MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE
ODESA NATIONAL MEDICAL UNIVERSITY
International Faculty
Department of Internal Medicine #2 with postgraduate training

APPROVED
Vice-rector for scientific and pedagogical work
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METHODICAL GUIDE FOR LECTURES IN EDUCATIONAL DISCIPLINE

International Faculty, V-th course

Educational discipline: **Internal Medicine**

Approved

At the meeting of the Department of Internal Medicine #2 with postgraduate training

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Lecture №1
Topic: Systemic Diseases of Connective Tissue (SDCT)

Objective: to prepare a specialist who is able to perform professional activities, applying the acquired knowledge on the problem of SDCT, in particular, Systemic Lupus Erythematosus (SLE) and Systemic Sclerosis (SS), from the inherent modern laboratory and instrumental research, medical manipulations, tactics and standards of patient management based on evidence medicine, to identify tasks and problems in the field of rheumatology in clinical practice and in further training.

Specific objectives of the lecture:

- Discuss the prevalence of SDCT and its impact on public health in the world and in Ukraine
- Define SDCT.
- Explain the etiology, pathogenesis of risk factors for the development and progression of SDCT.
- Discuss the clinical manifestations of the typical course of SDCT and complications of SDCT.
- Explain the current classification of SDCT.
- To substantiate the use of the main methods of diagnosis of SDCT, to discuss their informativeness, to determine the indications and contraindications for their use.
- Explain the basic principles of differential diagnosis in a patient with suspected SDCT using the analysis of clinical manifestations, laboratory data and instrumental examination, to substantiate the clinical diagnosis of SDCT. Give examples of diagnosis in patients with different variants of SDCT.
- Explain the basic principles of modern strategy of continuous organoprotection of patients with SDCT, as components of primary and secondary prevention of SDCT, treatment of patients with different stages of SDCT according to evidence-based medicine.
- Discuss modern approaches and methods of immunosupression and immunomodulation, indications and contraindications to it, complications.
- To present modern methods of assessment of the prognosis in patients with SDCT.
- Demonstrate moral and deontological principles of a medical specialist and the principles of professional subordination when working with patients with SDCT.

Basic concepts: SDCT, SLE, SS, risk factors (RFs), criteria for diagnosis of SLE and SS, stages of SLE and SS, immune system and autoimmunity, systemic injury of connective tissue, target organ injury, basic therapy, target therapy, immunosuppression, immunomodulation.

Lecture plan and organizational structure

N IO	The main stages of the lecture and their content	Goals in levels of abstraction	Type of lecture, methods and means of activating students, equipment	Time distributio n, min
1	*2*	*3*	*4*	*5*
1.	Preparatory stage: 1. setting educational goals 2. providing positive motivation - the importance of the problem of SDCT for the clinical practice of a family doctor - general practice.	I I	Clinical lecture: – with elements of problem, – with the use of clearness, – with the use of interactive communication–	5
2.	The main stage: presentation of lecture material according to the plan: 2.1.Epidemiology of SDCT	I	Visual tools: – multimedia presentation of the lecture in Power Point format, incl. using the Microsoft Teams platform,	75

	2.2. The role of the general practitioner in the management of patients with SDCT Lecture content: 2.3. Definition of SDCT 2.4. Risk factors for the development and progression of SDCT 2.5. Pathogenesis of lesions of organs and systems. 2.6. Classification of SDCT. Changes in laboratory parameters depending on the stage. 2.7. Clinical manifestations and typical course, complications. 2.8. Diagnosis and principles of differential diagnosis in a patient with SDCT. 2.9. Current strategy of managing patients with SDCT. Treatment at different stages of SDCT according to evidence-based medicine. 2.10. Renal replacement therapy: dialysis, kidney transplantation. Indications and contraindications to renal replacement therapy, complications. 2.11. Primary and secondary prevention. Strategy of continuous renoprotection. 2.12. Prognosis in patients with SDCT.	II III III III III II II II II II	– extracts from medical records of patients with SDCT (or thematic patient), – adapted clinical guidelines for the management of patients with SDCT, – KDIGO recommendations	
3.	Final stage: 3.1. Problems that need to be solved. 3.2. Questions and tasks to assess the degree of assimilation of lecture material The lecturer's answer to possible questions. 3.3. Tasks for self-preparation.	II III III III	Materials to control: - questions - situational tasks	10

Contents of the topic

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disorder of the connective tissue, primarily affecting the skin, joints, blood, and kidneys; however, other body systems/organs can also be affected. The disease process in systemic lupus is complex, with an often unpredictable course and a prognosis that varies from mild to severe to life-threatening. Improved treatment options have led to longer survival for people with SLE. Unfortunately, along with longer survival has come an increased risk for chronic diseases, especially cardiovascular disease. In addition, the disability caused by systemic lupus can be substantial. Studies and surveys have shown that the symptoms of fatigue, pain, and neurocognitive dysfunction cause many individuals with SLE to stop working. In one systematic review, 15% to 51% of individuals stopped working 3 to 15 years after diagnosis.

The prevalence of SLE has ranged from 56 to 150 per 100,000, with higher rates (108 to 250 per 100,000) among women.

Reflecting the female preponderance, the prevalence among adult women was 10% in NHANES III. Most women affected by the disease are of childbearing age; the average age at the time of diagnosis of adult-onset systemic lupus is 36.5 years. About 10% to 20% of cases occur in individuals 50 to 65 years of age. The risk of the disease is approximately 20 times more likely for the sibling of a person who has SLE.

POTENTIAL ENVIRONMENTAL RISK FACTORS

Several environmental factors have been evaluated as contributors to the development of systemic lupus, and the strongest evidence has been found for infection, cigarette smoking, and hormones. These same factors have been associated not only with a higher incidence of systemic lupus but also with disease of greater severity and/or increased disease activity.

A strong association has been identified between systemic lupus and Epstein-Barr infection, with research demonstrating that an immune response to the Epstein-Barr virus plays an important role in the development of systemic lupus in at least some individuals with systemic lupus.

The mechanisms of sex hormones as a risk factor in the development of systemic lupus are unclear. A review and meta-analysis found that levels of sex hormones are altered in the presence of systemic lupus, but strong evidence of causal relationships was lacking. Sex hormones and systemic lupus are more closely related among women than among men. Levels of dehydroepiandrosterone/ dehydroepiandrosterone-sulfate (DHEA/DHEAS), progesterone, and testosterone are lower and estradiol and prolactin are higher among women with systemic lupus, whereas an increased prolactin level is the only abnormality confirmed among men with systemic lupus. The effect of exogenous hormones has been debated, with some studies showing slightly increased risk for systemic lupus among women taking oral contraceptives or hormone-replacement therapy.

MOST COMMON SIGNS AND SYMPTOMS OF SYSTEMIC LUPUS ERYTHEMATOSUS

Organ/Body System	Symptoms
General	Fatigue Low-grade, unexplained, episodic fever Weight loss Generalized adenopathy
Cutaneous	Butterfly-shaped rash on face Photosensitivity Alopecia Oral mucosal sores, ulcers Raynaud phenomenon
Musculoskeletal	Arthralgia, arthritis Myalgia, muscle tenderness
Cardiovascular	Pericarditis Pericardial effusion

	Myocarditis
Respiratory	Pleuritic pain Pleurisy (with coughing and dyspnea)
Renal	Glomerulitis, glomerulonephritis
Neurologic	Cognitive dysfunction Headache Seizures Cranial or peripheral neuropathy
Gastrointestinal	Abdominal pain Nausea/vomiting
Ocular	Dry eye syndrome, uveitis, scleritis

The clinical manifestations of systemic lupus often differ among older individuals. Malar and discoid rash and glomerulonephritis are less common in the older population compared with the younger population, whereas arthritis, fever, serositis, dry eye syndrome, Raynaud phenomenon, lung disease, and neuropsychiatric symptoms are more common in the older population.

Definitions of SLE classification criteria.

Antinuclear antibodies (ANA) – ANA at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test at least once. Testing by immunofluorescence on HEp-2 cells or a solid phase ANA screening immunoassay with at least equivalent performance is highly recommended.

Fever – Temperature >38.3° Celsius.

Leukopenia – White blood cell count 0.5g/24h

Thrombocytopenia – Platelet count <100,000/mm^3

Autoimmune hemolysis – Evidence of hemolysis, such as reticulocytosis, low haptoglobin, elevated indirect bilirubin, elevated LDH AND positive Coomb's (direct antiglobulin) test.

Delirium – Characterized by (1) change in consciousness or level of arousal with reduced ability to focus, and (2) symptom development over hours to <2 days, and (3) symptom fluctuation throughout the day, and (4) either (4a) acute/subacute change in cognition (e.g. memory deficit or disorientation), or (4b) change in behavior, mood, or affect (e.g. restlessness, reversal of sleep/wake cycle).

Psychosis – Characterized by (1) delusions and/or hallucinations without insight and (2) absence of delirium.

Seizure – Primary generalized seizure or partial/focal seizure.

Non-scarring alopecia – Non-scarring alopecia observed by a clinician*.

Oral ulcers – Oral ulcers observed by a clinician*.

