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НЕФРОТИЧЕСКИЙ СИНДРОМ В АМБУЛАТОРНОЙ ПРАКТИКЕ

NEPHROTIC SYNDROME IN OUTPATIENT PRACTICE

Учебно-методическое пособие

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Представлены сведения о критериях и патофизиологии нефротического синдрома, рассмотрены вопросы дифференциальной диагностики и лечения.

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ABBREVIATIONS

ACE — Angiotensin-converting enzyme
ApoB — Apolipoprotein B
ANA — Antinuclear antibody
ARBs — Angiotensin receptor blockers
BUN — Blood urea nitrogen
CKD — Chronic kidney disease
ENaC — The epithelial sodium channel
FSGS — Focal segmental glomerulosclerosis
GI — Gastrointestinal tract
GFR — Glomerular filtration rate
HDL — High-density lipoprotein
KDIGO — Kidney Disease Improving Global Outcomes
LDL — Low-density lipoprotein
MCD — Minimal change disease
MDRD — Modified Diet in Renal Disease
MGN — Membranous glomerulonephritis
MPGN — Membranoproliferative glomerulonephritis
NS — Nephrotic syndrome
NSAID — Nonsteroidal anti-inflammatory drugs
RPGN — Rapidly progressive glomerulonephritis
SLE — Systemic lupus erythematosus
VLDL — Very-low-density lipoprotein

Nephrotic syndrome is a collection of symptoms that indicate kidney damage.

EPIDEMIOLOGY

Nephrotic syndrome (NS) can affect any age, although it mainly affects in adults, the ratio between adults and children being 26 to 1. The annual incidence of NS in adults is three per 100 000 persons. Approximately 80 % to 90 % of NS cases in adults are idiopathic. Membranous nephropathy is the most common cause in whites, and focal segmental glomerulosclerosis is most common in blacks; each of these disorders accounts for approximately 30 % to 35 % of NS cases in adults. Minimal change disease and immunoglobulin A nephropathy each account for approximately 15 % of cases. The remaining 10 % of cases are secondary to an underlying medical condition. The most frequent glomerulopathy in children is minimal change disease (66 % of cases), followed by focal segmental glomerulosclerosis (8 %) and mesangiocapillary glomerulonephritis (6 %).

There are also differences in epidemiology between the sexes, the disease is more common in men than in women by a ratio of 2 to 1.

CRITERIA OF NEPHROTIC SYNDROME

Nephrotic syndrome is characterized by:

– Large amounts of **proteinuria** (> 3.5 g per 1.73 m^2 body surface area per day, or > 40 mg per square meter of body surface area per hour in children). The ratio between urinary concentrations of albumin and creatinine can be used in the absence of a 24-hour urine test for total protein. This coefficient will be greater than 200–400 mg/mmol in nephrotic syndrome. This pronounced loss of proteins is due to an increase in glomerular permeability that allows proteins to pass into the urine instead of being retained in the blood. Under normal conditions a 24-hour urine sample should not exceed 80 milligrams or 10 milligrams per decilitre.

– **Hypoalbuminemia** of less than 2.5 g/dL, that exceeds the hepatic clearance level, that is, protein synthesis in the liver is insufficient to increase the low blood protein levels.

– **Edema** is thought to be caused by two mechanisms. The first being hypoalbuminemia which lowers the oncotic pressure within vessels resulting in hypovolemia and subsequent activation of the renin–angiotensin system and thus retention of sodium and water. Additionally, it is thought that albumin causes a direct effect on the epithelial sodium channel (ENaC) on the principal cell that leads to the reabsorption of sodium and water. Nephrotic syndrome edema initially appears in parts of the lower body (such as the legs) and in the eyelids. In the advanced stages it also extends to the pleural cavity and peritoneum (ascites) and can even develop into a generalized anasarca. It has been recently seen that intrarenal sodium handling abnormality is related to Atrial Natriuretic Peptide resistance associated with decreased abundance and altered subcellular localization of dopamine receptor in renal tubules.

– **Hyperlipidaemia** is caused by an increase in the synthesis of low and very low-density lipoproteins in the liver that are responsible for the transport of cholesterol and triglycerides. There is also an increase in the hepatic synthesis of cholesterol.

– **Thrombophilia, or hypercoagulability**, is a greater predisposition for the formation of blood clots that is caused by a decrease in the levels of antithrombin III in the blood due to its loss in urine.

– **Lipiduria or loss of lipids** in the urine is indicative of glomerular pathology due to an increase in the filtration of lipoproteins.

Clinical definition of adult nephrotic syndrome:

1. Proteinuria: ≥ 3.5 g/day and continuous (comparable to ≥ 3.5 g/gCr at spot urine).

2. Hypoalbuminemia: Serum albumin ≤ 3.0 g/dL.
Serum total protein ≤ 6.0 g/dL is helpful.

3. Edema.

4. Dyslipidemia (Hyper LDL cholesterolemia).

The above urine protein and hypoalbuminemia are indispensable prerequisites for the clinical diagnosis of nephrotic syndrome.

Edema is not an indispensable prerequisite but an important criterion for nephrotic syndrome.

Dyslipidemia is not an indispensable prerequisite for nephrotic syndrome.

Oval fat body is helpful for diagnosis of nephrotic syndrome.

PATHOPHYSIOLOGICAL ASPECTS OF NEPHROLOGY SYNDROME

Albumin is a protein that acts like a sponge, drawing extra fluid from the body into the bloodstream where it remains until removed by the kidneys. When albumin leaks into the urine, the blood loses its capacity to absorb extra fluid from the body, causing edema.

Nephrotic syndrome results from a problem with the kidneys' filters, called glomeruli. Glomeruli are tiny blood vessels in the kidneys that remove wastes and excess fluids from the blood and send them to the bladder as urine. As blood passes through healthy kidneys, the glomeruli filter out the waste products and allow the blood to retain cells and proteins the body needs. However, proteins from the blood, such as albumin, can leak into the urine when the glomeruli are damaged. In nephrotic syndrome, the damaged glomeruli allow 3 grams or more of protein to leak into the urine when measured over a 24-hour period, which is more than 20 times the amount that healthy glomeruli can cope with (fig. 1).

