GLOMERULAR DİSEASES:
NEPHROTİC SYNDROME

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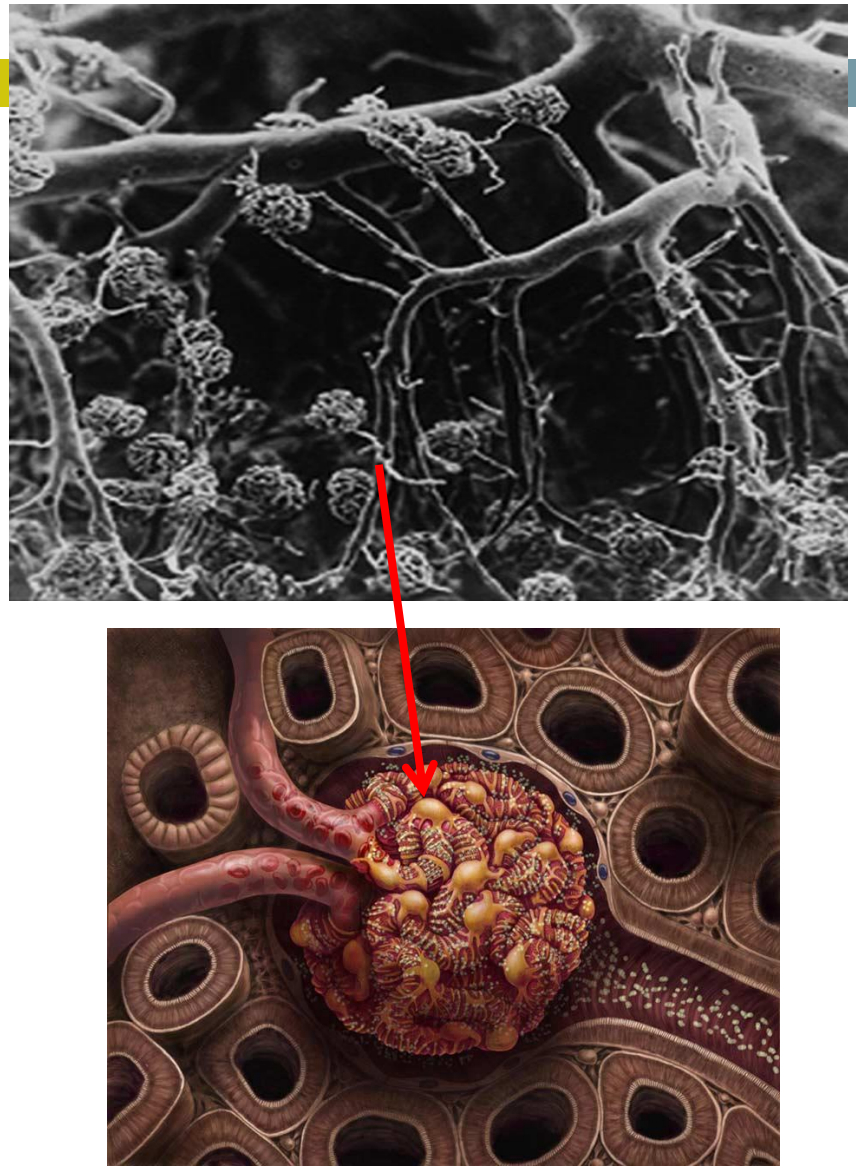
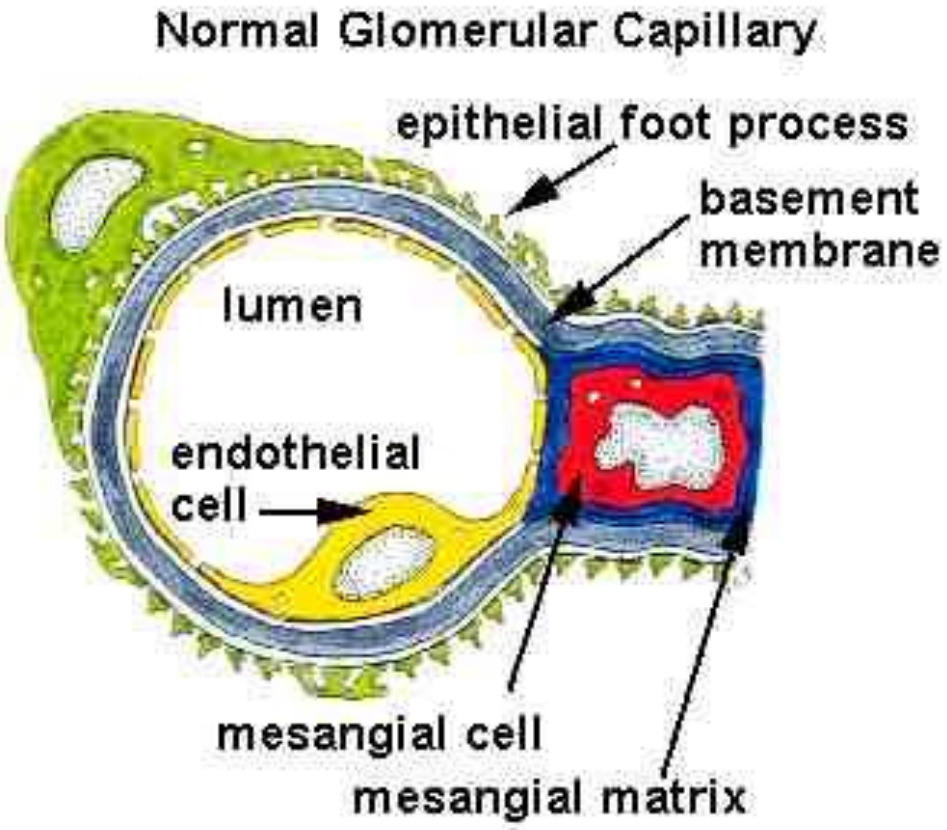
Aims & objectives