Subacute cutaneous or discoid lupus – Subacute cutaneous lupus erythematosus observed by a clinician*: Annular or papulosquamous (psoriasiform) cutaneous eruption, usually photodistributed. Discoid lupus erythematosus observed by a clinician*: Erythematous-violaceous cutaneous lesions with secondary changes of atrophic scarring, dyspigmentation, often follicular hyperkeratosis/ plugging (scalp), leading to scarring alopecia on the scalp. If skin biopsy is performed, typical changes must be present. Subacute cutaneous lupus: interface vacuolar dermatitis consisting of a perivascular lymphohistiocytic infiltrate, often with dermal mucin noted. Discoid lupus: interface vacuolar dermatitis consisting of a perivascular and/or periappendageal lymphohistiocytic infiltrate. In the scalp, follicular keratin plugs may be seen. In longstanding lesions, mucin deposition and basement membrane thickening may be noted.

Acute cutaneous lupus – Malar rash or generalized maculopapular rash observed by a clinician*. If skin biopsy is performed, typical changes must be present (Acute cutaneous lupus: interface vacuolar dermatitis consisting of a perivascular lymphohistiocytic infiltrate, often with dermal mucin noted. Perivascular neutrophilic infiltrate may be present early in the course.

Pleural or pericardial effusion – Imaging evidence (such as ultrasound, x-ray, CT scan, MRI) of pleural or pericardial effusion, or both.

Acute pericarditis – ≥2 of (1) pericardial chest pain (typically sharp, worse with inspiration, improved by leaning forward), (2) pericardial rub, (3) EKG with new widespread ST-elevation or PR depression, (4) new or worsened pericardial effusion on imaging (such as ultrasound, x-ray, CT scan, MRI).

Joint involvement – EITHER (1) synovitis involving 2 or more joints characterized by swelling or effusion OR (2) tenderness in 2 or more joints and at least 30 minutes of morning stiffness.

Proteinuria – >0.5g/24h by 24 hour urine or equivalent spot urine protein-to-creatinine ratio.

Class II or V lupus nephritis – on renal biopsy according to ISN/RPS 2003 classification. Class II: Mesangial proliferative lupus nephritis: Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposit. A few isolated subepithelial or subendothelial deposits may be visible by immune-fluorescence or electron microscopy, but not by light microscopy. Class V: Membranous lupus nephritis: Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations.

Class III or IV lupus nephritis – on renal biopsy according to ISN/RPS 2003. Class III: Focal lupus nephritis: Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations. Class IV: Diffuse lupus nephritis: Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation.

Positive anti-phospholipid antibodies – Anti-Cardiolipin antibodies (IgA, IgG, or IgM) at medium or high titer (> 40 APL, GPL or MPL, or >the 99th percentile) or positive anti-β2GP1 antibodies (IgA, IgG, or IgM) or positive lupus anticoagulant.

Low C3 OR low C4 – C3 OR C4 below the lower limit of normal.

Low C3 AND low C4 – Both C3 AND C4 below their lower limits of normal.

Anti-dsDNA antibodies OR Anti-Smith (Sm) antibodies – Anti-dsDNA antibodies in an immunoassay with demonstrated ≥ 90% specificity for SLE against relevant disease controls OR Anti-Smith (Sm) antibodies.

* – This may include physical examination or review of a photograph.

ANTIBODY TESTING FOR SYSTEMIC LUPUS

Diagnostic Test	Prevalence*	Comments
Antinuclear antibody titer	93% to 100%	Positive titer also found in systemic sclerosis (up to 80%) and Sjögren's syndrome (up to 70%), as well as many healthy individuals
Anti-double-stranded DNA	70% to 80%	Positive test highly specific for SLE. Associated with greater risk of skin disease and lupus nephritis
Anti-Ro	30% to 40%	Also associated with Sjögren's syndrome (up to 70%). Associated with greater risk of skin disease, lupus nephritis, and fetal heart problems
Antiphospholipid antibodies	20% to 30%	Associated with greater risk of thrombosis and pregnancy loss
Anti-Sm	10% to 30%	Positive test highly specific for SLE. Associated with greater risk of lupus nephritis
Anti-La	15% to 20%	Associated with Sjögren's syndrome (up to 50%). Associated with fetal heart problems.

The ANA titer is highly sensitive for systemic lupus, with a positive result in approximately

93% to 100% of individuals with the disease. However, the specificity is low, and a positive titer will also be found in 60% to 80% of people with systemic sclerosis and 40% to 70% of people with Sjögren's syndrome, as well as in a substantial number of healthy individuals. Given the low specificity, in combination with the low prevalence of systemic lupus in the primary care setting, the College of American Pathologists recommends an ANA titer when there is a "reasonable clinical suspicion" of systemic lupus on the basis of the history, physical examination, and other laboratory tests. A negative ANA titer (less than 1:160 on standard substrate) essentially rules out a diagnosis of systemic lupus. The ANA titer is best determined with fluorescent testing because it has better sensitivity and specificity than testing with enzyme-linked immunosorbent assay and can also demonstrate an ANA pattern.

Anti-double-stranded DNA and anti-Sm tests can help confirm a diagnosis of systemic lupus, as they have greater specificity than the ANA titer; however, they are not as sensitive as the ANA tier. The prevalence of positive anti-Ro/ SSA and anti-LA/SSB titers is also low, and these titers are more often positive among older people. Serum complement levels may also be use-ful, as decreased levels indicate active or impending exacerbation of disease. The prevalence of positive anti-double-stranded DNA titers and of decreased complement levels is lower among older individuals than among younger ones.

A positive finding of antiphospholipid antibodies is the last criterion in the ACR Classification. The presence of antiphospholipid antibodies is determined with testing for anticardiolipin antibodies or for lupus anticoagulant. About 20% to 30% of people with systemic lupus have antiphos-pholipid antibodies, which increase the risk for thromboembolism and pregnancy loss.

Treatment

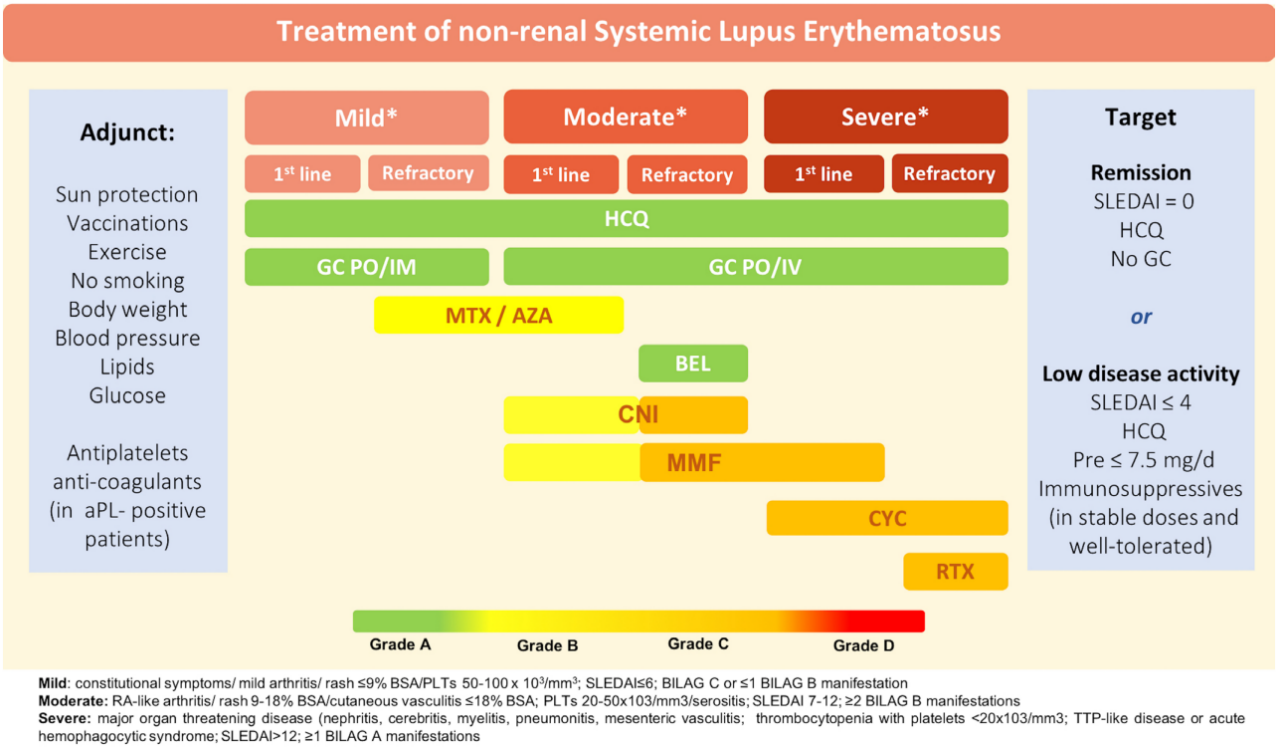


Figure. Treatment of non-renal SLE—recommended drugs with respective grading of recommendation. aPL, antiphospholipid antibodies; AZA, azathioprine; BEL, belimumab; BILAG: British Isles Lupus Assessment Group disease activity index; CNIs, calcineurin inhibitors; CYC, cyclophosphamide; GC, glucocorticoids; HCQ, hydroxychloroquine; IM, intramuscular; MMF, mycophenolate mofetil; MTX, methotrexate; Pre, prednisone; PO, per os; RTX, rituximab; PLTs: Platelets; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

