**Nephrotic Syndrome**  
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Dr. Nariman Fahmi  
Assistant professor / Baghdad medical college

**Nephrotic syndrome** is primarily a pediatric disorder and is 15 times more common in children than adults. The incidence is 2-3/100,000 children per year; and the majority of affected children will have steroid-sensitive minimal change disease.

The characteristic features of nephrotic syndrome are heavy proteinuria (>3.5 g/24 hr in adults or 40 mg/m²/hr in children), hypoalbuminemia (<2.5 g/dL), edema, and hyperlipidemia.

**ETIOLOGY.**

Most children (90%) with nephrotic syndrome have a form of the idiopathic nephrotic syndrome. Causes of idiopathic nephrotic syndrome include minimal change disease (85%), mesangial proliferation (5%), and focal segmental glomerulosclerosis (10%). The remaining 10% of children with nephrotic syndrome have secondary nephrotic syndrome related to systemic or glomerular diseases such as membranous nephropathy or membranoproliferative glomerulonephritis.

**PATHOPHYSIOLOGY.**

The underlying abnormality in nephrotic syndrome is an increase in permeability of the glomerular capillary wall, which leads to massive proteinuria and hypoalbuminemia.

The cause of the increased permeability is not well understood. In minimal change disease, it is possible that T-cell dysfunction leads to alteration of cytokines, which causes a loss of negatively charged glycoproteins within the glomerular capillary wall.

In focal segmental glomerulosclerosis, a plasma factor, perhaps produced by lymphocytes, may be responsible for the increase in capillary wall permeability. Alternately, mutations in podocyte proteins (podocin, α-actinin 4) are associated with focal segmental glomerulosclerosis.

Steroid-resistant nephrotic syndrome is associated with mutations in **NPHS2** (podocin) and **WT1** genes.

Although the mechanism of edema formation in nephrotic syndrome is incompletely understood, it seems likely that, in most instances, massive urinary protein loss leads to hypoalbuminemia, which causes a decrease in the plasma oncotic pressure and transudation of fluid from the intravascular compartment to the interstitial space. The
reduction in intravascular volume decreases renal perfusion pressure, activating the renin-angiotensin-aldosterone system, which stimulates tubular reabsorption of sodium. The reduced intravascular volume also stimulates the release of antidiuretic hormone, which enhances the reabsorption of water in the collecting duct.

This theory does not apply to all patients with nephrotic syndrome because some patients actually have increased intravascular volume with diminished plasma levels of renin and aldosterone. Therefore, other factors, including a primary renal avidity for sodium and water, may be involved in the formation of edema in some patients with nephrotic syndrome.

In the nephrotic state, serum lipid levels (cholesterol, triglycerides) are elevated for two reasons. Hypoalbuminemia stimulates generalized hepatic protein synthesis, including synthesis of lipoproteins. In addition, lipid catabolism is diminished, as a result of reduced plasma levels of lipoprotein lipase, related to increased urinary losses of this enzyme.

**Idiopathic Nephrotic Syndrome**

Approximately 90% of children with nephrotic syndrome have idiopathic nephrotic syndrome. Idiopathic nephrotic syndrome includes 3 histologic types: minimal change disease, mesangial proliferation, and focal segmental glomerulosclerosis. These 3 disorders may represent 3 separate diseases with a similar clinical presentation; alternately, these disorders may represent a spectrum of a single disease.

**PATHOLOGY.**

In **minimal change nephrotic syndrome (MCNS)** (85% of total cases of nephrotic syndrome in children), the glomeruli appear normal or show a minimal increase in mesangial cells and matrix. Findings on immunofluorescence microscopy are typically negative, and electron microscopy simply reveals effacement of the epithelial cell foot processes. More than 95% of children with minimal change disease respond to corticosteroid therapy.

**Mesangial proliferation** (5% of total cases) is characterized by a diffuse increase in mesangial cells and matrix on light microscopy. Approximately 50% of patients with this histologic lesion respond to corticosteroid therapy.

In **focal segmental glomerulosclerosis (FSGS)** (10% of total cases), glomeruli show mesangial proliferation and segmental scarring on light microscopy. Only 20% of patients with FSGS respond to prednisone. The disease is frequently progressive, ultimately involving all glomeruli, and leads to end-stage renal disease in most patients.
CLINICAL MANIFESTATIONS.