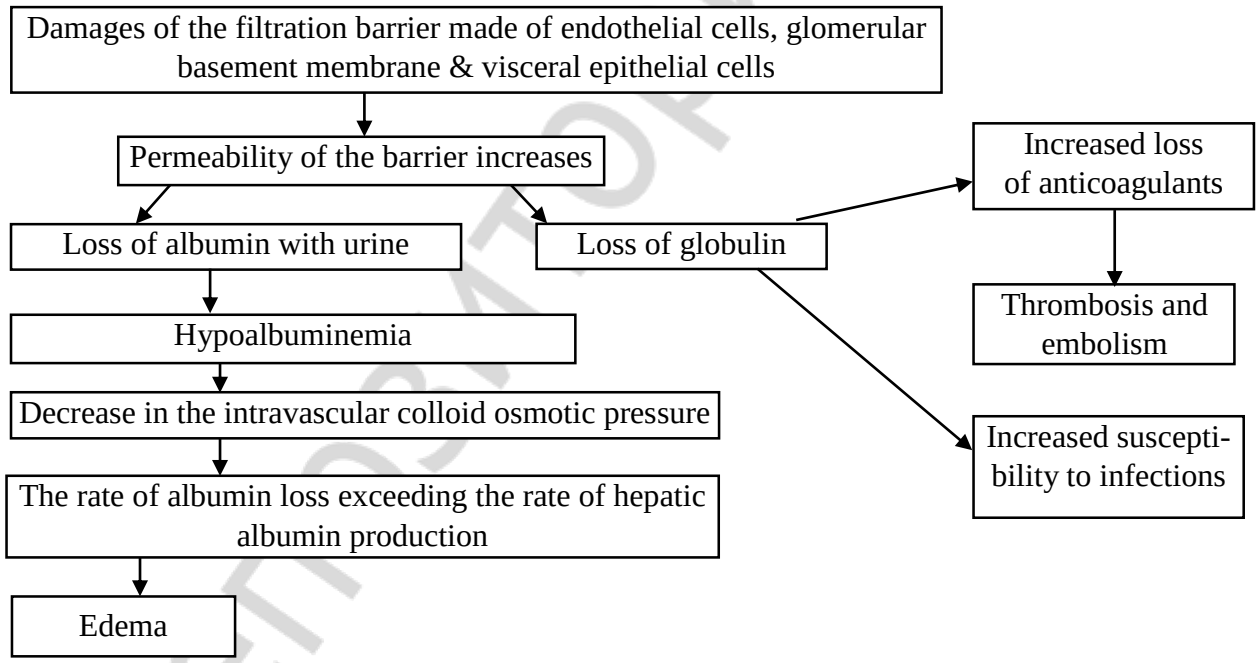

Fig. 1. The pathophysiology of nephrotic syndrome

As blood passes through healthy kidneys, the glomeruli filter out the waste products and allow the blood to retain cells and proteins the body needs.

Hyperlipidaemia is caused by two factors:

Hypoproteinemia stimulates protein synthesis in the liver, resulting in the overproduction of lipoproteins.

Lipid catabolism is decreased due to lower levels of lipoprotein lipase, the main enzyme involved in lipoprotein breakdown. Cofactors, such as apolipoprotein C2 may also be lost due to increased filtration of proteins.

Lower serum oncotic pressure causes fluid to accumulate in the interstitial tissues. Sodium and water retention aggravates the edema. This may take several forms:

- Puffiness around the eyes, characteristically in the morning.
- Pitting edema over the legs.
- Fluid in the pleural cavity causing pleural effusion. More commonly
- associated with excess fluid is pulmonary edema.
- Fluid in the peritoneal cavity causing ascites.
- Generalized edema throughout the body known as anasarca.

Most of the patients are normotensive but **hypertension** (rarely) may also occur.

Anaemia (iron resistant microcytic hypochromic type) may be present due to transferrin loss.

Dyspnea may be present due to pleural effusion or due to diaphragmatic compression with ascites.

Erythrocyte sedimentation rate is increased due to increased fibrinogen & other plasma contents.

Some patients may notice foamy or **frothy urine**, due to a lowering of the surface tension by the severe proteinuria. Actual urinary complaints such as **haematuria** or **oliguria** are uncommon, though these are seen commonly in nephritic syndrome.

May have features of the underlying cause, such as the **rash** associated with systemic lupus erythematosus, or the neuropathy associated with diabetes.

Examination should also exclude other causes of gross edema — especially the cardiovascular and hepatic system.

Muehrcke's nails: white lines (leukonychia) that extend all the way across the nail and lie parallel to the lunula are typically present.

WHAT CAUSES OF NEPHROTIC SYNDROME

Nephrotic syndrome can be caused by diseases that affect only the kidneys, such as focal segmental glomerulosclerosis (FSGS) or membranous nephropathy. Diseases that affect only the kidneys are called primary causes of nephrotic syndrome. The glomeruli are usually the targets of these diseases for reasons that are not fully understood. In FSGS — the most common primary cause of nephrotic syndrome — scar tissue forms in parts of the glomeruli. In membranous nephropathy, immune molecules form harmful deposits on the glomeruli.

Nephrotic syndrome can also be caused by systemic diseases, which are diseases that affect many parts of the body, such as diabetes or lupus. Systemic diseases that affect the kidneys are called secondary causes of nephrotic syndrome.

More than 50 % of nephrotic syndrome cases in adults have secondary causes, with diabetes being the most common cause.

PRIMARY GLOMERULONEPHROSIS

Primary causes of nephrotic syndrome are usually described by their histology (tabl. 1).

Table 1

Histologic patterns and features of primary nephrotic syndrome

Histologic pattern	Key pathologic features	Key clinical features
Focal segmental glomerulosclerosis	Sclerosis and hyalinosis of segments of less than 50 % of all glomeruli on electron microscopy	May be associated with hypertension, renal insufficiency, and hematuria
Membranous nephropathy	Thickening of the glomerular basement membrane on electron microscopy; immunoglobulin G and C3 deposits with immunofluorescent staining	eak incidence at 30 to 50 years of age; may have microscopic hematuria; approximately 25 % of patients have underlying systemic disease, such as systemic lupus erythematosus, hepatitis B, or malignancy, or drug-induced nephrotic syndrome
Minimal change disease	Normal-appearing glomeruli on renal biopsy microscopy; effacement of foot processes on electron microscopy	Relatively mild or benign cases of nephrotic syndrome; may occur following upper respiratory infection or immunization

Minimal change disease (MCD): is the most common cause of nephrotic syndrome in children. It owes its name to the fact that the nephrons appear normal when viewed with an optical microscope as the lesions are only visible using an electron microscope. Another symptom is pronounced proteinuria.

Focal segmental glomerulosclerosis (FSGS): is the most common cause of nephrotic syndrome in adults. It is characterized by the appearance of tissue scarring in the glomeruli. The term focal is used as some of the glomeruli have scars, while others appear intact; the term segmental refers to the fact that only part of the glomerulus suffers the damage.

Membranous glomerulonephritis (MGN): The inflammation of the glomerular membrane causes increased leakage to the kidney. It is not clear why this condition develops in most people, although an auto-immune mechanism is suspected.

Membranoproliferative glomerulonephritis (MPGN): is the inflammation of the glomeruli along with the deposit of antibodies in their membranes, which makes filtration difficult.

Rapidly progressive glomerulonephritis (RPGN): (Usually presents as a nephritic syndrome) The patient's glomeruli are present in a crescent moon shape. It is characterized clinically by a rapid decrease in the glomerular filtration rate (GFR) by at least 50 % over a short period, usually from a few days to 3 months.

They are considered to be «diagnoses of exclusion», i. e. they are diagnosed only after secondary causes have been excluded.

