

**MINISTRY OF HEALTHCARE OF UKRAINE
HSEEU "Ukrainian Medical Stomatological Academy"**

"Approved"
at the meeting of internal
medicine №1 department
Head of Department
Prof. Skrypnyk I.M.

Protocol № 4 from 13.10.2016

**GUIDELINES
FOR STUDENTS
INDEPENDENT WORK
IN THE PRACTICAL CLASSES PREPARING**

<i>Academic discipline</i>	Internal medicine
<i>Module</i>	Current practice of internal medicine
<i>Content module</i>	Management of the patients with main symptoms and syndromes in nephrology clinic
<i>Study subject</i>	Management of the patients with nephrotic syndrome
<i>Course</i>	VI
<i>Faculty</i>	of foreign students training

1. The aims of the training course:

To Know:

1. Differential diagnosis the oedema of different origin (heart, kidney, alimentary, etc.).
2. Test plan, the role of instrumental and laboratory methods of examination (ultrasound, X-ray, ECG, general and biochemical tests, urine tests for Zymnitsky, Nechiporenko).
3. Drug and non-medicamentous treatment.
4. Advantages and disadvantages of diuretic therapy.
5. Existing standards of treatment.
6. Primary and secondary prevention.
7. Weather and performance.

To be able to:

- Conduct surveys and examination of patients with major nephrological syndromes
- Know the basic invasive and noninvasive diagnostic techniques used in nephrology, indications and contraindications for their conduct, possible complications
- identify major and atypical variants of the course and complications of urinary system diseases
- draft examination of patients with major nephrological syndromes
- Based on analysis of laboratory and instrumental examination to conduct differential diagnosis, justify and formulate diagnoses for diseases of urinary system
- prescribe treatment, determine prognosis, to conduct primary and secondary prevention
- diagnose and assist in renal insufficiency

The contents of topic:

Text

Background

Merck Manual Professional Version <http://www.merckmanuals.com/professional>

Last full review/revision March 2013 by Navin Jaipaul, MD, MHS

Nephrotic syndrome is urinary excretion of > 3 g of protein/day due to a glomerular disorder plus edema and hypoalbuminemia. It is more common among children and has both primary and secondary causes. Diagnosis is by determination of urine protein/creatinine ratio in a random urine sample or measurement of urinary protein in a 24-h urine collection; cause is diagnosed based on history, physical examination, serologic testing, and renal biopsy. Prognosis and treatment vary by cause.

Etiology

Nephrotic syndrome occurs at any age but is more prevalent in children, mostly between ages 1½ and 4 yr. Congenital nephrotic syndromes appear during the first year of life. At younger ages, boys are affected more often than girls, but both are affected equally at older ages. Causes differ by age and may be primary or secondary.

The **most common primary causes** are the following:

- Minimal change disease
- Focal segmental glomerulosclerosis
- Membranous nephropathy

Secondary causes account for < 10% of childhood cases but > 50% of adult cases, most commonly the following:

- Diabetic nephropathy
- Preeclampsia

Amyloidosis, an underrecognized cause, is responsible for 4% of cases.

HIV-associated nephropathy is a type of focal segmental glomerulosclerosis that occurs in patients with AIDS

Pathophysiology

Proteinuria occurs because of 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 and secondary glomerular diseases, but evidence suggests that T cells may up-regulate a circulating permeability factor or down-regulate an inhibitor of permeability factor in response to unidentified immunogens and cytokines. Other possible factors include hereditary defects in proteins that are integral to the slit diaphragms of the glomeruli, activation of complement leading to damage of the glomerular epithelial cells and loss of the negatively charged groups attached to proteins of the GBM and glomerular epithelial cells.

Complications

The disorder results in urinary loss of macromolecular proteins, primarily albumin but also opsonins, immunoglobulins, erythropoietin, transferrin, hormone-binding proteins (including thyroid-binding globulin and vitamin D-binding protein), and antithrombin III. Deficiency of these and other proteins contribute to a number of complications; other physiologic factors also play a role.

Symptoms and Signs

Primary symptoms include anorexia, malaise, and frothy urine (caused by high concentrations of protein). Fluid retention may cause dyspnea (pleural effusion or laryngeal edema), arthralgia (hydrarthrosis), or abdominal pain (ascites or, in children, mesenteric edema).

Corresponding signs may develop, including peripheral edema and ascites. Edema may obscure signs of muscle wasting and cause parallel white lines in fingernail beds (Muehrcke lines).

Other symptoms and signs are attributable to the many complications of nephrotic syndrome.

Diagnosis

- Urine random (spot) protein/creatinine ratio ≥ 3 or proteinuria ≥ 3 g/24 h
- Serologic testing and renal biopsy unless the cause is clinically obvious

Diagnosis is suspected in patients with edema and proteinuria on urinalysis and confirmed by random (spot) urine protein and creatinine levels or 24-h measurement of urinary protein. The cause may be suggested by clinical findings (eg, SLE, preeclampsia, cancer); when the cause is unclear, additional (eg, serologic) testing and renal biopsy are indicated.

