6 months, the ratio may be up to 0.8 is often considered normal. The ratio > 2.0 suggests nephrotic range proteinuria. (High Yield)

For measurement of Uₚ/Ur, freshly voided first-morning urine (FMU) specimen is usually preferred, but a random sample is also acceptable. As the ratio is dependent on urinary creatinine, the ratio may be elevated in conditions with low creatinine excretion such as severe malnutrition or children with low muscle mass. In conditions with low glomerular filtration rate (GFR), interpretation of the ratio is difficult.

**Urinary dipstick test is the most common test** used initially; the reagent strip is analyzed within 60 seconds after immersing it in freshly voided urine. Tetrabromophore, a chromatophore impregnated on the strip, which changes color depending upon the number of proteins in the urine. The dipstick method is most sensitive to albumin and less sensitive to other proteins.

**It is a semiquantitative method, which can be interpreted as follows:**

<table>
<thead>
<tr>
<th>Dipstick result</th>
<th>Amount of protein in the urine</th>
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<tbody>
<tr>
<td>Negative:</td>
<td>&lt; 10 mg/dL</td>
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<tr>
<td>Trace:</td>
<td>10-29 mg/dL</td>
</tr>
<tr>
<td>1+</td>
<td>30-100 mg/dL</td>
</tr>
<tr>
<td>2+</td>
<td>100-300 mg/dL</td>
</tr>
<tr>
<td>3+</td>
<td>300-1000 mg/dL</td>
</tr>
<tr>
<td>4+</td>
<td>&gt; 1000 mg/dL</td>
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Causes for false-positive results in dipstick testing are alkaline urine (pH > 7.0), highly concentrated urine, prolonged immersion of dipstick in urine, pyuria, macroscopic hematuria, presence of antiseptic agents (hydrogen peroxide, chlorhexidine, benzalkonium chloride) in specimen, and phenazopyridine therapy. Causes for false-negative results are very dilute urine (specific gravity < 1.005) or when the predominant protein in urine is not albumin.

If urine specific gravity is < 1.010, ≥ trace proteinuria on the dipstick should be considered clinically significant, while if the specific gravity is > 1.015, dipstick reading suggestive of ≥ 1+ proteinuria should be considered clinically significant.

**Sulfosalicylic acid (SSA) turbidometric testing** is a less commonly used qualitative
test for proteinuria, but it can detect albumin, immunoglobulins, and Bence-Jones proteins in urine. As acidification of urine causes precipitation of urinary proteins, turbidity results when SSA reagent (three parts) is added to freshly voided urine sample (one part); the degree of turbidity can be compared with a predetermined scale.

**Urine protein electrophoresis** is helpful to identify the presence of proteins other than albumin in urine, such as β₂-microglobulin, retinol binding protein, α-globulins, monoclonal proteins, etc. Urine immunofixation electrophoresis is helpful when there is an overproduction of immunoglobulins as in certain malignancies.

Detection and quantification of **microalbuminuria** in children with diabetes mellitus are important, as it a predictor of diabetic nephropathy and cardiovascular morbidity. Urine microalbumin: creatinine ratio (MA:Cr) < 20-30 mg/g is considered normal. Urine albumin excretion 20-200 μg/min/1.73 m² or MA:Cr 30-300 mg/g suggests microalbuminuria, while > 200 μg/min/1.73 m² suggests frank proteinuria.

**Microscopic examination of urine** is helpful to diagnose the underlying medical condition. Presence of dysmorphic red blood cells (RBC) suggests glomerular disease; the presence of RBC casts suggests glomerulonephritis or vasculitis.

Presence of white blood cells (WBC) and WBC casts in urine suggests infective etiology, exudative glomerulonephritis or interstitial nephritis. Fatty casts or oval fat bodies may present in nephrotic syndrome or lupus nephritis, while granular casts suggest chronic renal disease. Presence of eosinophils in urine is highly suggestive of interstitial nephritis.

Renal ultrasonography is indicated in case of the glomerular disease to review the size and echogenicity of the kidneys.

Radiography of chest may be indicated if cardiac affections and chest affections are suspected. CT scan is suggested if indicated.