SECONDARY GLOMERULONEPHROSIS

Secondary causes of nephrotic syndrome have the same histologic patterns as the primary causes, though they may exhibit some difference suggesting a secondary cause, such as inclusion bodies (tabl. 2). They are usually described by the underlying cause.

Table 2

Common secondary causes of nephrotic syndrome

Cause	Key features
Diabetes mellitus	Glucosuria, hyperglycemia, polyuria
Systemic lupus erythematosus	Anemia, arthralgias, autoantibodies, photosensitivity, pericardial or pleural effusion, rash
Hepatitis B or C	Elevated transaminases; high-risk sexual activity, history of transfusion, intravenous drug use, or other risk factors for disease transmission
Nonsteroidal anti-inflammatory drugs	Cause minimal change disease
Amyloidosis	Cardiomyopathy, hepatomegaly, peripheral neuropathy
Multiple myeloma	Abnormal urine protein electrophoresis, back pain, renal insufficiency
HIV	Pathologically similar to focal segmental glomerulosclerosis; risk factors for HIV transmission, possibly reduced CD4 cell count
Preeclampsia	Edema and proteinuria during pregnancy; elevated blood pressure

Diabetic nephropathy: is a complication that occurs in some diabetics. Excess blood sugar accumulates in the kidney causing them to become inflamed and unable to carry out their normal function. This leads to the leakage of proteins into the urine.

Systemic lupus erythematosus: this autoimmune disease can affect a number of organs, among them the kidney, due to the deposit of immunocomplexes that are typical to this disease. The disease can also cause lupus nephritis.

Sarcoidosis: This disease does not usually affect the kidney but, on occasions, the accumulation of inflammatory granulomas (collection of immune cells) in the glomeruli can lead to nephrotic syndrome.

Syphilis: kidney damage can occur during the secondary stage of this disease (between 2 and 8 weeks from the onset).

Hepatitis B: certain antigens present in hepatitis can accumulate in the kidneys and damage them.

Sjogren's syndrome: this autoimmune disease causes the deposit of immunocomplexes in the glomeruli, causing them to become inflamed, this is the same mechanism as occurs in systemic lupus erythematosus.

HIV: the virus antigens provoke an obstruction of the glomerular capillary lumen that alters normal kidney function.

Amyloidosis: deposition of amyloid substances (proteins with anomalous structures) in the glomeruli modifies their shape and function.

Multiple myeloma: renal impairment is caused by accumulation and precipitation of light chains, which form casts in the distal tubules, resulting in renal

obstruction. In addition, myeloma light chains are also toxic to proximal renal tubules, further contributing to renal dysfunction.

Vasculitis: inflammation of the blood vessels at a glomerular level impedes the normal blood flow and damages the kidney.

Cancer: as it occurs in myeloma, the invasion of the glomeruli by cancerous cells impairs their normal functioning.

Genetic disorders: congenital nephrotic syndrome is a rare genetic disorder in which the protein nephrin, a component of the glomerular filtration barrier, is altered.

Drugs (e. g. gold salts, penicillin, captopril): gold salts can cause a more or less important loss of proteins in urine as a consequence of metal accumulation. Penicillin is nephrotoxic in patients with kidney failure and captopril can aggravate proteinuria.

COMPLICATIONS OF NEPHROTIC SYNDROME

Nephrotic syndrome can be associated with a series of complications that can affect an individual's health and quality of life:

Thromboembolic disorders: particularly those caused by a decrease in blood antithrombin III levels due to leakage. Antithrombin III counteracts the action of thrombin. Thrombosis usually occurs in the renal veins although it can also occur in arteries. Treatment is with oral anticoagulants (not heparin as heparin acts via anti-thrombin 3 which is lost in the case of proteinuria so it will be ineffective.) Hypercoagulopathy due to extravasation of fluid from the blood vessels (edema) is also a risk for venous thrombosis.

Infections: The increased susceptibility of patients to infections can be a result of leakage of immunoglobulins from the blood, loss of proteins in general and the presence of oedematous fluid (which acts as a nutritive base for infections). The most common infection is peritonitis, followed by lung, skin and urinary infections, meningoencephalitis and in the most serious cases septicaemia. The most notable of the causative organisms are Streptococcus pneumoniae and Haemophilus influenzae. The clinical features and management of common serious infections are summarized in tabl. 3.

Spontaneous bacterial peritonitis can develop in case of existing ascites. This is a frequent development in children but very rarely found in adults.

Acute kidney failure due to hypovolemia: the loss of vascular fluid into the tissues (edema) produces a decreased blood supply to the kidneys that causes a loss of kidney function. Thus it is a tricky task to get rid of excess fluid in the body while maintaining circulatory euvolemia.

Pulmonary edema: loss of proteins from blood plasma and a consequent fall in oncotic pressure causes an abnormal accumulation of liquid in the lungs causing hypoxia and dyspnoea.

Table 3

Clinical features and management of infections

Infection	Clinical features	Common organisms	Antibiotics, duration of treatment
Peritonitis	Abdominal pain, tenderness, distension; diarrhea, vomiting; ascitic fluid >100 leukocy-tes/mm^3; > 50 % neutrophils	S. pneumoniae, S. pyogenes, E. coli	Cefotaxime or ceftriaxone for 7–10 days; ampicillin and an aminoglycoside for 7–10 days
Pneumonia	Fever, cough, tachypnea, intercostal recessions, crepitations	S. pneumoniae, H. influenzae, S. aureus	Amoxicillin, co-amoxiclav, erythromycin, ampicillin and aminoglycoside; or cefotaxime/ceftriaxone for 7–10 days
Cellulitis	Cutaneous erythema, induration, tenderness	Staphylococci, Group A streptococci, H. influenzae	Cloxacillin and ceftriaxone for 7–10 days co-amoxiclav
Fungal infections	Pulmonary infiltrates, persistent Fever unresponsive to antibiotics, sputum/urine showing septate hyphae	Candida, Aspergillus spp.	Skin, mucosa: fluconazole for 10 days Systemic: amphotericin for 14–21 days

Hypothyroidism: deficiency of the thyroglobulin transport protein thyroxin (a glycoprotein that is rich in iodine and is found in the thyroid gland) due to decreased thyroid binding globulin.

Vitamin D deficiency can occur. Vitamin D binding protein is lost.

Hypocalcaemia: lack of 25-hydroxycholecalciferol (the way that vitamin D is stored in the body). As vitamin D regulates the amount of calcium present in the blood, a decrease in its concentration will lead to a decrease in blood calcium levels. It may be significant enough to cause tetany. Hypocalcaemia may be relative; calcium levels should be adjusted based on the albumin level and ionized calcium levels should be checked.

Microcytic hypochromic anaemia: iron deficiency caused by the loss of ferritin (compound used to store iron in the body). It is iron-therapy resistant.

Protein malnutrition: this occurs when the amount of protein that is lost in the urine is greater than that ingested, this leads to a negative nitrogen balance.

Growth retardation: can occur in cases of relapse or resistance to therapy. Causes of growth retardation are protein deficiency from the loss of protein in urine, anorexia (reduced protein intake), and steroid therapy (catabolism).