The idiopathic nephrotic syndrome is more common in males than in females (2:1) and most commonly appears between the ages of 2 and 6 yr. The initial episode and subsequent relapses may follow minor infections and, occasionally, reactions to insect bites. Children usually present with mild edema, which is initially noted around the eyes and in the lower extremities. Nephrotic syndrome may initially be misdiagnosed as an allergic disorder because of the periorbital swelling that decreases throughout the day. With time, the edema becomes generalized, with the development of ascites, pleural effusions, and genital edema. Anorexia, irritability, abdominal pain, and diarrhea are common; hypertension and gross hematuria are uncommon.

The differential diagnosis of the child with marked edema includes:

protein-losing enteropathy, hepatic failure, congestive heart failure, acute or chronic glomerulonephritis, and protein malnutrition.

DIAGNOSIS.

The urinalysis reveals 3+ or 4+ proteinuria; microscopic hematuria may be present in 20% of children.

urinary protein excretion exceeds 3.5 g/24 hr in adults and 40 mg/m²/hr in children.

The serum creatinine value is usually normal, but it may be increased because of diminished renal perfusion resulting from contraction of the intravascular volume.

The serum albumin level is generally <2.5 g/dL, and the serum cholesterol and triglyceride levels are elevated.

C3 and C4 levels are normal. Renal biopsy is not required for diagnosis in most children.

TREATMENT.

Children having the first episode of nephrotic syndrome and mild to moderate edema may be managed as outpatients. Affected children may attend school and participate in physical activities as tolerated. The pathophysiology and treatment of nephrotic syndrome should be carefully reviewed with the family to enhance their understanding of their child's disease.

Sodium intake should be reduced by the initiation of a low-sodium diet and may be normalized when the child enters remission. Because of the possibility of increasing the risk of thromboembolic complications, diuretic use should be reserved for patients with severe symptoms and must be closely monitored.
Children with **severe symptomatic edema**, including large pleural effusions, ascites, or severe genital edema, **should be hospitalized**. In addition to sodium restriction, fluid restriction may be necessary if the child is hyponatremic.

A swollen scrotum may be elevated with pillows to enhance the removal of fluid by gravity. Diuresis may be augmented by administration of chlorothiazide (10 mg/kg/dose IV every 12 hr) or metolazone (0.1 mg/kg/dose PO bid) followed by furosemide 30 min later (1–2 mg/kg/dose IV q 12 hr).

**IV administration of 25% human albumin** (0.5 g/kg/dose q 6–12 hr administered over 1–2 hr) followed by furosemide (1–2 mg/kg/dose IV) is often necessary **when fluid restriction and parenteral diuretics are not effective**. Such therapy mandates close monitoring of volume status, serum electrolyte balance, and renal function. Symptomatic volume overload, with hypertension and heart failure, is a potential complication of parenteral albumin therapy, particularly with rapid infusions.

**Indications of renal biopsy:**

Children with features that make MCNS less likely (hematuria, hypertension, renal insufficiency, hypocomplementemia, age <1 yr or >8 yr) should be considered for **renal biopsy** before treatment.

In children with presumed MCNS, prednisone should be administered (after confirming a negative PPD test) at a dose of 60 mg/m²/day (maximum daily dose, 80 mg divided into 2–3 doses) for at least 4 consecutive weeks. There is good evidence that an initial 6-wk course of **daily** steroid treatment may lead to a lower relapse rate, although the frequency of steroid-induced side effects is higher.

Eighty to 90% of children will respond to steroid therapy (urine trace or negative for protein for 3 consecutive days), by 2 wk. The vast majority of children who will respond to prednisone therapy will do so within the first 4 wk of treatment.

After the initial 6-wk course, the prednisone dose should be tapered to 40 mg/m²/day given every other day as a single morning dose. The **alternate-day** dose is then slowly tapered and discontinued over the next 2–3 mo. Children who continue to have **proteinuria (2+ or greater) after 8 wk of steroid therapy are considered steroid resistant, and a diagnostic renal biopsy should be performed.**

Many children with nephrotic syndrome will experience at least 1 relapse (3-4+ proteinuria plus edema). Relapses should be treated with daily divided-dose prednisone at the doses noted earlier until the child enters remission (urine trace or negative for protein for 3 consecutive days). The prednisone dose is then changed to alternate-day dosing and tapered over 1–2 mo.

A subset of patients will relapse while on alternate-day steroid therapy or within 28 days of stopping prednisone therapy. Such patients are termed **steroid dependent.** Patients
who respond well to prednisone therapy but relapse ≥4 times in a 12-mo period are termed **frequent relapers**. Children who fail to respond to prednisone therapy within 8 wk are termed **steroid resistant**.

Steroid-dependent patients, frequent relapers, and steroid-resistant patients may be candidates for alternative agents, particularly if the child suffers severe corticosteroid toxicity (cushingoid appearance, hypertension, cataracts, and/or growth failure).