- State the definition of nephrotic syndrome.
- Identify clinical signs of nephrotic syndrome.
- Explain the pathophysiology of nephrotic syndrome.
- Identify proteinuria and its' type
- Explain management of nephrotic syndrome.

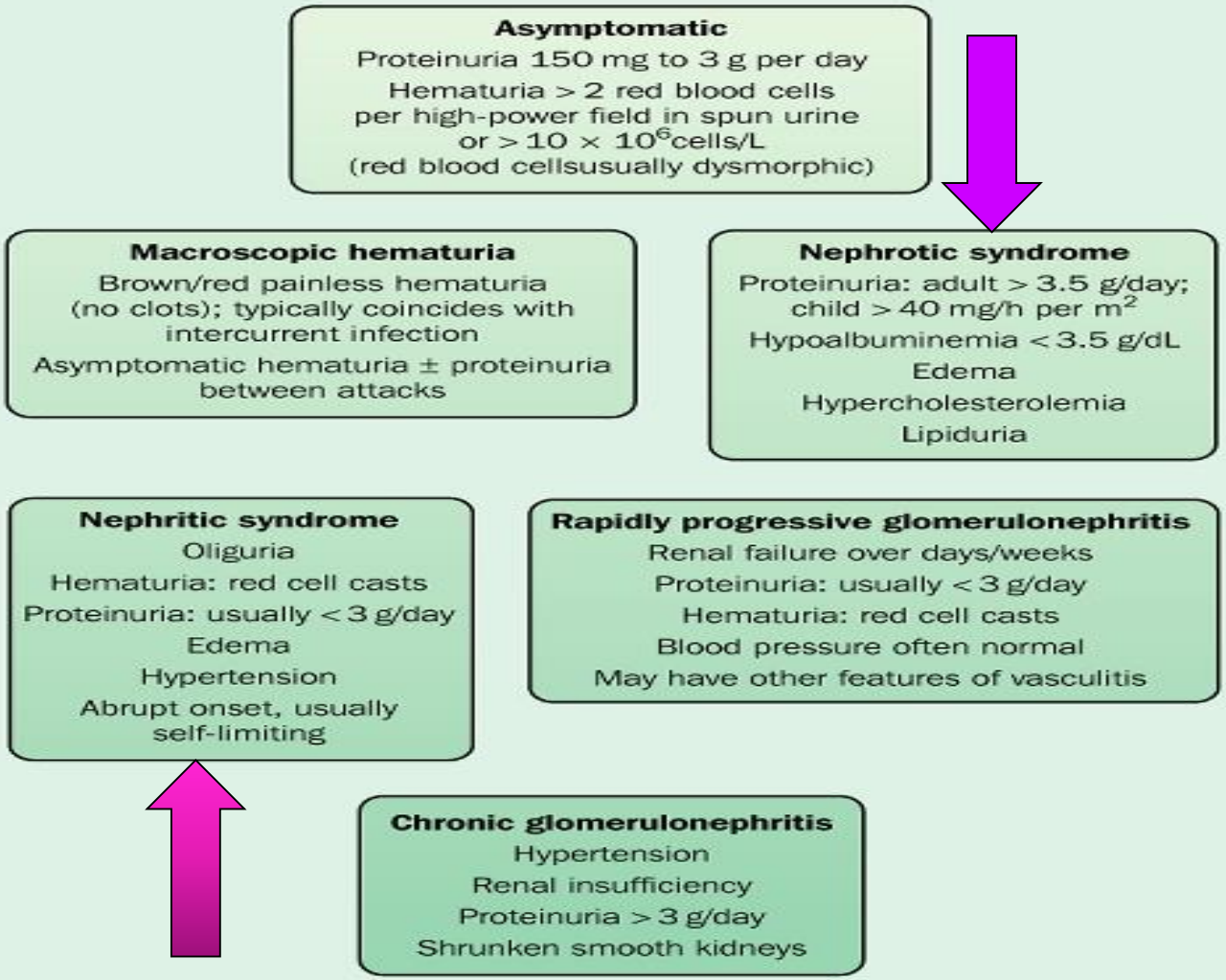
Glomerulus




Normal Glomerular Capillary
epithelial foot process
basement membrane
lumen
endothelial cell
mesangial cell
mesangial matrix

- the glomerular capillaries can be injured in a variety of ways, producing many different lesions and several unique changes to urinalysis.
- There are many forms of glomerular disease with pathogenesis variably linked to the presence of genetic mutations, infection, toxin exposure, autoimmunity, atherosclerosis, hypertension, emboli, thrombosis, or diabetes mellitus.
- Even after careful study, however, the cause often remains unknown, and the lesion is called idiopathic or primary.

Clinical presentations of glomerular disease



NEPHROTİC SYNDROME

- The nephrotic syndrome is caused by renal diseases that increase the permeability across the glomerular filtration barrier
- Two issues are important in the pathogenesis of nephrotic syndrome: the mechanisms of glomerular injury and proteinuria.