Cushing's syndrome is a collection of signs and symptoms due to prolonged exposure to glucocorticoids such as cortisol. Signs and symptoms may include high blood pressure, abdominal obesity but with thin arms and legs, reddish stretch marks, around red face, a fat lump between the shoulders, weak muscles, weak bones, acne, and fragile skin that heals poorly. Women may have more hair and irregular menstruation. Occasionally there may be changes in mood, headaches, and a chronic feeling of tiredness.

DIAGNOSIS OF NEPHROTIC SYNDROME

Diagnostic studies for nephrotic syndrome may include the following:
- Urinalysis;
- Urine sediment examination;
- Urinary protein measurement;
- Serum albumin;
- Serologic studies for infection and immune abnormalities;
- Renal ultrasonography;
- Renal biopsy (tabl. 4).

In infants with nephrotic syndrome, genetic testing for the NPHS1 and NPHS2-mutations may be useful. These are mutations of nephrin and podocin, respectively. In children with steroid-resistant nephrotic syndrome, testing for the NPHS2-mutation may be indicated.

Table 4

Diagnostic evaluation in persons with nephrotic syndrome

Diagnostic studies	Disorder suggested
Baseline	
Patient history	Identify medication or toxin exposure; risk factors for HIV or viral hepatitis; and symptoms suggesting other causes of edema Obtain history of diabetes, systemic lupus erythematosus, or other systemic illness
Urine dipstick	Confirm proteinuria
Random urine protein/creatinine ratio	Quantify the degree of proteinuria (ratio greater than 3 to 3.5)
Serum creatinine	Rule out acute renal failure, assess glomerular filtration rate
Serum albumin	Assess the degree of hypoalbuminemia
Lipid panel	Assess the degree of hyperlipidemia
Additional studies suggested by patient factors	
HIV screening test	Identify HIV
Hepatitis serology panel	Identify hepatitis B or C
Serum or urine protein electrophoresis	Suggests amyloidosis or multiple myeloma
Rapid plasma reagin	Identify syphilis
Antinuclear antibodies or complement (C3 and C4) levels	Identify systemic lupus erythematosus; complement levels may also be reduced in membranoproliferative disease

URINE STUDIES

Urinalysis. Urinalysis is the first test used in the diagnosis of nephrotic syndrome. Nephrotic-range proteinuria will be apparent by 3+ or 4+ readings on the dipstick, or by semiquantitative testing by sulfosalicylic acid. A 3+ reading represents 300 mg/dL of urinary protein or more, which correlates with a daily loss of 3 g or more and thus is in the nephrotic range. The chemistry of the dipsticks is such that albumin is the major protein that is tested.

Glucosuria points to diabetes.

Urine sediment examination. The urine sediment exam may show cells and/or casts.

Waxy casts mark proteinuric renal disease. By use of a polarizing microscope, one can see oval fat bodies and also fatty casts. These point to the nephrotic syndrome. They occur because of glomerular filtration of lipoproteins; the tubular cells that endocytose these lipoproteins then fall off into the urine. Viewed by polarizer, the oval fat bodies and fatty casts cause a «Maltese cross» appearance.

The presence of more than 2 red blood cells (RBCs) per high power field is indicative of microhematuria. Microhematuria may occur in membranous nephropathy but not in minimal-change nephropathy.

Glomerular disease may allow RBCs to traverse the damaged glomerular basement membrane, and the RBCs in the sediment may then be deformed, or dysmorphic. This points to glomerular disease with inflammation and destruction of the normal structures (ie, a nephritis, and thus a nephritic picture, with hematuria, oliguria, azotemia, and hypertension). This could occur in, for example, nephrotic syndromes associated with IgA nephropathy or proliferative glomerulonephritis.

More than 2 granular casts in the entire sediment is a biomarker for renal parenchymal disease. Variable-caliber and broad granular casts point to reduced renal function.

Urinary protein measurement. Albuminuria refers to the presence of urine albumin 30 to 300 mg per day. Microalbumin, considered an obsolete term as there is no such biochemical molecule, is now referred to simply as urine albumin. Albuminuria is used as a marker for detection of incipient nephropathy in diabetics; it is an independent marker for the cardiovascular disease since it indicated increased endothelial permeability and is also a marker of chronic renal impairment. Urine albumin may be measured in 24-hour urine collections or early morning/random specimens as an albumin/creatinine ratio. Presence of albuminuria on two occasions with the exclusion of a urinary infection indicates glomerular dysfunction. The presence of albuminuria for 3 or more months is indicative of chronic kidney disease. Frank proteinuria is defined as greater than 300 mg per day of protein. Normal urine protein is up to 150 mg per day (30 % albumin; 30 % globulins; 40 % Tamm Horsfall protein). Increased amounts of protein in urine may be due to:

– Glomerular proteinuria: Caused by defects in permanent selectivity of the glomerular filtration barrier to plasma proteins (for example, glomerulonephritis or nephrotic syndrome)

– Tubular proteinuria: Caused by incomplete tubular reabsorption of proteins (for example, interstitial nephritis)

– Overflow proteinuria: Caused by increased plasma concentration of proteins (for example, multiple myeloma-Bence Jones protein, myoglobinuria)

– Urinary tract inflammation or tumor

Urine protein may be measured using either a 24-hour urine collection or random urine protein: creatinine ratio (early morning sample is preferred and is more representative of the 24-hour sample).

The KDIGO classification defines 3 stages of albuminuria:

– A1: Less than 30 mg/g creatinine
– A2: 30 to 300 mg/g creatinine
– A3: Greater than 300 mg/g creatinine

In nephrotic syndrome, urine protein excretion exceeds 3.5 g per day and is associated with edema, hypoalbuminemia, and hypercholesterolemia (tabl. 5, 6).

Table 5

Examination findings of primary nephrotic syndrome

Examination	Measurement items	Major findings
Urinalysis	Urine volume, urine protein increase: urine protein, albuminemia (24-h collection or spot urine) fatty cast, oval fat body. Fraction of urine protein. Occult blood, urinary sediments. Granular cast, waxy cast. Selectivity of urine protein (clearance ration of IgG and transferrin)	Increase: urine protein, albuminemia fatty cast, oval fat body
Blood examination	Peripheral blood examination	red blood cell, hemoglobin are decreased
	Biochemical examination	Decrease: total protein, albumin Sometimes decrease: Na, vitamin D, GFR
	Lipid examination	Increase: total cholesterol, LDL, VLDL, La(a) ApoB, ApoC II, HDL-3 Stable: HDL Decrease: HDL-2
	Coagulation test	Increase: fibrinogen, FDP, D-dimer Decrease: antithrombin III, plasminogen
	Immunological test	Decrease: IgG and other immunoglobulins, complements
Chest X-ray	Cardiothoratic ratio, pulmonary vascular shadow cost-phrenic angle shadow of lung field	Sometimes: pulmonary congestion
Ultrasonography	Deep vein thrombosis in lower extremities	Collapse of venous system due to decrease of circular blood volume
Renal biopsy	Light microscopy Immunofluorescence microscopy	The definitive diagnosis is usually determined on electron microscopy by renal biopsy