TREATMENT OPTIONS FOR SYSTEMIC LUPUS

Agent	Typical Dose*	Indication	Side Effects
Nonsteroidal anti-inflammatory drugs (NSAIDs)	At or near the upper limit of the dose range	Mild-to-moderate arthritis, fever, mild serositis	Gastrointestinal bleeding, renal and hepatic toxicity
Immuno-suppressants / cytotoxic agents	Dose varies	Usually used in conjunction with a low-dose glucocorticoid	Infection, leukopenia, anemia, thrombocytopenia, myelosuppression, lymphoma, gastrointestinal effects, alopecia
Hydroxychloro-quine	200 mg PO twice daily	Preferred first-line	Dizziness, nausea and diarrhea (usually resolves over time), macular damage
Prednisone (low dose)	≤10 mg PO daily	Usually used in conjunction with hydroxychloroquine	Osteopenia/osteoporosis, infection, hypertension, avascular necrosis of bone, weight gain, glaucoma, cataracts, psychologic effects
Prednisone (moderate dose)	≤20 mg PO daily	Moderate disease (without organ involvement) with inadequate response to first-line treatment	
Methylprednisolone (high dose)	40–60 mg PO daily or 1 g IV daily X3	Lupus nephritis, cerebritis, thrombocytopenia	
Topical glucocorticoids	Low or intermediate dose	Facial lesions	Skin atrophy, infection, contact dermatitis
	Intermediate dose	Lesions on trunk or extremities	
	High dose	Lesions on palms or soles	
Azathioprine	25–150 mg PO daily	Nonarthritic disease refractory to antimalarial agent and/or glucocorticoids; maintenance therapy for lupus nephritis, neuropsychiatric lupus	Hepatitis, pancreatitis
Methotrexate	7.5–20 mg PO weekly	Mild-to-moderate disease refractory to first-line treatment; lupus nephritis, neurologic complications	Hepatic fibrosis, cirrhosis, pulmonary infiltrates, stomatitis, mucositis; teratogenic
Cyclophosphamide	IV, dose varies	Digital vasculitis; disease with organ involvement (lupus nephritis, cerebritis)	Irreversible ovarian or testicular failure (with long-term use); nausea, alopecia, herpes zoster; teratogenic
Mycophenolate mofetil	1.5–3 g PO daily	Mild-to-moderate lupus	Diarrhea, nausea;

		nephritis (induction and maintenance therapy); refractory thrombocytopenia; cutaneous manifestations; uncontrolled disease	teratogenic
Leflunomide	10–20 mg PO daily	Mild-to-moderate disease refractory to first-line treatment	Diarrhea, alopecia, rash; teratogenic
Tacrolimus or pimecrolimus	0.1%	Severe cutaneous lesions resistant to other agents	Peeling and burning sensation
Belimumab	10 mg/kg IV every 2 weeks for 6 weeks, then every 4 weeks	Adjunctive therapy for autoantibody-positive, mild-to-moderate systemic lupus	Nausea, fever, diarrhea, nasopharyngitis, insomnia; possibly teratogenic

*For most drugs, the typical dose may vary, as no recommended dose has been established because of the lack of FDA approval.

Mild Disease (No Organ Involvement)

The cornerstone of treatment of mild systemic lupus without major organ involvement is typically an antimalarial drug and a low-dose glucocorticoid (usually prednisone), two of only three drugs approved by the FDA for use in systemic lupus. Antimalarial agents include chloroquine and hydroxychloroquine, and the latter is preferred because of its better side effect profile. Antimalarial agents offer many benefits. They can alleviate joint-related, cutaneous, constitutional, and serosal manifestations of systemic lupus; they can prevent disease flares; they are well tolerated; they have been associated with a lower risk of infection than other treatment approaches; and they have a protective effect on survival. Despite all these advantages, hydroxychloroquine is underutilized in practice.

A low-dose oral glucocorticoid is typically used in conjunction with an antimalarial agent to provide further relief of symptoms. For most patients with mild disease (and no major organ involvement), prednisone at a dose of 5 mg per day is effective, although some patients may need 10 mg per day. NSAIDs may also be used to provide symptomatic relief of joint manifestations. The use of both glucocorticoids and NSAIDs should be carefully considered because of their associated toxicity. Glucocorticoids should be given at the lowest possible dose that suppresses manifestations of disease activity and prevents flares.

Although antimalarial drugs usually resolve systemic lupus-related rash, the mainstay of treatment for this manifestation is a topical glucocorticoid, available as a cream, liquid, or gel. Intermediate-dose rather than high-dose topical glucocorticoids should be used on areas where atrophy is more likely, such as the face. Novel therapies for cutaneous lesions are calcineurin inhibitors, most notably tacrolimus and pimecrolimus. The use of these immunomodulators has been shown to be effective, but studies have been small. The FDA has approved tacrolimus and pimecrolimus for the treatment of moderate and severe atopic dermatitis in adults and children but have not approved them for use in systemic lupus.

If the disease response to antimalarial drugs and tolerable doses of glucocorticoids (i.e., daily dose of prednisone of 10 mg or less) is inadequate, treat-ment with an immunosuppressant should be started as a glucocorticoid-sparing approach. Methotrexate and leflunomide have been evaluated in mild-to-moderate systemic lupus, and many studies have indicated benefit, especially with regard to joint- and skin-related symptoms, but the data have been conflicting. Azathioprine is often the drug of choice for nonarthritic manifestations that have not responded to antimalarial treatment and low-dose glucocorticoid. Because of the increased risk for infection associated with immunosuppressants,

screening for tuberculosis and chronic viral infections should be completed before treatment with an immunosuppressant agent begins.

In March 2011, the FDA approved belimumab, the first new drug for lupus in more than 50 years. Belimumab, a monoclonal antibody against B-lymphocyte stimulator, has shown better clinical response compared with placebo. More research is necessary to determine if the drug is effective in black patients and patients with severe manifestations. Belimumab is approved to treat patients with active, autoantibody-positive lupus who are receiving standard therapy. It is administered via an intravenous infusion at an initial dose of 10 mg/kg every 2 weeks for 6 weeks; the maintenance dose is 10 mg/kg every 4 weeks.

Systemic lupus often affects the eyes, with about one-third of patients having dry eye syndrome (keratoconjunctivitis sicca). Symptoms are usually relatively mild (e.g., irritation and redness), and artificial tear drops can be used to treat milder forms of the condition. Pain in the eye or significant visual impairment at any time during the course of disease warrants immediate referral to an ophthalmologist.

Neuropsychiatric disorders have been shown to have a persistent negative effect on quality of life for people with systemic lupus. According to EULAR guidelines, appropriate treatment depends on the cause of the disorder: glucocorti-coids and immunosuppressants are recommended for disorders that reflect an immune/inflammatory process and antiplatelet/anticoagulation therapy is recommended for disorders thought to be related to antiphospholipid antibodies. Prophylaxis with low-dose aspirin may be of benefit for people with positive results on testing for antiphospholipid antibodies, as thromboembolic events occur in approximately 50% of these patients.

Systemic lupus is associated with reduced exercise capacity and decreased muscle strength, which are exacerbated by disease-related fatigue and sleep disturbances. To address these issues, routine exercise should be part of the overall treatment plan for people with mild-to-moderate disease. Individuals with systemic lupus who participated in a supervised cardiovascular training program had significant improvements in exercise tolerance, aerobic capacity, quality of life, and depression. Exercise programs should focus on aerobic exercises as well as strength training to improve isometric strength and should begin with a formal, supervised program, as adherence has been better for such programs than for home-based ones.

Uncontrolled or Moderate-to-Severe Disease

Uncontrolled disease is defined as the persistence of clinical manifestations during treatment. Several manifestations indicate uncontrolled disease, including:

- Pleurisy, pericarditis, and/or arthritis not controlled by NSAIDs
- Rash not controlled by topical therapies
- Vasculitis
- Digital ulcers
- Muscle weakness and/or elevated creatine phosphokinase despite glucocorticoid therapy
- Any central nervous system manifestation
- Continuing evidence of active renal disease, cardiopulmonary disease, or hematologic manifestations despite therapy

The primary care provider should refer patients with uncontrolled disease to a rheumatologist. Moderate doses of a glucocorticoid may be effective for moderately severe disease without major organ involvement (arthritis, dermatitis, serositis, systemic symptoms). Glucocorticoids should be tapered as tolerated until a maintenance level can be established.

As systemic lupus progresses to moderate-to-severe disease, it can affect any major organ system. However, the kidneys are most commonly involved. Lupus nephritis occurs in 50% to 70% of individuals with systemic lupus and leads to end-stage renal disease in 17% to 25% of patients. The prevalence of lupus nephritis is higher in the black, Hispanic, and Asian populations than in the white

population. The goal of treating nephritis is to reduce the risk of end-stage renal disease and

death, but controlling proteinuria and preventing disease flares are also important aims.

Recommended treatment for proliferative lupus nephritis is a glucocorticoid plus another immu-nosuppressant agent. However, a definitive standard of care has not been established. Initial (induction) therapy for lupus nephritis was once azathioprine until intravenous cyclophosphamide became an accepted standard because of its superiority in improving renal function. However, this improvement was tempered by several factors, including a failure to achieve remission in many patients, even with maintenance therapy; no increase in overall survival; and considerable toxicity. Studies showed that toxicity could be reduced if maintenance therapy was with another drug—azathioprine or mycophenolate mofetil, a drug approved for the prevention of allograft rejection.