**Symptoms of Fanconi syndrome are:**
- Presence of glycosuria
- Phosphaturia
- Aminoaciduria
- Bicarbonate wasting

Initial evaluation of an asymptomatic child with persistent proteinuria should include FMU sample for a complete urinalysis and Uₚ/Urₐ. Dipstick negative or trace proteinuria and Uₚ/Urₐ < 0.2 in FMU sample for three consecutive days confirms the diagnosis of orthostatic proteinuria. For the collection of FMU, the child must empty bladder before going to bed and the urine must be collected immediately upon rising in the morning.

Children with transient or confirmed orthostatic proteinuria require no further diagnostic evaluation.

For children with persistent proteinuria, further laboratory evaluation is required to diagnose the underlying condition. Such evaluation includes complete blood counts (CBC), serum electrolytes, renal function tests, serum albumin, serum complement levels (C3, C4), etc. Additional tests include streptococcal markers (anti-streptolysin O and anti-DNAase B titers), serum antinuclear antibody (ANA) level, serum cholesterol, chest X-ray (to look for signs of volume overload), a renal ultrasound (to diagnose renal structural abnormalities), etc.

**Indications for referral to pediatric nephrologist include:**
Persistent non-orthostatic proteinuria

Abnormal urine findings

Presence of hypertension or edema

Presence of systemic manifestations

Abnormal renal function or serum electrolytes

Abnormal imaging studies

Family history of renal disease.

Possible indications for percutaneous renal biopsy include persistent microscopic or macroscopic hematuria, hypertension, increased serum creatinine, hypocomplementemia, or family history of the chronic renal disease or end-stage renal disease. Renal biopsy is also considered if ANCA (anti-neutrophil cytoplasmic antibody) vasculitis is suspected or is indicated for the management of the nephrotic syndrome.

**Differential Diagnoses of Proteinuria in Children**

<table>
<thead>
<tr>
<th>Proteinuria</th>
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<tr>
<td><strong>Nephrotic-range proteinuria</strong></td>
<td>Minimal change nephrotic syndrome, focal segmental glomerulosclerosis, membranous nephropathy, membranoproliferative glomerulonephritis, IgA nephropathy (rare)</td>
</tr>
<tr>
<td><strong>Proteinuria + hematuria</strong></td>
<td>Post-infectious glomerulonephritis, IgA nephropathy, membranoproliferative glomerulonephritis, lupus nephritis, Alport syndrome</td>
</tr>
<tr>
<td><strong>Proteinuria + systemic findings</strong></td>
<td>HSP, HUS, lupus nephritis, Wegener’s granulomatosis or other ANCA vasculitis, Goodpasture’s disease</td>
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**Therapy of Proteinuria in Children**

Transient proteinuria and orthostatic proteinuria do **not require any specific treatment**. For children with orthostatic proteinuria, long-term periodic monitoring (every 6-12 months) of first-morning urine and of blood pressure is required.

For children with isolated proteinuria, initial thorough diagnostic evaluation, periodic monitoring of FMU and blood pressure, and referral to a pediatric nephrologist are recommended. Proteinuria lowering medications be considered.

Treatment of persistent proteinuria consists of management of the underlying disease and role of medications that can reduce proteinuria.

**Angiotensin-converting enzyme (ACE) inhibitors** or angiotensin receptor blockers (ARB) are proteinuria lowering agents. ACE inhibitors are helpful as a primary or adjunctive treatment in patients with high grade or nephrotic-range proteinuria. They are often started in children with diabetes mellitus at the onset of microalbuminuria. They have an additional advantage of lowering blood pressure by stopping arteriolar vasoconstriction in hypertensive patients.

ARBs have similar effects, but they are more commonly used in older adolescents due to lack of sufficient evidence in the pediatric population. Combination of ACE inhibitor and ARB may have additional advantages. Patients with the overload of fluid can be managed with diuretics. Calcium channel antagonists helps in reduction of proteinuria.
Progression and Prognosis of Proteinuria in Children

Transient proteinuria is a benign condition that resolves with a resolution of associated factor/condition. Orthostatic proteinuria is also a benign condition with no long-term effects; however, **progression to glomerulosclerosis is seen in rare patients.**

Long-term prognosis of children with isolated proteinuria is good; however, ~20% of them have a risk of progressive renal disease within the next 10 years.

Salt restriction and protein restriction is advised in patients of nephrotic syndrome with proteinuria.

References


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