Table 6

Examination findings of secondary nephrotic syndrome

Examination	Measurement items	Major findings
Urinalysis	Occult blood Urine Bence Jones protein	Positive in purpura nephritis or vasculitis positive in paraproteinemia

End tabl. 6

Examination	Measurement items	Major findings
Blood examination	Peripheral blood examination	Pancytopenia or hemolytic anemia in lupus nephritis Leukocytosis and thrombocytosis in cases of infectious diseases and vasculitis
	Biochemical examination	Blood sugar markers such as blood glucose, HbA1c, and glycoalbumin in diabetic nephropathy CRP and inflammatory reactions increase in vasculitis and purpura nephritis Paraprotein or cryoglobumin is confirmed in in cases of paraproteinemia
	Lipid examination	The abnormality of IDL or ApoE is confirmed in lipoprotein glomerulopathy
	Immunological test	Anti-nuclear antibody , anti-ds-DNA antibody, anti-Sm antibody, anti-phosphlipid antibody increase and complements decrease in lupus nephritis. The positive findings are confirmed in bacterial culture and antigen/antibody detection for pathogenic microbes.
Imaging test		Neoplastic diseases are diagnosed by various imaging tests such as CT, MRI, ultrasonography and bone marrow aspiration.
Genetic test		Genetic tests are useful in the genetic illnesses.
Renal biopsy		The specific findings are observed in each secondary disease, thus the renal biopsy is useful for the definitive diagnosis of secondary diseases.

Renal Biopsy. Adult nephrotic syndrome of unknown origin may require a renal biopsy for diagnosis. Reaching a pathological diagnosis is important because minimal-change disease, focal glomerulosclerosis, and membranous nephropathy have different treatment options and prognoses. It is important to differentiate minimal-change disease presenting in adults from focal glomerulosclerosis, as the former has an excellent response to steroids. Another entity called immunoglobulin M (IgM) nephropathy falls in between the two and has an intermediate response to steroids.

A renal biopsy is not indicated in adults with nephrotic syndrome from an obvious cause. For example, in a patient with longstanding diabetes and diabetic retinopathy, the nephrotic syndrome is likely to be secondary to diabetic nephropathy, so kidney biopsy may be unnecessary. However, it is important not to consider diabetic nephropathy as the only causative factor for nephrotic syndrome in all diabetic persons. A duration of diabetes of less than 5 years and the absence of retinopathy and neuropathy are clues to non-diabetic kidney disease.

It is worth noting that in clinical experience with kidney biopsies, the cause of nephrotic-range proteinuria is glomerular disease, not tubular disease. This contradicts the proposal that tubular function determines proteinuria.

Indications for kidney biopsy

At onset

Age of onset < 1 year
Gross hematuria, persistent microscopic hematuria or low serum C3
Sustained hypertension
Renal failure not attributable to hypovolemia
Suspected secondary causes of nephrotic syndrome

After initial treatment

Proteinuria persisting despite 4-weeks of daily corticosteroid therapy
Before treatment with cyclosporin A or tacrolimus

LABORATORY STUDIES

Kidney function. Serum tests for kidney function are essential. Serum creatinine will be in the normal range in uncomplicated nephrotic syndrome, such as that occurring in minimal-change nephropathy. In children, the serum creatinine level will be lower than it is in adults. The normal adult serum creatinine level is approximately 1 mg/dL, whereas that of a child aged 5 years will be about 0.5 mg/dL. Values higher than this in children indicate reduced kidney function.

There are a number of clinical laboratory tests that are useful in investigating and evaluating kidney function. Clinically, the most practical tests to assess renal function is to get an estimate of the glomerular filtration rate (GFR) and to check for proteinuria (albuminuria).

Glomerular Filtration Rate. The best overall indicator of the glomerular function is the glomerular filtration rate (GFR). The normal GFR for an adult male is 90 to 120 mL per minute. GFR is the rate in milliliters per minutes at which substances in plasma are filtered through the glomerulus, in other words, the clearance of a substance from the blood. The characteristics of an ideal marker of GFR are as follows:

- It should appear endogenously in the plasma at a constant rate.
- It should be freely filtered by the glomeruli.
- It can be neither reabsorbed nor secreted by the renal tubule.
- It should not undergo extrarenal elimination.

As no such endogenous marker currently exists, exogenous markers of GFR are used. Assessment of GFR using inulin, a polysaccharide, is considered the reference method for assessment of GFR. It involves the infusion of inulin and then measurement of blood levels after a specified period to determine the rate of clearance of inulin. Other exogenous markers used are radioisotopes such as chromium-51 ethylene-diamine-tetra-acetic acid (51 Cr-EDTA), and technetium-99-labeled diethylene-triamine-pentaacetate (99 Tc-DTPA). The most promising exogenous marker is the non-radioactive contrast agent, iohexol, especially in children.

The inconvenience associated with the use of exogenous markers, specifically that testing has to be performed in specialized centers, and the difficulty to assay these substances, has encouraged the use of endogenous markers.

Creatinine. The most commonly used endogenous marker for assessment of glomerular function is creatinine. The calculated clearance of creatinine is used to provide an indicator of GFR. This involves the collection of urine over a 24-hour period or preferably over an accurately timed period of 5 to 8 hours since 24-hour collections are notoriously unreliable. Creatinine clearance is then calculated using the equation:

$$C = (U \times V) / P,$$

C = clearance, U = urinary concentration; V = urinary flow rate (volume/time i. e. ml/min); P = plasma concentration

Creatinine clearance should be corrected for body surface area. Improper or incomplete urine collection is one of the major issues affecting the accuracy of this test, hence timed collection is advantageous. Furthermore, due to tubular secretion, creatinine overestimates GFR by around 10 % to 20 %.

Creatinine is the by-product of creatine phosphate in muscles, and it is produced at a constant rate by the body. For the most part, creatinine is cleared from the blood entirely by the kidney. Decreased clearance by the kidneys results in an increased blood creatinine. The amount of creatinine produced per day depends on the muscle bulk, and thus, there is a difference in creatinine ranges between males and females with lower creatinine values in children and those with decreased muscle bulk. The Diet also influences creatinine values. Creatinine can change as much as 30% after ingestion of red meat. As GFR increases in pregnancy, lower creatinine values are found in pregnancy. Additionally, serum creatinine is a later indicator of renal impairment — renal function is decreased by 50 % before a rise in serum creatinine is observed.

Serum creatinine is also utilized in GFR estimating equations such as the Modified Diet in Renal Disease (MDRD) and the CKD-EPI equation. These eGFR equations are superior to serum creatinine alone since they include race, age, and gender variables. GFR is classified into the following stages based on the kidney disease.

