Proteinuria (Protein in Urine) in Children — Symptoms and Treatment

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Proteinuria is common 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. The clinical management of proteinuria usually includes treating the underlying condition with drug therapy.

Definition of Proteinuria in Children

Proteinuria can be defined as the excretion of protein in urine at levels > 100 mg/m^2/day or > 4 mg/m^2/hr. Other definitions are listed in the table below.

Type	Definition
Fixed proteinuria	dipstick urinalysis reveals ≥ 1+ proteinuria; protein/creatinine ratio (U_{Pr}/U_{Cr}) > 0.2 in the first-morning urine (FMU) sample on three consecutive days
Persistent proteinuria	dipstick urinalysis reveals ≥ 1+ proteinuria (equivalent to ≥ 30 mg/dL) in at least three urine specimens obtained over several weeks

Isolated proteinuria	Asymptomatic proteinuria in an otherwise healthy child (normal physical condition, blood pressure, and diagnostic parameters except for the presence of proteinuria)

Heavy proteinuria is marked when protein excretion is more than 2–3 g/day with a protein:creatinine ratio ranging from 200–300. Low levels of proteinuria occur when urine-protein levels drop to < 1 g/day or protein:creatinine ratio is < 100.

Orthostatic proteinuria is a benign condition and not kidney disease. It is a condition characterized by urine protein levels > 1000 mg in a 24-hour urine collection.

Epidemiology of Proteinuria in Children

Although 10% of children may exhibit proteinuria in a single-voided specimen of urine, only 0.1% of children have persistent or pathological proteinuria. Prevalence of proteinuria peaks during adolescence. Approximately 60% of children and 3–5% of adolescents with persistent proteinuria have **orthostatic proteinuria.**

Etiology of Proteinuria in Children

Benign proteinuria can be classified as follows:

- Transient proteinuria, which manifests during fever, exercise, dehydration, stress, seizure, exposure to a clod, or heart failure
- Orthostatic (postural) proteinuria

Glomerular proteinuria can occur in the following conditions:

- Minimal change (idiopathic) nephrotic syndrome
- Focal segmental glomerulosclerosis (FSGS)
- Mesangial proliferative glomerulonephritis
- Membranous nephropathy
- Membranoproliferative glomerulonephritis
- IgA nephropathy
- Acute postinfectious glomerulonephritis
- Henoch-Schönlein 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) is the most common cause of tubular proteinuria and can occur due to hypovolemic shocks. ATN can also be caused by drugs such as NSAIDs, aminoglycosides, amphotericin, and lithium. Tubular proteinuria is also seen in the following conditions:

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

Overflow proteinuria is seen in the following conditions:

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

Pathophysiology of Proteinuria in Children

In children, urinary protein excretion up to 100 mg/m^2/day or 150 mg/day is considered normal, while in neonates, protein excretion can be as high as up to 300 mg/m^2/day. Normally excreted urinary proteins include Tamm-Horsfall protein (uromodulin, ~50%), albumin (~40%), and low-molecular-weight (LMW) proteins (~10%) including β_2-microglobulin and amino acids.

Normally, proteins with molecular weight < 25,000 Da cannot cross the glomerular basement membrane (GBM). Since the GBM is negatively charged owing to the presence of heparan sulfate proteoglycans, it repels anionic proteins such as albumin. The majority of LMW proteins that undergo glomerular filtration are reabsorbed by the proximal tubule. Proteinuria occurs when any of these mechanisms are disrupted.

Proteinuria can cause damage to the glomerular epithelium leading to podocyte loss and production of chemokines and cytokines that can cause an inflammatory response. Albumin is filtered in the proximal tubules, which can process up to 250 g of albumin/day; therefore, any disruption in this process may result in nephrotic syndrome.

Glomerular proteinuria occurs due to the increased permeability of glomeruli, while tubular proteinuria occurs due to decreased reabsorption of LMW proteins by the renal tubules. Glomerular proteinuria consists mostly of albumin and can result in high-grade proteinuria, while tubular proteinuria comprises LMW proteins and usually results in low-grade proteinuria (U_{Pr}/U_{Cr} < 1.0).

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

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

The possible mechanisms that explain **orthostatic proteinuria** include renal hemodynamic changes associated with postural change, partial renal vein occlusion, increased glomerular capillary wall permeability, and the role of circulating immune complexes. In renal diseases with persistent proteinuria, proteinuria itself can be responsible for injury to the renal tubular cells and lead to fibrosis and sclerosis, possibly via the generation of reactive oxygen species.