Subsequent studies were done to compare mycophenolate mofetil with cyclophosphamide as induction therapy, and some studies showed that mycophenolate mofetil was as at least as effective, while other studies showed significant benefits. As induction therapy and maintenance therapy, mycophenolate mofetil led to higher rates of remission and relapse-free survival and lower rates of progression to chronic renal failure.

However, more recent head-to-head comparisons and a systematic review/meta-analysis have demonstrated no significant differences between mycophenolate mofetil and intravenous cyclophos-phamide. The rates of adverse events, serious adverse events, and infection have also been similar for the two treatment drugs, except that a significantly lower rate of leukopenia was found among patients treated with mycophenolate mofetil in one study. Another study showed that hydroxychloroquine had a protective effect for patients with lupus nephritis. In that study, patients who received hydroxychloroquine were less likely to have proliferative nephritis, had lower disease activity, and received lower glucocorticoid doses than those who did not take hydroxychloroquine.

Biologic agents, including anti-TNF-α factors, IL-6 inhibitors, co-stimulation blockers, and anti-CD20 agents, have also been evaluated for efficacy in systemic lupus but have not been as successful as in rheumatoid arthritis, due to a lack of efficacy and/ or high rates of adverse events. Rituximab had preliminary success in treating resistant lupus manifestations, including central nervous system, vasculitic, hematologic, and renal manifestations; however, the results of two large phase II/III placebo-controlled randomized controlled trials were negative.

Approximately 40% of people with systemic lupus seek symptomatic relief with complementary and alternative methods. However, data are lacking on a variety of these methods, including herbal medicines, dietary supplements, and acupuncture, and none has provided evidence of efficacy.

Treatment During Pregnancy

Pregnancy in women with systemic lupus is associated with risks for both the mother and the fetus, and pregnant women should be managed as high-risk obstetric patients. Pregnancy may cause disease flares, especially in the third trimester and postnatal period, but flares are usually mild and can be controlled without excessive risk to either the mother or the fetus. Many treatment agents may be used during pregnancy, including hydroxychloroquine, prednisone, and azathioprine; evidence suggests that mycophenolate mofetil, cyclophosphamide, and methotrexate should be avoided. Systemic lupus increases the risk for fetal loss, especially in women who have antiphospholipid antibodies. A history of lupus nephritis, antiphospholipid antibodies, and anti-Ro and/or anti-La antibodies are associated with increased risk for preeclampsia, miscarriage, stillbirth, premature delivery, intrauterine growth restriction, and fetal congenital heart bloc. Heparin and aspirin are usually given throughout pregnancy to reduce the risk of miscarriage and thrombotic events.

Disease Activity/Response to Treatment

Disease activity should be assessed by a validated instrument, and the most widely used tools are the Systemic Lupus Activity Measure (SLAM), Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Lupus Activity Index (LAI), British Isles Lupus Assessment Group (BILAG) index, and the European Consensus Lupus Activity Measure (ECLAM). EULAR also recommends evaluation of quality of life through patient history and/or a patient global assessment at each visit and annual assessment of organ damage.

Monitoring and Treatment of Drug Side Effects

Infection, osteopenia/osteoporosis, and bone mar-row suppression are the major side effects of treatment for systemic lupus; gastrointestinal, hepatic, renal/genitourinary, cardiovascular, and neurologic effects may also occur. Recommended testing for individuals receiving methotrexate, mycophenolate mofetil, or azathioprine is a CBC and platelet count every 3 months. Individuals treated with methotrexate should also have liver function studies done every 3 months. A serum glucose level should be obtained yearly for patients treated with glucocorticoids. Monitoring during treatment with cyclophosphamide should be done monthly, with a CBC, platelet count, and urinalysis. No laboratory testing is recommended to monitor treatment with hydroxychloroquine.

Prevention of Osteoporosis

As noted, long-term use of glucocorticoids is associated with a wide range of potential adverse events, including osteopenia/osteoporosis, hypertension, cataracts, glaucoma, dyspepsia, weight gain, avascular necrosis of bone, Cushingoid changes, and adverse psychologic effects. Of these side effects, osteoporosis is of particular concern, with a prevalence of 4% to 24% among patients with systemic lupus. According to the 2010 ACR guidelines, the following are recommended for the prevention and treatment of glucocorticoid-induced osteoporosis:

- Daily calcium intake (dietary plus supplement) of 1,200 to 1,500 mg and supplemental vitamin D (400 to 800 IU) to prevent osteoporosis in all individuals taking glucocorticoids
- Use of bisphosphonates according to an individual's risk (noting that risk is best assessed with the FRAX tool, which provides a better overall clinical risk profile than bone mineral density alone)
- Dual x-ray absorptiometry, height, prevalent fragility fractures, and serum 25-hydroxyvitamin D level at baseline (before treatment starts) and at intervals throughout the course of treatment

Prevention of Treatment-Related Eye Disease

As discussed, hydroxychloroquine increases the risk for retinopathy, although this toxicity is rare at doses of less than 6.5 mg/kg/day for fewer than 5 years. Still, ophthalmologic follow-up is important for early detection and minimization of this potentially serious side effect. The AAO recommends a complete ophthalmologic examination within the first year after treatment. Routine examination of the eyes should be done for patients treated with glucocorticoids who are at high risk for cataracts and glaucoma.

Prognosis

Systemic lupus is one of the leading causes of death among autoimmune disorders, and its associated mortality is higher than that expected for the general population. Mortality among women is consistent across all age-groups. Survival has improved substantially over the years, from a 4-year survival of 50% in the 1950s to a 5-year survival rate of 95% today. Ten-year and 15-year survival rates have been reported to be approximately 90% and 80%, respectively. Improved survival is thought to be the result of earlier diagnosis, recognition of mild disease, increased use of ANA testing, and better treatment options. Lower survival rates are associated with a younger age at the time of diagnosis, and mortality rates are twofold to threefold higher in the black population than in the white population.

SYSTEMIC SCLEROSIS (SCLERODERMA)

Systemic sclerosis (SSc) is a rare chronic disease of unknown cause characterized by diffuse fibrosis, degenerative changes, and vascular abnormalities in the skin, joints, and internal organs (especially the esophagus, lower GI tract, lungs, heart, and kidneys). Common symptoms include Raynaud phenomenon, polyarthralgia, dysphagia, heartburn, and swelling and eventually skin tightening and contractures of the fingers. Lung, heart, and kidney involvement accounts for most

deaths. Diagnosis is clinical, but laboratory tests help with confirmation. Specific treatment is difficult, and emphasis is often on treatment of complications.

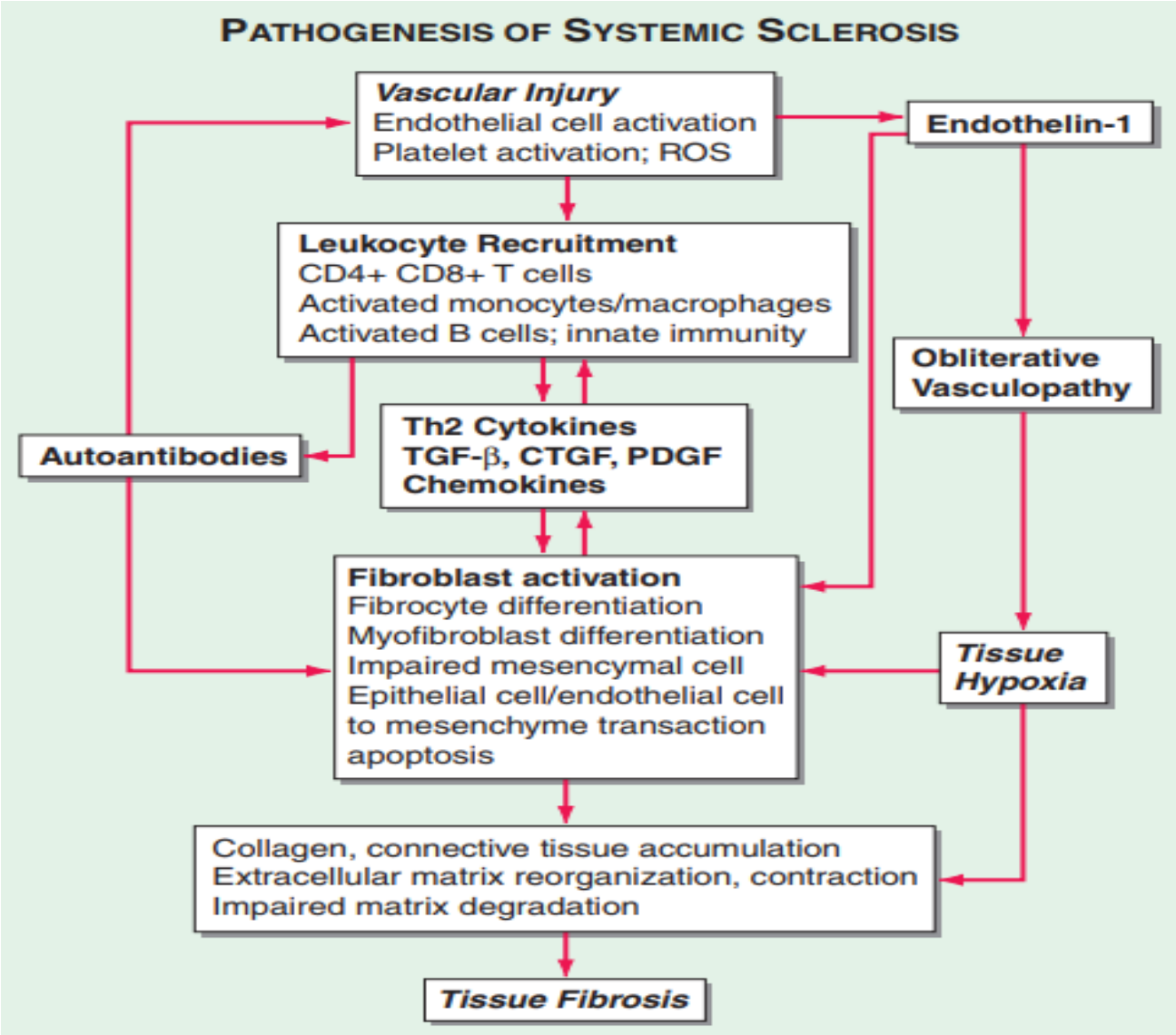
SSc is about 4 times more common among women than men. It is most common among people aged 20 to 50 and is rare in children. SSc can develop as part of mixed connective tissue disease.