Improving Global Outcomes (KDIGO) stages of chronic kidney disease (CKD):

- Stage 1: GFR greater than 90 ml/min/1.73 m;
- Stage 2: GFR-between 60 to 89 ml/min/1.73 m;
- Stage 3a: GFR 45 to 59 ml/min/1.73 m;
- Stage 3b: GFR 30 to 44 ml/min/1.73 m;
- Stage 4: GFR of 15 to 29 ml/min/1.73 m;
- Stage 5: GFR less than 15 ml/min/1.73 m (end-stage renal disease).

These provide an easier estimation of GFR without collection of urine or use of exogenous materials. However, as they utilize serum creatinine, they are also affected by the issues around serum creatinine measurement, hence the correction for race, gender, and age.

Blood Urea Nitrogen (BUN). Urea or BUN is a nitrogen-containing compound formed in the liver as the end product or protein metabolism and urea cycle.

About 85 % of urea is eliminated via kidneys; the rest is excreted via the gastrointestinal (GI) tract. Serum urea is increased in conditions where renal clearance decreased (in acute and chronic renal failure/impairment). Urea may also increase in other conditions not related to renal diseases such as upper GI bleeding, dehydration, catabolic states, and high protein diets. Urea may be decreased in starvation, low-protein diet, and severe liver disease. Serum creatinine is a more accurate assessment of renal function than urea; however, urea is increased earlier in renal disease.

The ratio of BUN: Creatinine can be useful to differentiate prerenal from renal causes when the BUN is increased. In pre-renal disease the ratio is close to 20:1, while in intrinsic renal disease it is closer to 10 : 1.

Cystatin C. Cystatin C is a low-molecular-weight protein which functions as a protease inhibitor produced by all nucleated cells in the body. It is formed at a constant rate and freely filtered by the kidneys. Serum levels of cystatin C are inversely correlated with the glomerular filtration rate. In other words, high values indicate low GFRs, while lower values indicate higher GFRs, similar to creatinine. The renal handling of cystatin C differs from creatinine. While both are freely filtered by glomeruli, once cystatin C is filtered, it is reabsorbed and metabolized by proximal renal tubules, unlike creatinine. Thus, under normal conditions, cystatin C does not enter the final excreted urine to any significant degree. Cystatin C is measured in serum and urine. The advantages of cystatin C over creatinine are that it is not affected by age, muscle bulk, or diet, and various reports have indicated that it is a more reliable marker of GFR than creatinine particularly in early renal impairment. Cystatin C has also been incorporated into eGFR equations such as the combined creatinine-cystatin KDIGO CKD-EPI equation.

Cystatin C concentration may be affected by the presence of cancer, thyroid disease, and smoking.

Serologic studies. In adults with nephrotic syndrome, tests for hepatitis B and C, HIV, and even syphilis may be useful. Tests for lupus, including antinuclear antibody (ANA), anti–double stranded DNA (anti-dsDNA) antibodies, and complement, may be useful. Testing for antineutrophil cytoplasmic antibodies (ANCA) is not indicated in typical nephrotic syndrome, because that test is associated with rapidly progressive glomerulonephritis, which presents with a nephritic picture rather than one that is typically nephrotic.

Tests for previous streptococcal infection, such as antistreptolysin O, are not usually indicated for nephrotic syndrome, since postinfectious glomerulonephritis usually causes a nephritic rather than a nephrotic syndrome.

Phospholipase A2 receptor. Phospholipase A2 receptor (PLA2 R) is a cell surface transmembrane receptor expressed on the surface of podocytes. Seventy percent of patients with idiopathic membranous nephropathy have autoantibodies directed against PLA2 R. Levels of this antibody have a strong correlation with clinical disease activity and thus help in monitoring disease activity and treatment efficacy. Absence of these antibodies may suggest secondary membranous nephropathy such as that associated with cancers.

During treatment, the levels of the antibodies generally decline before remission of proteinuria. After treatment, about half the patients who are PLA2R negative remain in remission for 5 years, but those who remain PLA2R positive relapse in just 2 years. Use of the PLA2R antibody test has changed the diagnosis and treatment of idiopathic membranous nephropathy.

ULTRASONOGRAPHY

Ultrasonographic scanning shows whether a patient has two kidneys. Individuals with a single kidney may be prone to developing focal glomerulosclerosis. Having only one kidney is also a relative contraindication to kidney biopsy. Ultrasonography also demonstrates renal echogenicity. Increased renal echogenicity is consistent with intrarenal fibrosis (i. e., chronic disease with reduced kidney function).

DIFFERENTIAL DIAGNOSIS

Some symptoms that are present in nephrotic syndrome, such as edema and proteinuria, also appear in other illnesses. Therefore, other pathologies need to be excluded in order to arrive at a definitive diagnosis.

Edema: in addition to nephrotic syndrome there are two other disorders that are often present with edema; these are heart failure and liver failure. Congestive heart failure can cause liquid retention in tissues as a consequence of the decrease in the strength of ventricular contractions. The liquid is initially concentrated in the ankles but it subsequently becomes generalized and is called anasarca. Patients with congestive heart failure also experience an abnormal swelling of the heart cardiomegaly, which aids in making a correct diagnosis. Jugular venous pressure can also be elevated and it might be possible to hear heart murmurs. An echocardiogram is the preferred investigation method for these symptoms.

Liver failure caused by cirrhosis, hepatitis and other conditions such as alcoholism, drug use or some hereditary diseases can lead to swelling in the lower extremities and the abdominal cavity. Other accompanying symptoms include jaundice, dilated veins over umbilicus («caput medusa»), scratch marks (due to widespread itching, known as pruritus), enlarged spleen, spider angiomata, encephalopathy, bruising, nodular liver and anomalies in the liver function tests. Less frequently symptoms associated with the administration of certain pharmaceutical drugs have to be considered. These drugs promote the retention of liquid in the extremities such as occurs with NSAIs, some antihypertensive drugs, the adrenal corticosteroids and sex hormones.

Acute fluid overload can cause edema in someone with kidney failure. These people are known to have kidney failure, and have either drunk too much or missed their dialysis. In addition, when metastatic cancer spreads to the lungs or abdomen it causes effusions and fluid accumulation due to obstruction of lymphatic vessels and veins, as well as serous exudation.

Proteinuria: the loss of proteins from the urine is caused by many pathological agents and infection by these agents has to be ruled out before it can be certain that a patient has nephrotic syndrome. Multiple myeloma can cause a proteinuria that is not accompanied by hypoalbuminemia, which is an important aid in making a differential diagnosis; other potential causes of proteinuria include asthenia, weight loss or bone pain. In diabetes mellitus there is an association between increases in glycated hemoglobin levels and the appearance of proteinuria. Other causes are amyloidosis and certain other allergic and infectious diseases.

TREATMENT OF NEPHROTIC SYNDROME

Treating nephrotic syndrome includes addressing the underlying cause as well as taking steps to reduce high blood pressure, edema, high cholesterol, and the risks of infection. Treatment usually includes medications and changes in diet.