Components of nephrotic syndrome

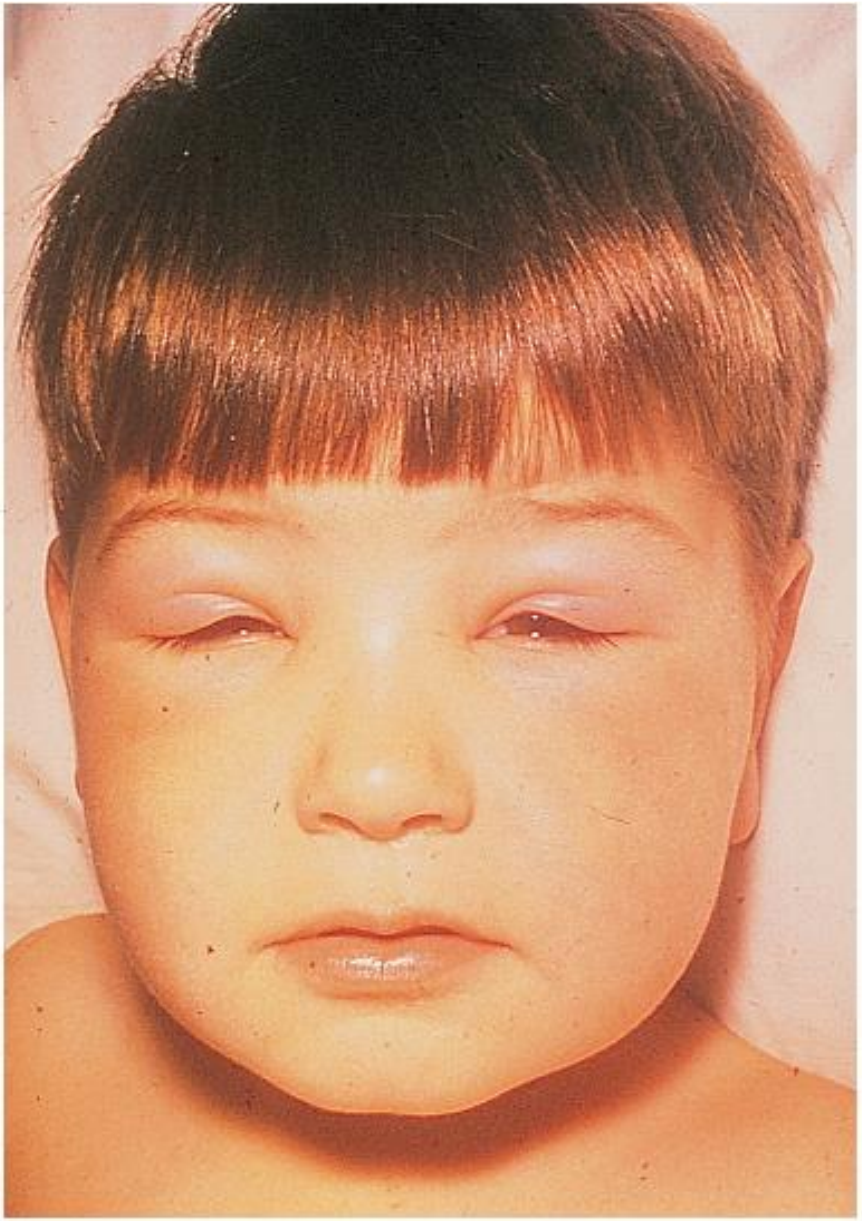
- Proteinuria- adult 3.5g/24 hr/1.73m^2
- Hypoalbum. (serum alb<3.5 g/d)
- Hypercholesterolemia (>200mg/dl)
- Peripheral edema ± anasarca