Symptoms of Proteinuria in Children

Proteinuria is mostly asymptomatic and can be detected during routine urinalysis or diagnostic evaluation. **Transient proteinuria is** accompanied by a fever [temperature > 38.3°C (101 °F)] and dehydration,. It can occur after stress or heart failure, or following exercise, seizure, or exposure to cold weather. Dipstick test shows 2+ or lower proteinuria, which resolves after the resolution of the causative condition. Sometimes, exercise-induced proteinuria may last for as long as 48 hours following exercise.

Image : “Going to the Hospital with Scott” by Marc van der Chijs.
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In **orthostatic proteinuria**, increased protein excretion (up to 1000 mg/day) is seen in an upright position, while protein excretion is normal when in the supine position. The child does not exhibit hypertension, edema, hematuria, hypoalbuminemia, or renal dysfunction. This condition is seen in tall and thin young adults < 30 years of age. Children with **isolated proteinuria** are otherwise healthy and asymptomatic with normal blood pressure and functional parameters. Proteinuria is usually < 2 g/day.

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

The child may present with the following symptoms:

- Periorbital or pedal edema
- Ascites
- Anasarca or abdominal pain
- Hematuria or hypertension
- Frothy 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 2–4 weeks before presenting with an acute episode of nephrotic syndrome, hematuria, proteinuria, hypertension, or acute renal failure.

IgA nephropathy (Henoch-Schönlein purpura or HSP) is characterized by episodes of macroscopic hematuria, proteinuria, abdominal or flank pain, and fever within 72 hours of a respiratory infection. Additionally, purpuric lesions, especially over the buttocks and lower extremities are observed, and the condition is accompanied by abdominal pain, edema, and arthralgia. Children with HUS may present with 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 such as a skin rash.

Diagnosis of Proteinuria in Children

Collection of 24-hour urine is a gold standard for urinary protein quantification; however, such collection is often impractical or not possible in children. A 24-hour urine protein level > 100–150 mg/m^2/day is usually suggestive of proteinuria, although preterm infants and neonates may normally exhibit higher levels of excreted proteins. Urinary protein levels > 1000–2000 mg/day is usually considered pathological in children, except in those with orthostatic proteinuria.

Urinary protein excretion ≤ 4 mg/m^2/h is considered normal, 4–40 mg/m^2/h is considered as proteinuria, and > 40 mg/m^2/h is considered to be nephrotic-range proteinuria.

The urine protein:creatinine ratio (U_{Pr}/U_{Cr}) is widely used to diagnose proteinuria. U_{Pr}/U_{Cr} > 0.5 (in children aged < 2 years) or U_{Pr}/U_{Cr} > 0.2 (in children aged > 2 years) is suggestive of proteinuria. However, in children < 6 months of age, a ratio up to 0.8 is often considered normal, while a ratio > 2.0 suggests nephrotic-range proteinuria (high yield).

For U_{Pr}/U_{Cr} determination, a freshly voided FMU specimen is usually preferred, although a random sample is also acceptable. As the ratio is dependent on urinary creatinine levels, the U_{Pr}/U_{Cr} ratio may be elevated in conditions with low creatinine excretion such as severe malnutrition or in children with low muscle mass. In conditions characterized by low glomerular filtration rates (GFRs), the interpretation of this ratio is difficult.

The urinary dipstick test is most commonly used for the preliminary detection of urinary protein. A reagent strip is processed within 60 seconds of immersion in freshly voided urine. Tetrabromophore, a chromatophore impregnated on the strip, changes color depending on the concentration of protein in the urine. The dipstick method is most sensitive to albumin and less sensitive to other proteins.

The dipstick test is a semiquantitative method and can be interpreted as follows:

Dipstick result	Urine protein concentration
Negative	< 10 mg/dL
Trace	10–30 mg/dL
1+	30–100 mg/dL
2+	100–300 mg/dL
3+	300–1000 mg/dL
4+	> 1000 mg/dL

False-positive results may be encountered due to alkaline urine (pH > 7.0), highly concentrated urine, the prolonged immersion of the dipstick in a urine sample, pyuria, macroscopic hematuria, presence of antiseptic agents (hydrogen peroxide, chlorhexidine, benzalkonium chloride) in the voided sample, 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 the specific gravity of the urine sample is < 1.010, values ≥ trace proteinuria on the dipstick should be considered clinically significant, while if the specific gravity is > 1.015, dipstick results corresponding to ≥ 1+ proteinuria should be considered clinically

significant.