Medications that lower blood pressure can also significantly slow the progression of kidney disease causing nephrotic syndrome. Two types of blood pressure lowering medications, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), have proven effective in slowing the progression of kidney disease by reducing the pressure inside the glomeruli and thereby reducing albuminuria. Many people require two or more medications to control their blood pressure. In addition to an ACE inhibitor or an ARB, a diuretic — a medication that aids the kidneys in removing fluid from the blood — can also be useful in helping to reduce blood pressure as well as edema. Beta blockers, calcium channel blockers, and other blood pressure medications may also be needed.

Diuretics are the mainstay of medical management; however, there is no evidence to guide drug selection or dosage. Based on expert opinion, diuresis should aim for a target weight loss of 1 to 2 lb (0,5 to 1 kg) per day to avoid acute renal failure or electrolyte disorders.

Loop diuretics, such as furosemide or bumetanide, are most commonly used. Large doses (e. g., 80 to 120 mg of furosemide) are often required, and these drugs typically must be given intravenously because of the poor absorption of oral drugs caused by intestinal edema. Low serum albumin levels also limit diuretic effectiveness and necessitate higher doses. Thiazide diuretics, potassium-sparing diuretics, or metolazone may be useful as adjunctive or synergistic diuretics (fig. 2).

Treatment with **corticosteroids** remains controversial in the management of nephrotic syndrome in adults. It has no proven benefit, but is recommended in some persons who do not respond to conservative treatment. Treatment of children with nephrotic syndrome is different, and it is more clearly established that children respond well to corticosteroid treatment.

Classically, minimal change disease responds better to corticosteroids than FSGS; however, this difference is found primarily in children with nephrotic syndrome. One older study found that corticosteroid treatment improved proteinuria

and renal function in persons with minimal change disease, but not membranous nephropathy or proliferative glomerulonephritis. Another small older study found that persons with less severe glomerular changes responded well to corticosteroids. One case series in black persons with FSGS found no benefit from corticosteroid treatment. Two Cochrane reviews on the treatment of nephrotic syndrome in adults found no benefit for mortality or need for dialysis with corticosteroid therapy for membranous nephropathy or minimal change disease, but found a weak benefit for disease remission and proteinuria in persons with membranous nephropathy.

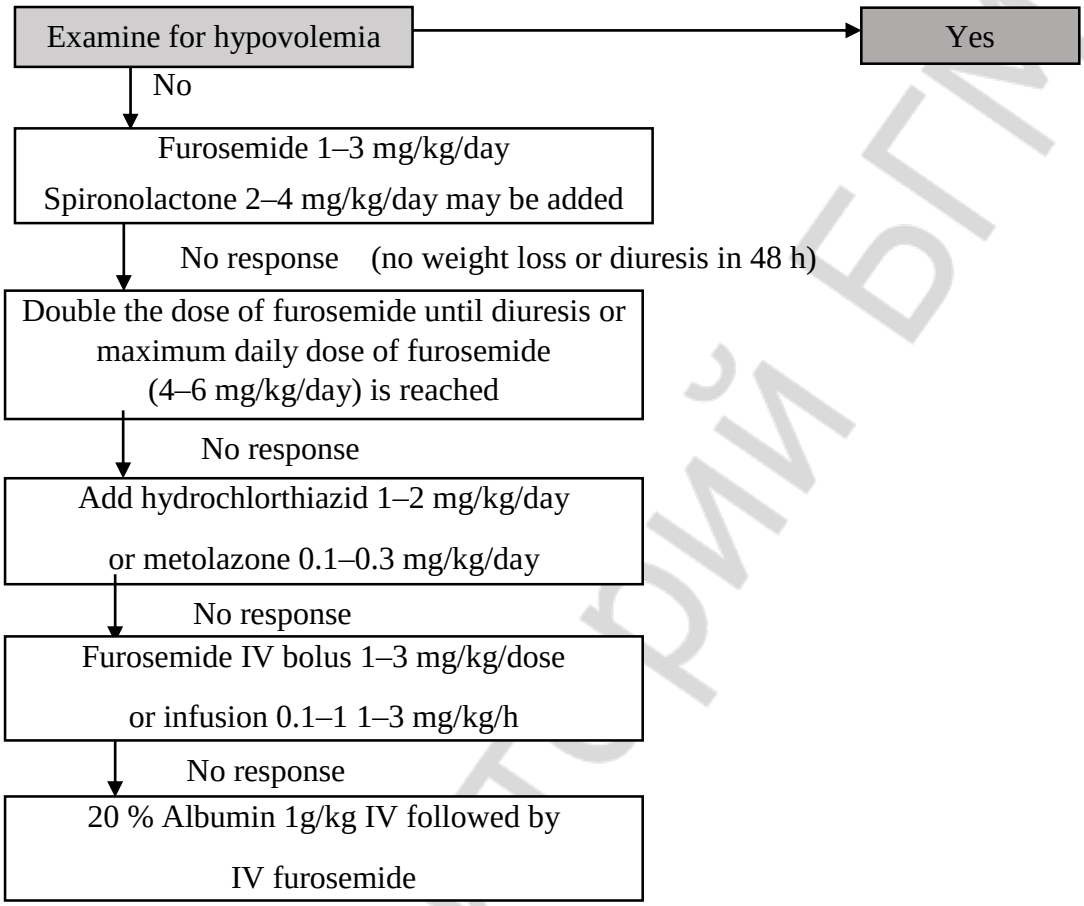

Fig. 2. Management of edema in patients with nephrotic syndrome [9]

However, the findings for minimal change disease were based on only one randomized trial, and the role of corticosteroid treatment remains unclear. Many experts recommend the use of corticosteroids, particularly for persons with minimal change disease; however, adverse effects from corticosteroids often lead to discontinuation.

The classification by the response to treatment of nephrotic syndrome.

Steroid resistant nephrotic syndrome: The sufficient dose of steroid treatment fails to achieve complete remission or incomplete remission I within 1 month after the initiation of treatment.

Refractory nephrotic syndrome: The various treatments including steroid and immunosuppressive agents fail to achieve complete remission or incomplete remission I within 6 months after the initiation of treatment.

Steroid dependent nephrotic syndrome: Steroid treatment is impossible to discontinue, because repeated over 2 times relapses appear after the reduction or discontinuation of steroid

Frequent relapse nephrotic syndrome: Over 2 times relapses appear in 6 months

Nephrotic syndrome requiring chronic treatment: Nephrotic syndrome to be treated by steroid or immunosuppressive agents over 2 years (fig. 3).