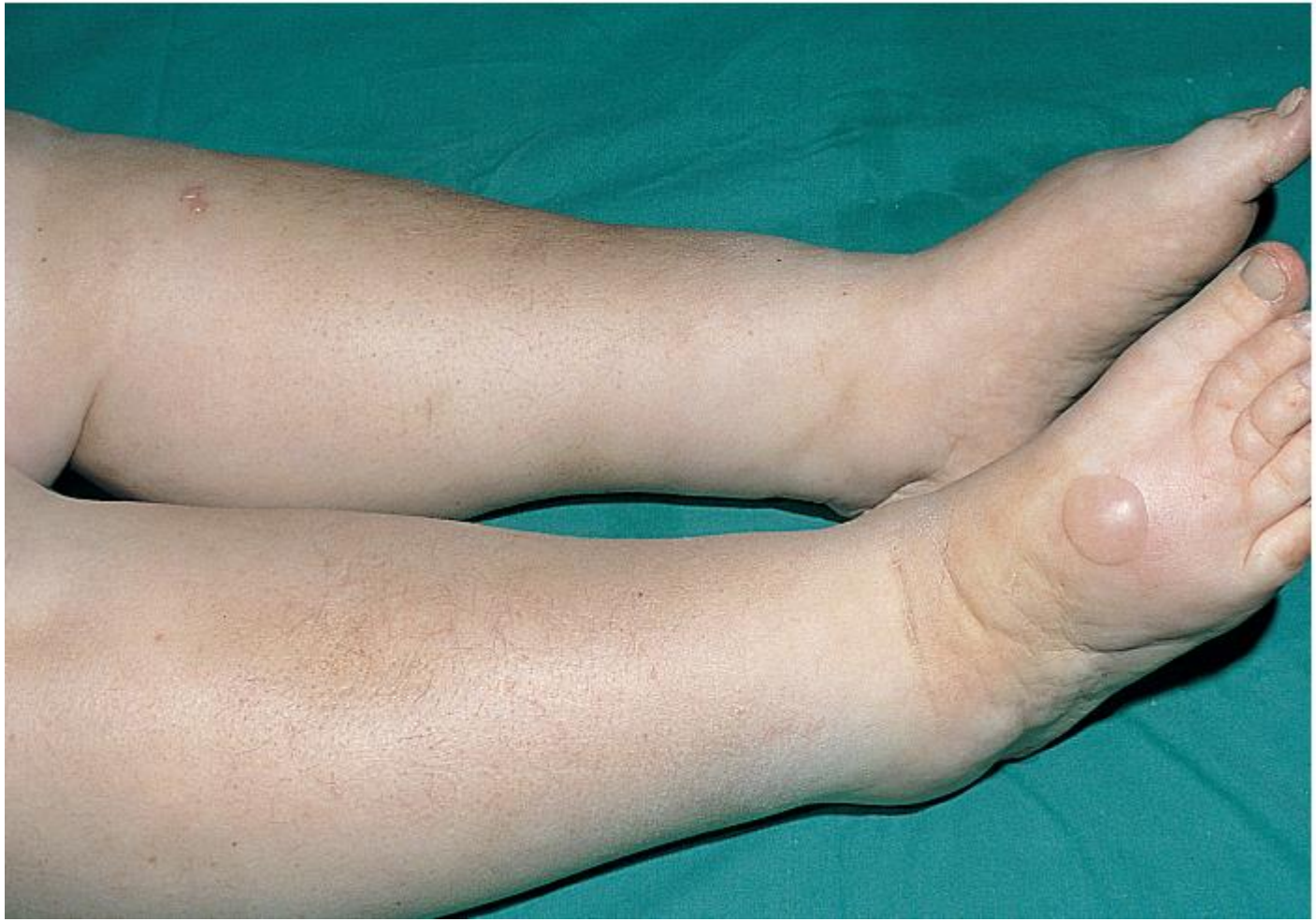
Epidemiology

- % of cases of idiopathic nephrotic syndrome is primitive
- It affects children aged 2-10 years.
- It affects mainly males (but not exclusively!).
- Is 15 times more common in children than in adults.
- The incidence is 2-7 cases per 100 000 children under 16 years.

-epidemiology

- Incidence of nephrotic syndrome corticorezistent seems to be in black race and hispanic population greater than in the general population.
- The Asian population is 6 times more affected than the European (as The Kidney Disease: Improving Global Outcomes - KDIGO). Congenital nephrotic syndrome have an increased incidence (1 / 10000-1 / in 5000 births) in the Finnish population.





Tendencies of glomerular diseases to manifest Nephrotic Features

- Minimal change glomerulopathy
- Membranous GN
- Diabetic GS
- Amyloidosis
- Focal segmental GS
- Fibrilary GN

Common causes of NS

- Primary glomerular disorders

- Minimal Change Disease
- FSGS
- Membranous GN
- Orthostatik or postural proteinuria
- Idiopatic MPGN
- IgA nephropathy
- Proliferatif GN

Common causes of NS

- Secondary glomerular disorders

Hereditary-familial: DM, Alport's Syndrome, Sickle cell disease

Autoimmun: SLE, Goodpasture's syndrome, Wegener's granulomatosis, PAN, RA

Infectious: postinfectious glomerulonephritis, HIV→ FSGS

Drug-induced: NSAIDs, Heroin,gold, mercury,

Neoplastic: Hodgkin's D., Lymphomas, leukemia, MM.