Etiology

Immunologic mechanisms and heredity (certain HLA subtypes) play a role in etiology. SSc-like syndromes can result from exposure to vinylchloride, bleomycin, pentazocine, epoxy and aromatic hydrocarbons, contaminated rapeseed oil, or L-tryptophan.

Pathophysiology

Pathophysiology involves vascular damage and activation of fibroblasts; collagen and other extracellular proteins in various tissues are overproduced.



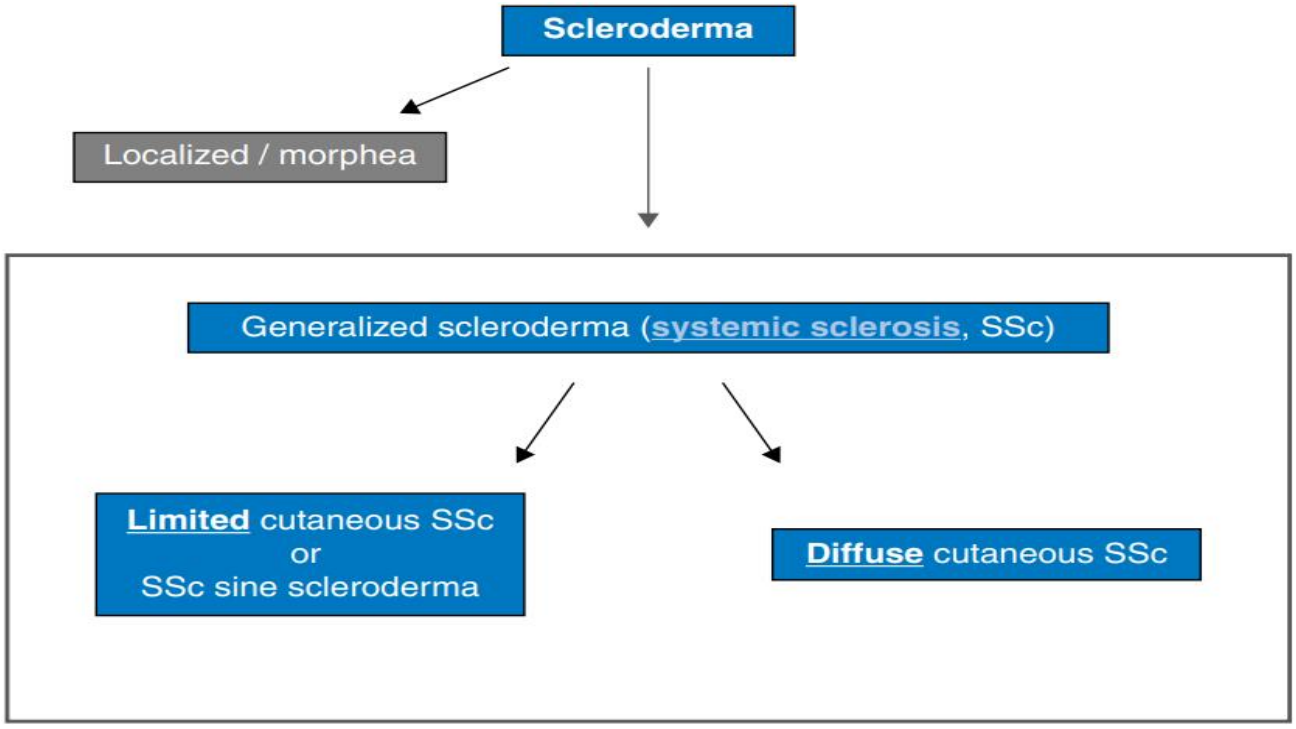
***Notes**: ROS – reactive oxygen species; TGF-β – transforming growth factor β; CTGF - connective tissue growth factor; PDGF - platelet-derived growth factor*

In SSc, the skin develops more compact collagen fibers in the reticular dermis, epidermal thinning, loss of rete pegs, and atrophy of dermal appendages. T cells may accumulate, and extensive fibrosis in the dermal and subcutaneous layers develops. In the nail folds, capillary loops dilate and some microvascular loops are lost. In the extremities, chronic inflammation and fibrosis of the synovial membrane and surfaces and periarticular soft tissues occur.

Esophageal motility becomes impaired, and the lower esophageal sphincter becomes incompetent; gastroesophageal reflux and secondary strictures can develop. The intestinal muscularis mucosa degenerates, leading to pseudodiverticula in the colon and ileum. Interstitial and peribronchial fibrosis or intimal hyperplasia of small pulmonary arteries can develop; if long-standing, pulmonary hypertension can result. Diffuse myocardial fibrosis or cardiac conduction abnormalities occur. Intimal hyperplasia of interlobular and arcuate arteries can develop within the kidneys, causing renal ischemia and hypertension.

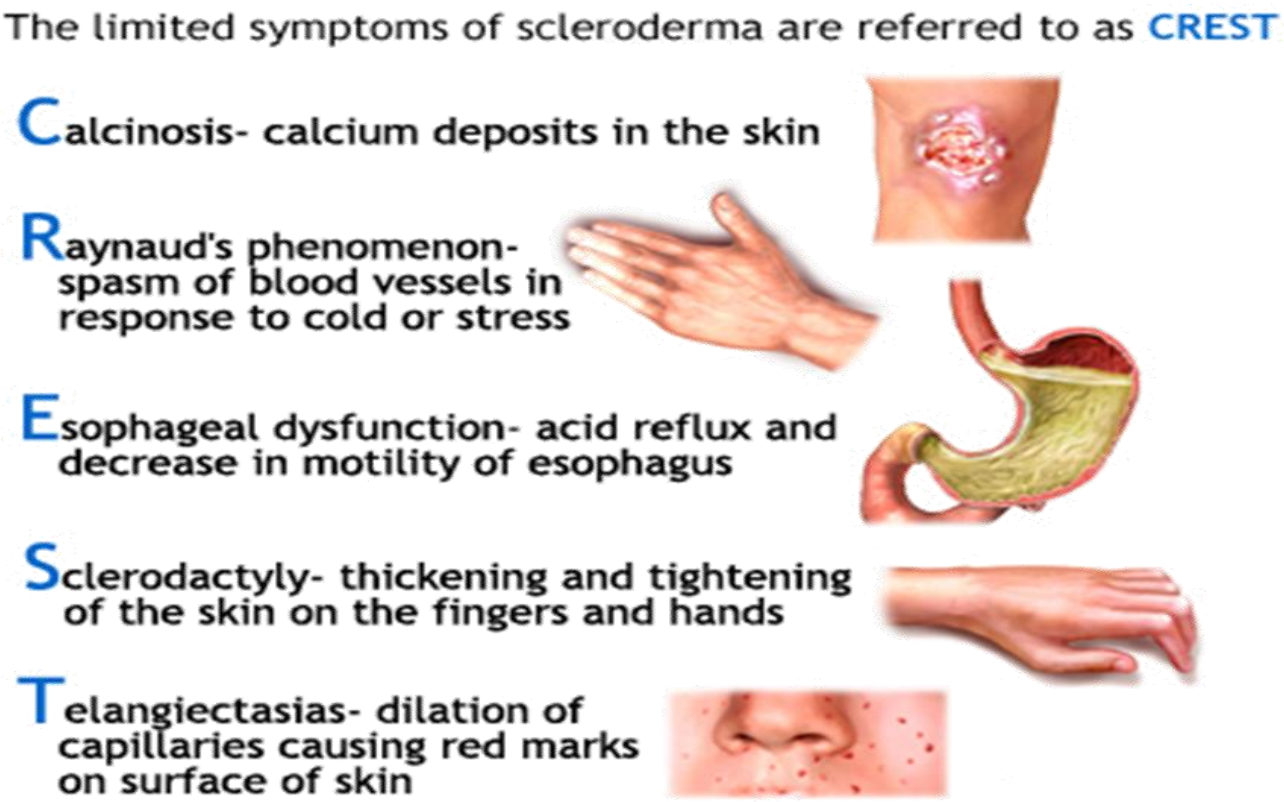
SSc varies in severity and progression, ranging from generalized skin thickening with rapidly progressive and often fatal visceral involvement (SSc with diffuse scleroderma) to isolated skin involvement (often just the fingers and face) and slow progression (often several decades) before visceral disease develops. The latter form is termed limited cutaneous scleroderma or CREST syndrome (calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias). In addition, SSc can overlap with other autoimmune rheumatic disorders—eg, sclerodermatomyositis (tight skin and muscle weakness indistinguishable from polymyositis) and mixed connective tissue disease.