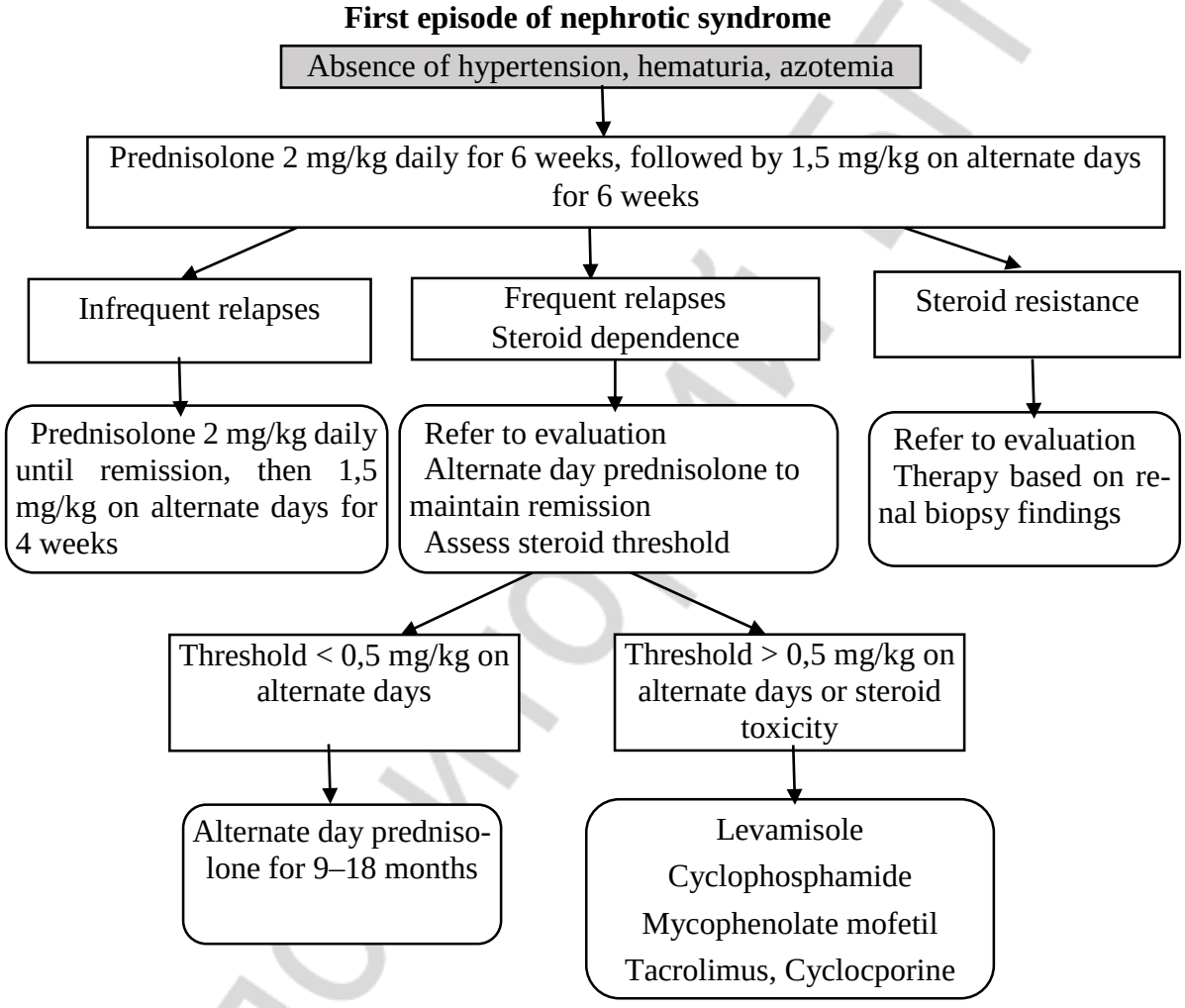

Fig. 3. Management of patients with steroid-sensitive nephrotic syndrome

Family physicians should discuss with patients and consulting nephrologists whether treatment with corticosteroids is advisable, weighing the uncertain benefits and possibility of adverse effects. Alkylating agents (e. g., cyclophosphamide also have weak evidence for improving disease remission and reducing proteinuria, but may be considered for persons with severe or resistant disease who do not respond to corticosteroids.

Statin medications may be given to lower cholesterol.

People with nephrotic syndrome should receive **the pneumococcal vaccine**, which helps protect against a bacterium that commonly causes infection, and yearly flu shots.

Blood thinning medications are usually given only to people with nephrotic syndrome who develop a blood clot; these medications are not used as a preventive measure (tabl. 7).

Table 7

The main groups of drugs for the treatment of nephrotic syndrome

	Effect	Group of drugs	
Blood pressure medications	Reduce blood pressure and also reduce the amount of protein released in urine	Angiotensin-converting enzyme (ACE)	Lisinopril captopril enalapril
		Angiotensin II receptor blockers (ARBs)	Losartan valsartan
Water pills (Diuretics)	help control swelling by increasing the kidneys' fluid output	High ceiling/loop diuretic	furosemide
		Potassium-sparing diuretics	spironolactone
		Thiazides	hydrochlorothiazide
Cholesterol-reducing medications	help lower cholesterol levels	atorvastatin fluvastatin lovastatin pravastatin rosuvastatin simvastatin	
Blood thinners / anticoagulants	decrease the ability of blood to clot	heparin warfarin dabigatran apixaban rivaroxaban	
Immune system-suppressing medications	may decrease the inflammation	Corticosteroids Prednisolone	

Eating, diet, and nutrition have not been shown to play a role in causing or preventing nephrotic syndrome in adults. For people who have developed nephrotic syndrome, limiting intake of dietary sodium, often from salt, and fluid may be recommended to help reduce edema. A diet low in saturated fat and cholesterol may also be recommended to help control hyperlipidemia.

Therapeutic evaluation of nephrotic syndrome

The therapeutic evaluation is done by the amount of urine protein in 1 and 6 months after the initiation of treatment:

- *Complete remission*: urine protein <3.0 g/day
- *Incomplete remission I*: 0.3 g/day ≤ urine protein < 1.0 g/day
- *Incomplete remission II*: 1.0 g/day ≤ urine protein < 3.5 g/day
- *Non-response:* urine protein ≥ 3.5 g/day

The diagnosis of nephrotic syndrome and therapeutic evaluation should be done by 24-hour urine collection. If it is impossible to collect 24-hour urine, the ratio of urine protein and urine creatinine (g/gCr) in spot urine is available for the diagnosis of nephrotic syndrome and therapeutic evaluation

In principle, the evaluation of complete remission or incomplete remission within 6 months after the initiation of treatment includes the improvement of clinical findings and serum albumin.

PROGNOSIS

The prognosis for nephrotic syndrome under treatment is generally good although this depends on the underlying cause, the age of the patient and their response to treatment. It is usually good in children, because minimal change disease responds very well to steroids and does not cause chronic renal failure. Any relapses that occur become less frequent over time; the opposite occurs in case of mesangiocapillary glomerulonephritis, in which the kidney fails within three years of the disease developing, making dialysis and subsequent kidney transplant necessary. In addition, children under the age of 5 generally have a poorer prognosis than prepubescents, as do adults older than 30 years of age as they have a greater risk of kidney failure.

Other causes such as focal segmental glomerulosclerosis frequently lead to terminal stage of renal disease. Factors associated with a poorer prognosis in these cases include the level of proteinuria, blood pressure control and kidney function (GFR).

Without treatment nephrotic syndrome has a very bad prognosis, especially in rapidly progressing glomerulonephritis, which leads to acute kidney failure after a few months.

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NEPHROTIC SYNDROME IN OUTPATIENT PRACTICE

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На английском языке

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