miscellaneous: amyloidosis, preeclampsia-eclampsia, renovascular HT, intertitial nephritis, fever, exercise

Proteinuria

- changes to capillary endothelial cells, the glomerular basement membrane (GBM), or podocytes, which normally filter serum protein selectively by **size** and **charge.**
- **The mechanism of damage to these structures is unknown** in primary glomerular disease
- The result is urinary loss of macromolecular proteins, primarily **albumin** but also opsonins, Ig's, erythropoietin, transferrin, hormone-binding proteins, and antithrombin III in conditions that cause nonselective proteinuria.

Pathophysiology of proteinuria

1. Glomerular retention and leakage of protein molecules
2. Damage of glomeruler size and charge selectivity

Size:(molecular radius) <17 Å readly pass the glomerular filter,

>44 Å can not pass)

- Albumin 36 Å

Charge: glomerular capillary wall→ fix negative charge

- Normally 1500mg/24 hr Protein filtered, most is reabsorbed
- <150 mg of protein excreted each day in the urine

Types of proteinuria

- **'Glomerular' proteinuria** (more than about 1.5 g protein/24 h, mostly albumin)
- **'Tubular' proteinuria** (never excretion of more than 1.5 g/24 h)
- **'Overflow' proteinuria:** immunoglobulin light chains in the urine
- **Benign proteinuria** 'Jogger's nephritis' , orthostatic proteinuria

Acute Complications of Nephrotic Syn.

- **peripheral edema, ascites, and effusions** →increased risk for infection (especially cellulitis and, in 2 to 6%, spontaneous bacterial peritonitis);
- **anemia; abnormal thyroid function;**
- **Thromboembolism** (especially renal vein thrombosis and pulmonary embolism in up to 5% of children and 40% of adults).
- Thromboembolism may develop not only because of urinary loss of antithrombin III but also because of increased hepatic synthesis of clotting factors, platelet abnormalities, and hyperviscosity from hypovolemia.

-acute complications of NS

- **Hypercholesterolaemia** is present in 90 per cent of patients with a urinary protein excretion of over 3 g/24 h
- **Hyperlipidemia** in the NS is the result of both increased synthesis and decreased catabolism of lipoproteins.

Chronic complications of NS

- malnutrition in children,
- coronary artery disease in adults,
- chronic renal failure, and bone disease. Malnutrition may mimic kwashiorkor, including brittle hair and nails, alopecia, and stunted growth. Coronary artery disease develops because NS causes hyperlipidemia, hypertension, and hypercoagulability.

Chronic complications of NS

- Bone disease develops because of vitamin D deficiency and corticosteroid use.
- hypothyroidism from loss of thyroid-binding globulin
- proximal tubular dysfunction causing glucosuria, aminoaciduria, K depletion, phosphaturia, and renal tubular acidosis

Symptoms and Signs

- anorexia, malaise, and frothy urine caused by high concentrations of protein.
- Edema may cause dyspnea (pleural effusion or laryngeal edema), chest discomfort (pericardial effusion),
- arthralgia (hydrarthrosis),
- abdominal pain (ascites or, in children, mesenteric edema).
- Edema may obscure signs of muscle wasting and cause parallel white lines in fingernail beds (Muehrcke's lines).

Diagnosis

- suspected in patients with edema and proteinuria on **urinalysis** and confirmed by **24-h measurement of urinary protein**. The cause may be suggested by history (eg, cancer); when the cause is unclear, serologic testing and **renal biopsy** are indicated.
- Besides proteinuria, urinalysis may demonstrate RBCs and casts (hyaline, granular, fatty, waxy, RBC, or epithelial cell).
- Lipiduria, the presence of free lipid or lipid within tubular cells (oval fat bodies), within casts (fatty casts), or as free globules

Renal Bx

- In adults, a renal biopsy is indicated to diagnose the underlying cause of **idiopathic NS.**
- Idiopathic NS in children is most likely **minimal change disease** and is usually presumed without biopsy unless the patient fails to improve on a trial of corticosteroids.