Classification



Symptoms and Signs

The most common initial symptoms and signs are Raynaud phenomenon and insidious swelling of the distal extremities with gradual thickening of the skin of the fingers. Polyarthralgia is also prominent. GI disturbances (eg, heartburn, dysphagia) or respiratory complaints (eg, dyspnea) are occasionally the first manifestations.



Skin and nail manifestations:

Swelling of the skin is usually symmetric and progresses to induration. It may be confined to the fingers (sclerodactyly) and hands, or it may affect most or all of the body. The skin eventually becomes taut, shiny, and hypopigmented or hyperpigmented; the face becomes masklike; and telangiectases may appear on the fingers, chest, face, lips, and tongue. Subcutaneous calcifications may develop, usually on the fingertips (pulps) and over bony eminences. Digital ulcers are common, especially on the fingertips, overlying the finger joints, or over calcinotic nodules. Abnormal capillary and microvascular loops in the nails can be seen with an ophthalmoscope or dissecting microscope.

Joint manifestations:

Polyarthralgias or mild arthritis can be prominent. Flexion contractures may develop in the fingers, wrists, and elbows. Friction rubs may develop over the joints, tendon sheaths, and large bursae.

GI manifestations:

Esophageal dysfunction is the most frequent visceral disturbance and occurs in most patients. Dysphagia (usually retrosternal) usually develops first. Acid reflux can cause heartburn and stricture. Barrett esophagus occurs in one third of patients and predisposes to complications (eg, stricture, adenocarcinoma). Hypomotility of the small bowel causes anaerobic bacterial overgrowth that can lead to malabsorption. Air may penetrate the damaged bowel wall and be visible on x-rays (pneumatosis intestinalis). Leakage of bowel contents into the peritoneal cavity can cause peritonitis. Distinctive wide-mouthed diverticula can develop in the colon. Biliary cirrhosis may develop in patients with CREST syndrome.

Cardiopulmonary manifestations:

Lung involvement generally progresses indolently, with substantial individual variability, but is a common cause of death. Lung fibrosis can impair gas exchange, leading to exertional dyspnea and restrictive disease with eventual respiratory failure. Acute alveolitis (potentially responsive to therapy) can develop. Esophageal dysfunction can lead to aspiration pneumonia. Pulmonary hypertension may develop, as can heart failure, both of which are poor prognostic findings. Pericarditis with effusion or pleurisy can occur. Cardiac arrhythmias are common.

Renal manifestations:

Severe, often sudden renal disease (renal crisis) may occur, most commonly in the first 4 to 5 yr and in patients with diffuse scleroderma. It is usually heralded by sudden, severe hypertension with features of thrombotic microangiopathic hemolytic anemia.

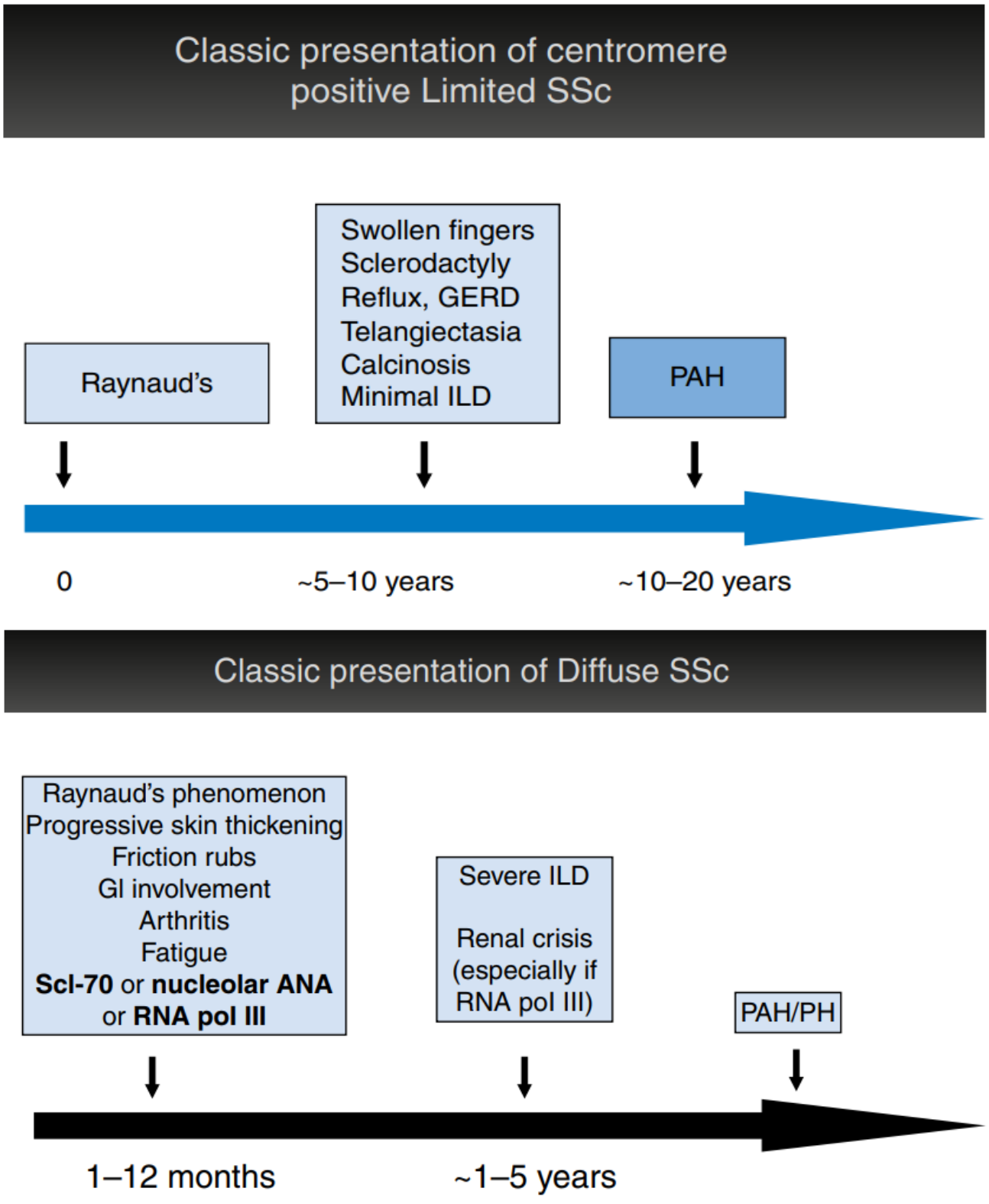
Diagnosis

- Clinical evaluation
- Usually antinuclear antibodies (ANA), Scl-70 (topoisomerase I), and anticentromere antibodies

AUTOANTIBODIES AND ASSOCIATED FEATURES IN SYSTEMIC SCLEROSIS (SSc)

TARGET ANTIGEN	SSc SUBSET	CHARACTERISTIC CLINICAL ASSOCIATION
Topoisomerase-I	dcSSc	Tendon friction rubs, ILD, cardiac involvement, scleroderma renal crisis
Centromere proteins	lcSSc	Digital ischemia, calcinosis, isolated PAH; renal crisis rare
RNA polymerase III	dcSSc	Extensive skin, tendon friction rubs, renal crisis
U3-RNP	dcSSc	PAH, ILD, scleroderma renal crisis, myositis
Th/T0	lcSSc	ILD, PAH
PM/Scl	lcSSc	Calcinosis, myositis
U1-RNP	MCTD	PAH

***Notes**: dcSSc – diffuse cutaneous SSc; ILD – interstitial lung disease; lcSSc – limited cutaneous SSc; MCTD – mixed connective tissue disease; PAH – pulmonary arterial hypertension.*



SSc should be considered in patients with Raynaud phenomenon, typical musculoskeletal or skin manifestations, or unexplained dysphagia, malabsorption, pulmonary fibrosis, pulmonary hypertension, cardiomyopathies, or conduction disturbances. Diagnosis can be obvious in patients with combinations of classic manifestations, such as Raynaud phenomenon, dysphagia, and tight skin. However, in some patients, the diagnosis cannot be made clinically, and confirmatory laboratory tests can increase the probability of disease but do not rule it out.

Serum ANA and Scl-70 antibody should be obtained. ANA are present in ≥ 90%, often with an antinucleolar pattern. Antibody to centromeric protein (anticentromere antibody) occurs in the

serum of a high proportion of patients with CREST syndrome and is detectable on the ANA. Scl-70 antigen is a DNA-binding protein sensitive to nucleases. Patients with diffuse scleroderma are more likely than those with CREST to have anti–Scl-70 antibodies. Rheumatoid factor also is positive in one third of patients.