Urine testing

A finding of significant **proteinuria** (3 g protein in a 24-h urine collection) is diagnostic (normal excretion is <150 mg/day). Alternatively, the protein/creatinine ratio in a random urine specimen usually reliably estimates grams of protein/ 1.73 m^2 BSA in a 24-h collection (eg, values of 40 mg/dL protein and 10 mg/dL creatinine in a random urine sample are equivalent to the finding of 4 g/ 1.73 m^2 in a 24-h specimen). Calculations based on random specimens may be less reliable when creatinine excretion is high (eg, during athletic training) or low (eg, in cachexia). However, calculations based on random specimens are usually preferred to 24-h collection because random collection is more convenient and less prone to error (eg, due to lack of adherence); more convenient testing facilitates monitoring changes that occur during treatment.

Besides proteinuria, **urinalysis** may demonstrate casts (hyaline, granular, fatty, waxy,- 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, suggests a glomerular disorder causing nephrotic syndrome. Urinary cholesterol can be detected with plain microscopy and demonstrates a Maltese cross pattern under crossed polarized light; Sudan staining must be used to show triglycerides.

Adjunctive testing

Adjunctive testing helps characterize severity and complications.

- BUN and creatinine concentrations vary by degree of renal impairment.
- Serum albumin often is < 2.5 g/dL.
- Total cholesterol and triglyceride levels are typically increased.

It is not routinely necessary to measure levels of α - and γ -globulins, immunoglobulins, hormone-binding proteins, ceruloplasmin, transferrin, and complement components, but these levels may also be low.

Secondary causes

The role of testing for secondary causes is controversial because yield may be low. Tests are best done as indicated by clinical context. Tests may include the following:

- Serum glucose or glycosylated Hb (HbA_{1c})
- Antinuclear antibodies
- Hepatitis B and C serologic tests
- Serum or urine protein electrophoresis
- Cryoglobulins
- Rheumatoid factor
- Serologic test for syphilis (eg, rapid plasma reagin)
- HIV antibody test
- Complement levels (CH50, C3, C4)

Test results may alter management and preclude the need for biopsy. For example, demonstration of cryoglobulins suggests mixed cryoglobulinemia (eg, from chronic inflammatory disorders such as SLE, Sjögren syndrome, or hepatitis C virus infection), and demonstration of a monoclonal protein on serum or urine protein electrophoresis suggests a monoclonal gammopathy (eg, multiple myeloma), especially in patients > 50 yr who have anemia.

Renal biopsy is indicated in adults to diagnose the disorder causing idiopathic nephrotic syndrome. Idiopathic nephrotic syndrome in children is most likely minimal change disease and is usually presumed without biopsy unless the patient fails to improve during a trial of corticosteroids. Specific biopsy findings are discussed under the individual disorders.

Prognosis

Prognosis varies by cause. Complete remissions may occur spontaneously or with treatment. The prognosis generally is favorable in corticosteroid-responsive disorders.

In all cases, prognosis may be worse in the presence of the following:

- Infection
- Hypertension
- Significant azotemia
- Hematuria
- Thromboses in cerebral, pulmonary, peripheral, or renal veins

The recurrence rate is high in kidney transplantation patients with focal segmental glomerulosclerosis, IgA nephropathy, and membranoproliferative glomerulonephritis (especially type 2).

Treatment

- Treatment of causative disorder
- Angiotensin inhibition
- Na restriction

- Statins
- Diuretics for excessive fluid overload
- Rarely, nephrectomy

Causative disorder

Treatment of underlying disorders may include prompt treatment of infections (eg, staphylococcal endocarditis, malaria, syphilis, schistosomiasis), allergic desensitization (eg, for poison oak or ivy and insect antigen exposures), and stopping drugs (eg, gold, penicillamine, NSAIDs); these measures may cure nephrotic syndrome in specific instances.

Proteinuria

Angiotensin inhibition (using ACE inhibitors or angiotensin II receptor blockers) is indicated to reduce systemic and intraglomerular pressure and proteinuria. These drugs may cause or exacerbate hyperkalemia in patients with moderate to severe renal insufficiency.

Protein restriction is no longer recommended because of lack of demonstrated effect on progression.

Edema

Na restriction (< 2 g Na, or about 100 mmol/day) is recommended for patients with symptomatic edema.

Loop diuretics are usually required to control edema but may worsen preexisting renal insufficiency and hypovolemia, hyperviscosity, and hypercoagulability and thus should be used only if Na restriction is ineffective or there is evidence of intravascular fluid overload.

Hyperlipidemia

Statins are indicated for hyperlipidemia.

Limitation of saturated fat and cholesterol intake is recommended to help control hyperlipidemia.