Treatment Objectives:

- Complete remission
- Relapse prevention
- Treatment of acute complications or those related to long-term medication
- Patient's quality of life

Management of odema

- - Bed rest - need in case of important generalized edema
- - Diet – no salt, normoproteic, normocaloric, hypolipidaemic, hypoglucidic diet, imposed by dyslipidaemia associated with cortisone therapy. Oliguria is required fluid restriction (intake = 400 ml + diuresis)

-management

- - Diuretic therapy: only recommended short courses at patient in preserved diuresis (in case of hypovolemia may precipitate acute interstitial nephritis or acute tubular necrosis) . Generally used loop diuretics (furosemide) 1-2mg/kg/dosis, after infusion of albumin /plasma. Spironolactone can be associated to the potassium - sparing effect.

-Management

- - Hypovolemia associating severe hypotension and tachycardia can be improved by albumin infusion 1g/kg (5ml/kg of 20% solution), infused slowly direct iv way, diluted with glucose 5% with BP control. A low serum albumin level is not an indication for albumin infusion!
  - Immunization: the live attenuated vaccines are contraindicated during cortisone therapy and at least 6 months thereafter .

Specific therapy

-Primitive NS: oral prednisone 5 mg/tb

- One month coticoterapie attack: daily 60mg/m2/day (or 2mg/kg/day),

- A month discontinuous, the same dose

- 2 months - gradual dose reduction with 10mg/week up to 0.25 mg / kg and stop the therapy after 4 months. After ISKDC (International Study of Kidney Disease in Children) Classic mode : Prednisone

• 60 mg/m2/day (maximum 60 mg / day) 4 weeks

• 40 mg/m2/la 2 days , 4 weeks

-specific therapy

- Prednisone therapy should receive adjuvant, needed to counter adverse effects :
  - Gastric protector (protector or nhibitor mucosa proton pump)
  - Calcium and vitamin D for osteoporosis
  - KCl
  - Antiplatelet agents - in situations of significant thrombocytosis

Management of Complications:

- Hypertension:
  - Sodium restrictions
  - Exercise
  - Weight loss if is associated obesity
  - First line therapy consists of inhibitopri angiotensin converting enzyme and angiotensin receptor
- Obesity:
  - Monitoring of BMI, stimulating sport for weight control
  - Decreasing doses of glucocorticoids / change medications
- Dyslipidemia:
  - Low- fat diet containing < 30 % of the daily calorie intake (saturated <10 %)
  - Lipid-lowering statin class if the LDL cholesterol remains > 160mg/dl

-managements of complications

- Infections are an important cause of morbidity and mortality in children with nephrotic syndrome. Streptococcus pneumoniae is the main bacteria involved in the genesis of peritonitis in patients with primitive NS. In this respect pneumococcal vaccination is recommended for all children with NS. Prophylaxis with varicella-zoster virus is also required in these children. In patients with onset varicella Acyclovir therapy is indicated. Immunization was repeated every 5 years. Live vaccines attenuated contraindicated during treatment with corticosteroids and at least 3 months after.

-management of complications

- Thromboembolism
  Up to 25 % of children with NS have thromboembolic complications. The risk seems to be greater in patients with Steroid-resistant nephrotic syndrome to those with corticosensibil NS. Specific therapy includes heparin, low molecular weight heparin and oral anticoagulants. During anticoagulant therapy encourage movement and contraindicate rest time

-Evolution

- EVOLUTION for NS with minimal damage:
  -1/3 patients had a single episode
  -1/3 patients have occasional relapses
  -1/3 patients become steroid dependent after attack period therapy

-Prognosis

- PROGNOSIS
  - NS with minimal damage: favorable prognosis
  - NS with histological lesions - depends to the etiology, morphology and therapeutic response
  - Secondary SN:
  * good prognosis: allergic and toxic drug NS
- * poor prognosis systemic diseases