If lung involvement is suspected, pulmonary function testing, chest CT, and echocardiography can begin to define its severity. Acute alveolitis is often detected by high-resolution chest CT.

Diagnostic criteria for SSc (ACR & EULAR, 2013)

Items	Sub-items	Weight
Skin thickening of fingers of both hands extending proximal to metacarpophalangeal (MCP) joints		9
Skin thickening of fingers (only count the highest score)	Puffy fingers Whole finger, distal to MCP	2 4
Fingertip lesions (only count the highest score)	Digital tip ulcers Pitting scars	2 3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or interstitial lung disease		2
Raynaud's phenomenon		3
Scleroderma-related antibodies (any of anti-centromere, anti-topoisomerase I [anti-ScL 70], anti-RNA polymerase III)		3
Patients with a total score of ≥9 are classified as having definite systemic sclerosis (sensitivity 91%, specificity 92%)		

***Notes**: ≥ 9 → definite SSc*

Prognosis

The course depends on the type of SSc but is unpredictable. Typically, progression is slow. Overall 10-yr survival is about 65%. Most patients with diffuse skin disease eventually develop visceral complications, which are the usual causes of death. Prognosis is poor if cardiac, pulmonary, or renal manifestations are present early. Heart failure may be intractable. Ventricular ectopy, even if asymptomatic, increases the risk of sudden death. Acute renal insufficiency, if untreated, progresses rapidly and causes death within months. Patients with CREST syndrome may have disease that is limited and nonprogressive for long periods; visceral changes (eg, pulmonary hypertension caused by vascular disease of the lung, a peculiar form of biliary cirrhosis) eventually develop, but the course is often remarkably benign.

Treatment

Treatment directed at symptoms and dysfunctional organs.

No drug significantly influences the natural course of SSc overall, but various drugs are of value in treating specific symptoms or organ systems. NSAIDs can help arthritis but may cause GI problems. Corticosteroids may be helpful if there is overt myositis or mixed connective tissue disease but may predispose to renal crisis and thus are used only if necessary. Penicillamine, long used for treatment of skin thickening, has not shown clear efficacy in recent trials.

Various immunosuppressants, including methotrexate, azathioprine, mycophenolate mofetil, and cyclophosphamide, may help pulmonary alveolitis. Successful lung transplantation has been reported. Epoprostenol (prostacyclin) and bosentan may be helpful for pulmonary hypertension. Ca channel blockers, such as nifedipine 20 mg po tid or as an extended-release formulation, may help Raynaud phenomenon but may worsen gastric reflux. Bosentan, sildenafil, tadalafil, andvardenafil are other alternatives for severe Raynaud phenomenon. Patients should dress warmly, wear mittens,

and keep their head warm. IV infusions of prostaglandin E1 (alprostadil) orepoprostenol or sympathetic blockers can be used for digital ischemia. Reflux esophagitis is relieved by frequent small feedings, high-dose proton pump inhibitors, and sleeping with the head of the bed elevated. Esophageal strictures may require periodic dilation; gastroesophageal reflux may possibly require gastroplasty. Tetracycline 500 mg po bid or another broad-spectrum antibiotic can suppress overgrowth of intestinal flora and may alleviate malabsorption symptoms. Physiotherapy may help preserve muscle strength but is ineffective in preventing joint contractures. No treatment affects calcinosis.

For acute renal crisis, prompt treatment with an ACE inhibitor can dramatically prolong survival. BP is usually, but not always, controlled. The mortality rate of renal crisis remains high. If end-stage renal disease develops, it may be reversible, but dialysis and transplantation may be necessary.

3.2. Questions and tasks to assess the degree of assimilation of lecture material

1. The definition of SDCT
2. Markers of target organs damages.
3. Risk factors and causes of SDCT development and progression.
4. Methods of clinical, laboratory and instrumental diagnostics of SDCT.
5. Classification of SLE and SS.
6. Describe clinical manifestation of SDCT depended on stages.
7. The complications of SDCT
8. SDCT management programs

3.3. Tasks

1. A 32 y.o. patient has been suffering from systematic scleroderma for 14 years. She was repeatedly exposed to treatment in the in-patient department. Complains of periodical dull cardiac pain, dyspnea, headache, eyelid edemata, weight loss, pain and deformation of extremities joints. What organ's lesion deteriorates the prognosis for the disease?

A. Kidneys
B. Heart
C. Lungs
D. Gastrointestinal tract
E. Skin and joints

2. A 38-year-old patient is under observation having polyneuritic syndrome with considerable loss of weight, fever, rise in BP. Blood test: considerable inflammatory changes. What examination is the most expedient to make the diagnosis?

A Determination of antinuclear antibodies
B Muscular biopsy with histological investigation of the material
C Electromyography
D Blood culture
E Determination of HLA antigens

3. A 41 y.o. woman complains of weakness, fatigue, fever up to 38^0C, rash on the face skin, pain in the wrists and the elbows. On physical examination: erythematous rash on the cheeks with "butterfly" look, the wrists and elbow joints are involved symmetrically, swollen, sensitive, friction rub over the lungs, the heart sounds are weak, regular, HR- 88/min, BP- 160/95 mm Hg. Hematology shows anemia, leucopenia, lymphopenia; on urinalysis: proteinuria, leukocyturia, casts. What is the main mechanism of disease development?

A Production of antibodies to double-stranded DNA
B Production of myocytes antibodies

C Production of antibodies to endothelial cells
D Production of myosin antibodies
E Production of antimitochondrial antibodies

4. A 30-year-old patient presented with body temperature rise up to 38,5°C, pain in the small joints of hands; face edemata and erythema. In blood: RBCs - $2,6*10^{12}$/l; Hb- 98 г/л; WBCs – $2*10^{9}$/l; ESR - 58 mm/h. In the urine: protein - 3,1 g/l; RBCs - 10-15 in the vision field. What disease can be suspected in this case?

A Periarteritis nodosa
B Sepsis
C Systemic scleroderma
D Systemic lupus erythematosus
E Acute glomerulonephritis

5. The 28 y.o. woman applied to doctor because of limited loss of the hair. In the anamnesis - she had frequent headache indisposition, arthromyalgia, fever, irregular casual sexual life, drug user. RW is negative. What examination must be done first?

A Examination for trichomoniasis
B Examination for neuropathology
C Examination for gonorrhea
D Examination for fungi
E Examination for HIV

Standard answers: 1-A, 2-B, 3-A, 4-D, 5-E

CLINICAL CASE

Patient S., female, 22 years old. Complaints of pain in large and small joints of hands and feet, limbs, weakness, loss of weight. 2 years ago after a sore throat developed arthritis. Diagnosed rheumatism. After 2 weeks appeared erythematous rash on her neck, cheeks, nose. Last worsening after hypothermia (cooling): arthralgia of small joints of hands, low-grade fever, pain in the left side.

At admission: the state of medium gravity. The temperature of 38,5 C °. On the face erythematous rash. Right in the armpit palpable enlarged lymph nodes. Contours interphalangeal joints are smoothed, the movement in them in full volume. Other joints without changes. In the lungs: a slight shortening of percussion sound and noise of friction of the pleura in the underarm area under 5-th ribs. The heart was normal, pulse 88 per minute, rhythmical. Blood pressure 110/70 mmHg Abdomen soft, painless. Liver and spleen were not enlarged.

Blood test: Hb - 60 g / l, E - $3,2 * 10^{12}$ / l, L. - $4,2 * 10^{9}$ / l, ESR - 68 mm / hour. Urine: the relative density of 1006, protein 3.3 g / l, leukocytes in the 10-15 f / v, erythrocytes leached 3-4 in f / v. ECG: sinus tachycardia, PQ 0,22 sec.

Questions:

1. Primary clinical diagnosis?
2. Plan of additional investigation?
3. Differential diagnosis?
4. Treatment?
5. Whether physiotherapy treatment indicated?

Answering standards

- SLE, acute, active phase.
- Nonspecific indicators of inflammation, including protein fractions, LE-cells, antinuclear factor, the titre of antibodies to DNA, X-ray of the chest, X-ray of the joints, EhoCS.

- It should be a differential diagnosis of rheumatoid arthritis, rheumatic heart disease, nodular periarteriitis etc. connective tissue diseases.
- Glucocorticoids, aminochinoline derivatives, cytostatics.
- Due to severity of activity - physical therapy procedures are contraindicated.

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Lecture № 2
Topic: Chronic kidney disease (CKD)

Objective: to prepare a specialist who is able to perform professional activities, applying the acquired knowledge on the problem of chronic kidney disease (CKD), from the inherent modern laboratory and instrumental research, medical manipulations, tactics and standards of patient management based on evidence medicine, to identify tasks and problems in the field of nephrology in clinical practice and in further training.