**Cyclophosphamide** prolongs the duration of remission and reduces the number of relapses in children with **frequently relapsing** and **steroid-dependent** nephrotic syndrome. The potential side effects of the drug (neutropenia, disseminated varicella, hemorrhagic cystitis, alopecia, sterility, increased risk of future malignancy) should be carefully reviewed with the family before initiating treatment. The dose of cyclophosphamide is 2–3 mg/kg/24 hr given as a single oral dose, for a total duration of 8–12 wk. Alternate-day prednisone therapy is often continued during the course of cyclophosphamide administration. During cyclophosphamide therapy, the white blood cell count must be monitored weekly and the drug should be withheld if the count falls below 5,000/mm$^3$.

An additional option for the child with complicated nephrotic syndrome is **high-dose pulse methylprednisolone**. Methylprednisolone is usually given as a 30-mg/kg bolus (maximum 1,000 mg), with the first 6 doses given every other day, followed by a tapering regimen for periods up to 18 mo. Cyclophosphamide may be added to this regimen in selected patients.

**Cyclosporine** (3–6 mg/kg/24 hr divided q 12 hr) or **tacrolimus** (0.15 mg/kg/24 hr divided q 12 hr) are also effective in maintaining prolonged remissions in children with nephrotic syndrome and are useful as steroid-sparing agents. Children must be monitored for side effects, including hypertension, nephrotoxicity, hirsutism, and gingival hyperplasia. **Mycophenolate** may maintain remission in children with steroid-dependent or frequently relapsing nephrotic syndrome. Most children who respond to cyclosporine, tacrolimus, or mycophenolate therapy tend to relapse when the medication is discontinued.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II blockers may be helpful as adjunct therapy to reduce proteinuria in steroid-resistant patients.

**COMPLICATIONS.**

**Infection** is the major complication of nephrotic syndrome. Children in relapse have increased susceptibility to bacterial infections because of:

- urinary losses of immunoglobulins and properdin factor B,
- defective cell-mediated immunity, immunosuppressive therapy, malnutrition, and edema/ascites acting as a potential “culture medium.”
Spontaneous bacterial peritonitis is the most frequent type of infection, although sepsis, pneumonia, cellulitis, and urinary tract infections may also be seen. Although *Streptococcus pneumoniae* is the most common organism causing peritonitis, gram-negative bacteria such as *Escherichia coli* may also be encountered.

Because fever and physical findings may be minimal in the presence of corticosteroid therapy, a high index of suspicion, prompt evaluation (including cultures of blood and peritoneal fluid), and early initiation of antibiotic therapy are critical. The role of prophylactic antibiotic therapy during nephrotic syndrome relapse is controversial.

Thromboembolic events. Children with nephrotic syndrome are also at increased risk of thromboembolic events. Both arterial and venous thromboses may be seen, including renal vein thrombosis, pulmonary embolus, sagittal sinus thrombosis, and thrombosis of indwelling arterial and venous catheters.

The risk of thrombosis is related to: increased prothrombotic factors (fibrinogen, thrombocytosis, hemoconcentration, relative immobilization) and decreased fibrinolytic factors (urinary losses of antithrombin III, proteins C and S).

Prophylactic anticoagulation is not recommended in children unless they have had a previous thromboembolic event. Overaggressive diuresis should be avoided and use of indwelling catheters limited because these factors may increase the likelihood of clotting complications.

Hyperlipidemia, particularly in complicated patients with nephrotic syndrome, may be a risk factor for cardiovascular disease; myocardial infarction is a rare complication in children.

PROGNOSIS.

The majority of children with steroid-responsive nephrotic syndrome have repeated relapses, which generally decrease in frequency as the child grows older.

Although there is no proven way to predict an individual child's course, those children who respond to steroids rapidly and those who have no relapses during the first 6 mo after diagnosis are likely to follow an infrequently relapsing course.

It is important to indicate to the family that the child with steroid-responsive nephrotic syndrome is unlikely to develop chronic kidney disease, that the disease is generally not hereditary, and that the child (in the absence of prolonged cyclophosphamide therapy) will remain fertile.

To minimize the psychological effects of the condition, the physician should emphasize that the child should be considered normal when in remission and may have unrestricted diet and activity, without the need for urine testing for protein.
Children with steroid-resistant nephrotic syndrome, most often caused by FSGS, generally have a much poorer prognosis. These children develop progressive renal insufficiency, ultimately leading to end-stage renal disease requiring dialysis or renal transplantation.

Recurrent nephrotic syndrome develops in 30–50% of transplant recipients with FSGS.