Sulfosalicylic acid (SSA) turbidometric testing is not often used in the qualitative determination of proteinuria; however, this technique can detect albumin, immunoglobulins, and Bence-Jones proteins in urine. As acidification of urine causes the precipitation of urinary proteins, turbidity results when SSA reagent (three parts) is added to a freshly voided urine sample (one part). The degree of turbidity correlates with the protein levels in the urine, which can be compared to a reference scale to determine the protein concentration of the sample.

Urine protein electrophoresis is helpful to identify proteins other than albumin, such as β_2-microglobulin, retinol-binding protein, α-globulins, and monoclonal proteins. Urine immunofixation electrophoresis is helpful when there is an overproduction of immunoglobulins as in the case of certain malignancies.

Detection of **microalbuminuria** in children with diabetes mellitus is important as it is 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 m^2 or MA:Cr 30–300 mg/g suggests microalbuminuria, while MA:Cr > 200 µg/min/1.73 m^2 is suggestive of frank proteinuria.

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

The 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 are observed in chronic renal disease. The presence of eosinophils in urine is highly suggestive of interstitial nephritis.

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

Radiography of the chest may be indicated if cardiac and chest affections are suspected; a computed tomography (CT) scan is suggested if required.

Symptoms of Fanconi syndrome are as follows:

- Presence of glycosuria
- Phosphaturia
- Aminoaciduria
- Bicarbonate wasting

The initial evaluation of an asymptomatic child with persistent proteinuria should include an FMU sample for urinalysis and the determination of U_{Pr}/U_{Cr}. Dipstick negative or trace proteinuria, and $U_{Pr}/U_{Cr} < 0.2$ in the FMU sample for three consecutive days confirms the diagnosis of orthostatic proteinuria. For the collection of FMU, bladder emptying must be ensured before bedtime; the urine must be collected immediately upon waking up the following 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. These include a complete blood count (CBC) and renal

function test, and the determination of serum electrolyte, serum albumin, and serum complement levels (C3, C4). Additional tests include the determination of streptococcal markers (anti-streptolysin O and anti-DNAase B titers), serum antinuclear antibody (ANA) levels, and serum cholesterol levels, as well as a chest X-ray (to determine signs of volume overload), and renal ultrasound (to diagnose renal structural abnormalities).

Indications for referral to a pediatric nephrologist include the following:

- Persistent non-orthostatic proteinuria
- Abnormal urine findings
- Hypertension or edema
- Systemic manifestations
- Abnormal renal function or serum electrolyte levels
- 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 chronic or end-stage renal disease. Renal biopsy is also considered if ANCA (anti-neutrophil cytoplasmic antibody) vasculitis is suspected.

Differential Diagnoses of Proteinuria in Children

Proteinuria	Transient proteinuria, orthostatic proteinuria, persistent proteinuria, isolated proteinuria
Nephrotic-range proteinuria	Minimal change nephrotic syndrome, focal segmental glomerulosclerosis, membranous nephropathy, membranoproliferative glomerulonephritis, IgA nephropathy (rare)
Proteinuria + hematuria	Post-infectious glomerulonephritis, IgA nephropathy, membranoproliferative glomerulonephritis, lupus nephritis, Alport syndrome
Proteinuria + systemic findings	HSP, HUS, lupus nephritis, Wegener’s granulomatosis or ANCA vasculitis, Goodpasture’s disease

Therapy of Proteinuria in Children

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

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

Treatment of persistent proteinuria is centered around the management of the underlying disease and drug therapy to reduce proteinuria.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) can reduce proteinuria. ACE inhibitors are helpful as a primary or adjunctive treatment in patients with high-grade or nephrotic-range proteinuria. These drugs are often started in children with diabetes mellitus at the onset of microalbuminuria. They have an additional advantage of lowering blood pressure in hypertensive patients due to vasodilation.

ARBs have similar effects but are more commonly used in adolescents owing to a lack of sufficient evidence in the pediatric population. The combination of ACE inhibitors and ARBs may have additional advantages.
Patients with a fluid overload can be managed using diuretics. Calcium channel antagonists help in reducing proteinuria.

Progression and Prognosis of Proteinuria in Children

Transient proteinuria is a benign condition that resolves when the associated factors or conditions are treated. Orthostatic proteinuria is also a benign condition with no long-term effects; however, **progression to glomerulosclerosis may occur in rare cases.**

Long-term prognosis in children with isolated proteinuria is good; however, ~20% can be at risk of progressive renal disease within the next 10 years.

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

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Notes