Hypercoagulability

Anticoagulants are indicated for treatment of thromboembolism, but few data exist to support their use as primary prevention.

Infection risk

All patients should receive pneumococcal vaccination if not otherwise contraindicated.

Nephrectomy

Rarely, bilateral nephrectomy is necessary in severe nephrotic syndrome because of persistent hypoalbuminemia. The same result can sometimes be achieved by embolizing the renal arteries with coils, thus avoiding surgery in high-risk patients. Dialysis is used as necessary.

Key Points

- - Nephrotic syndrome is most common in young children, usually idiopathic, and most often minimal change disease.
- In adults, nephrotic syndrome is usually secondary, most often to diabetes or preeclampsia.
- Consider nephrotic syndrome in patients, particularly young children, with unexplained edema or ascites.
- Confirm nephrotic syndrome by finding spot protein/creatinine ratio ≥ 3 or urinary protein ≥ 3 g/24 h.
- Do tests for secondary causes and renal biopsy selectively, based on clinical findings.
- Assume minimal change disease if a child with idiopathic nephrotic syndrome improves after treatment with corticosteroids.
- Treat the causative disorder and with angiotensin inhibition, Na restriction, and often diuretics and/or statins.

Last full review/revision March 2013 by Navin Jaipaul, MD, MHS

Self preparation at class:

Listen information;

Work with patients (with cardiac pathology);

Ask about the problems that have not been found in information given.

Self preparation at home:

Compose the plan of your answer;

Answer the questions to the topic;

Do the test given above.

1. What is the most likely cause of the combination of generalized edema, hypoalbuminemia, hypercholesterolemia, marked proteinuria, and fatty casts and oval fat bodies in the urine?
 - a. Nephritic syndrome
 - b. Nephrotic syndrome
 - c. Acute renal failure
 - d. Renal tubular defect
 - e. Urinary tract infection

Recommended literature:

A. Main:

1. "Harrison's principles of internal medicine", Editors: Anthony S. Fauci, Dennis L. Kasper, Stephen L Hauser, Dan L. Longo, Joseph Loscalzo, McGraw-Hill Education / Medical; 19 edition (April 8, 2015), 1-2 volumes, 3000 p.

2. CURRENT Medical Diagnosis and Treatment 2012, Fifty-First Edition (LANGE CURRENT Series) by Stephen McPhee, Maxine Papadakis and Michael W. Rabow (Paperback - Sep 12, 2011)
 3. Davidson's Principles and Practice of Medicine: With STUDENT CONSULT Online Access, 21e (Principles & Practice of Medicine (Davidson's)) by Nicki R. Colledge BSc FRCP(Ed), Brian R. Walker BSc MD FRCP(Ed) and Stuart H. Ralston MB ChB MD FRCP FMedSci FRSE (Paperback - Mar 11, 2010)Kumar and Clark's Clinical Medicine, 7e (Kumar, Kumar and Clark's Clinical Medicine) by Parveen J. Kumar (Paperback - Jul 2, 2009)
 4. CURRENT Diagnosis and Treatment Emergency Medicine, Seventh Edition (LANGE CURRENT Series) by C. Keith Stone (May 23, 2011)
 5. Goldman's Cecil medicine / [edited by] Lee Goldman, Andrew I. Schafer.—24th ed. Elsevier Sanders. Rev. ed. of: Cecil medicine. 23rd ed. – 2012. p.
 6. Sonographer's Handbook of Diagnostic Ultrasound by Jason R. Young M.D. (Feb 23, 2011)
1. The answer is b. Glomerular diseases may clinically produce either nephrotic syndrome or nephritic syndrome. Nephrotic syndrome is characterized by marked proteinuria, that is, proteinuria greater than 3.5 g per 24 h. Because of this marked proteinuria, patients lose albumin (hypoalbuminemia), which leads to peripheral edema. Patients also characteristically have increased serum lipid levels (hyperlipidemia) due to increased hepatic synthesis of cholesterol. The cholesterol is carried within LDL and spills into the urine (lipiduria), where it produces microscopic fatty casts and oval fat bodies. The latter are renal tubular epithelial cells or macrophages that have excess cholesterol in the cytoplasm. Polarization of this excess cholesterol produces Maltese crosses. In contrast to nephrotic syndrome, nephritic syndrome is mainly caused by inflammatory glomerular diseases and produces hematuria (blood in the urine). Red blood cell casts may be present. These patients also may have proteinuria, but it is generally less severe than that in patients with nephrotic syndrome and is generally less than 3.5 g/day. Patients also retain salt and water, which leads to hypertension and peripheral edema. In contrast to these two glomerular syndromes, renal tubular defects produce symptoms of polyuria, nocturia, and electrolyte abnormalities (such as metabolic acidosis), while infections of the urinary tract cause bacteriuria and pyuria (bacteria and leukocytes in the urine).

Methodical recommendations consisted by

Kulishov S.K.