Specific objectives of the lecture:

- Discuss the prevalence of CKD and its impact on public health in the world and in Ukraine
- Define CKD.
- Explain the etiology, pathogenesis of risk factors for the development and progression of CKD.
- Discuss the clinical manifestations of the typical course of CKD and complications of CKD.
- Explain the current classification of CKD.
- To substantiate the use of the main methods of diagnosis of CKD, to discuss their informativeness, to determine the indications and contraindications for their use.
- Explain the basic principles of differential diagnosis in a patient with suspected CKD using the analysis of clinical manifestations, laboratory data and instrumental examination, to substantiate the clinical diagnosis of CKD. Give examples of diagnosis in patients with different variants of CKD.
- Explain the basic principles of modern strategy of continuous reno- and cardioprotection of patients with CKD, as components of primary and secondary prevention of CKD, treatment of patients with different stages of CKD according to evidence-based medicine.
- Discuss modern approaches and methods of renal replacement therapy (NRT): hemodialysis, peritoneal dialysis, kidney transplantation, indications and contraindications to NRT, complications.
- To present modern methods of assessment of the prognosis in patients with CKD.
- Demonstrate moral and deontological principles of a medical specialist and the principles of professional subordination when working with patients with CKD.

Basic concepts: chronic kidney disease (CKD), risk factors (RFs), criteria for diagnosis of CKD, stages of CKD, urinary syndrome, uremia, electrolyte disorder, erythropoietin-deficient anemia, calcium-phosphorus metabolism disorders, glomerular filtration rate, renal protection strategy, renal replacment therapy (RRT).

Lecture plan and organizational structure

N IO	The main stages of the lecture and their content	Goals in levels of abstraction	Type of lecture, methods and means of activating students, equipment	Time distribution, min
1	*2*	*3*	*4*	*5*
1.	Preparatory stage: 1. setting educational goals 2. providing positive motivation - the importance of the problem of CKD for the clinical practice of a family doctor - general practice.	I I	Clinical lecture: – with elements of problem, – with the use of clearness, – with the use of interactive communication-	5
2.	The main stage: presentation of lecture material according to the plan: 2.1.Epidemiology of CKD	I II	Visual tools: – multimedia presentation of the lecture in Power Point format, incl. using the Microsoft Teams platform,	75

	2.2. The role of the general practitioner in the management of patients with CKD Lecture content: 2.3. Definition of CKD 2.4. Risk factors for the development and progression of CKD 2.5. Pathogenesis of lesions of organs and systems. 2.6. Classification of CKD. Changes in laboratory parameters depending on the stage. 2.7. Clinical manifestations and typical course, complications. 2.8. Diagnosis and principles of differential diagnosis in a patient with CKD. 2.9. Current strategy of managing patients with CKD. Treatment at different stages of CKD according to evidence-based medicine. 2.10. Renal replacement therapy: dialysis, kidney transplantation. Indications and contraindications to renal replacement therapy, complications. 2.11. Primary and secondary prevention. Strategy of continuous renoprotection. 2.12. Prognosis in patients with CKD.	III III III III II II II II	– extracts from medical records of patients with CKD (or thematic patient), – adapted clinical guidelines for the management of patients with CKD, – KDIGO recommendations	
3.	Final stage: 3.1. Problems that need to be solved. 3.2. Questions and tasks to assess the degree of assimilation of lecture material The lecturer's answer to possible questions.	II III III III	Materials to control: - questions - situational tasks	10

	3.3. Tasks for self-preparation.			

Contents of the topic

2.1. Epidemiology of CKD

For many years, the seriousness of the CKD problem was underestimated. The surge of interest in the problem of CKD began at the beginning of the XXI century, when data from large epidemiological studies (NHANES, etc.) showed a high incidence of renal dysfunction in the population, and when it became clear that dialysis services around the world, despite to open new dialysis centers, do not cope with the influx of patients with end-stage disease.

In the United States, for example, $ 21.3 billion was spent on the treatment of patients with terminal stage of CKD in 2005, accounting for 6.4% of Medicare's budget. These costs increase by 7.7% annually. In the EU, 2% of the health budget is spent annually on dialysis alone [3.В. Бабенко, 2019]. According to a study conducted in 12 countries (Bangladesh, Bolivia, Bosnia and Herzegovina, China, Egypt, Georgia, India, Iran, Moldova, Mongolia, Nepal and Nigeria) with a total of 75058 participants, the prevalence of CKD among adults was quite high: 14 , 3% in the general population, 36.1% - in high-risk groups (hypertension, diabetes, cardiovascular disease (CVD)[6].

CKD causes profound damage to public health and has serious socio-economic consequences. The most obvious consequence of CKD is the high cost of life-saving renal replacement therapy (RRT) (dialysis and kidney transplantation), which is a heavy burden on health systems [3.В. Бабенко, 2019]. The number of patients in need of specialized nephrological care in Ukraine is growing every year. Every year, 250 patients with stage V CKD are registered per 1 million population.

According to the National Register of Ukraine, in 2014, 7,079 patients received treatment with RRT (5,335 - were treated with hemodialysis (HD), 966 - peritoneal dialysis (PD)), ie the prevalence of RRT was 157 per 1 million population.

The number of patients with a functioning kidney transplant was 845, thus, the increase in the number of such patients from 2012 to 2014 was 0.6% [7].

Thus, analyzing all the data, we can say that the number of patients with CKD, as well as patients treated with NRT, in Ukraine, as well as around the world, is growing steadily, and the state of medical care to patients wants to be better.

2.2. The role of the general practitioner in the management of patients with CKD.

The effectiveness of actions in the treatment of a particular patient and the achievement of success in the correction of CKD largely depends on the coordination of actions of general practitioners – family medicine and nephrologists, which provides a unified diagnostic and therapeutic approach. The central figure in the primary prevention of CKD is the family doctor, who should screen this condition, dispensary observation of patients at risk. If the patient is diagnosed with risk factors (RF) for the development and progression of CKD, the physician should provide recommendations for the correction of modified PF and further monitor the patient's compliance with these recommendations, identify and correct clinical conditions associated with CKD development [8].

2.3. Definition of CKD

CKD - the presence of signs of kidney damage lasting > 3 months, manifested by structural or functional disorders of the kidneys, with a decrease in glomerular filtration rate (GFR) or without it, and have one or more of the following signs:

- disorders in blood or urine tests;
- damages detected during imaging studies;
- violation detected by kidney biopsy;
- GFR <60 ml / min / 1.73 m2 for > 3 months, with other signs of kidney damage listed above, or without them.

Chronic renal failure is a symptom complex that occurs as a result of primary or secondary CKD due to progressive sclerosis of kidney tissue and death of nephrons.

Therefore, the criteria for determining CKD are (see Tables 1 and 2):

Table 1

Criteria for the diagnosis of chronic kidney disease (CKD) according to KDIGO 2012

Criterion	Comment
Duration ≥3 months	the criterion is necessary for the diagnosis of CKD
GFR <60 ml / min / 1.73 m2 (categories G3a – G5)	evaluation (eGFR [ml / min / 1.73 m2]), using formulas based on the concentration of creatinine: 1) CKD-EPI formula 2) abbreviated formula MDRD
Albuminuria	- urinary loss ≥30 mg / day or albumin / creatinine index ≥30 mg / h; - categories of albuminuria (Table 2)
Abnormalities of urine sediment	- isolated microhematuria with altered erythrocytes - erythrocyte, fat, granular cylinders or epithelial cells
Renal tubular dysfunction	- renal tubular acidosis, - renal diabetes mellitus, - loss of potassium or magnesium by the kidneys, - Fanconi syndrome, – cystinuria, different from albuminuria proteinuria
Anatomical (structural) disorders detected by imaging studies	- polycystic kidney disease, - renal dysplasia, - hydronephrosis as a consequence of obstruction of urine outflow, - scarring of the renal cortex as a result of infarcts, - pyelonephritis or vesicoureteral reflux, - kidney tumors or infiltrative diseases, - stenosis of the renal artery, • - small kidneys with increased echogenicity (widespread ultrasound picture of progressive CKD in many atherosclerotic diseases)
Known histopathological changes (kidney biopsy) or reasonable suspicion of them	- glomerulopathies (GN, diabetes, autoimmune diseases, amyloidosis, systemic infection, tumors) - vascular diseases (atherosclerosis, hypertension, anemia, vasculitis, thrombotic microangiopathy, cholesterol embolism) - tubulointerstitial diseases (urinary tract infections, nephrolithiasis, urinary tract obstruction, sarcoidosis, toxic effects of drugs, exogenous toxins) • diseases accompanied by cystosis and hereditary (Alport's disease, Fabry's disease)
Condition after kidney transplantation	in most cases, biopsy of the transplanted kidney reveals pathological changes, even if the GFR> 60 ml / min / 1.73 m2 and no albuminuria

a. simple cysts of the kidneys are not a basis for the diagnosis of CKD

Table 2

Categories of albuminuria in CKD according to KDIGO 2012

Categories	Daily excretion with urine (mg / 24 years)	Albumin / creatinine ratio (mg / day)
A1	<30	<30
A2	30–300	30–300
A3	>300	>300

Why is GFR used to establish the stage of CKD instead of creatinine? Not only the level of creatinine, but also the clearance of creatinine today is not an indicator of the functional state of the kidneys, because it depends on many factors: gender, age, muscle mass, etc.

Objective methods that characterize the functional state of the kidneys include radioisotope methods using EDTA or Cr51. However, scientists have concluded that to determine the functional state of the kidneys are also suitable calculation methods recommended, of which e CRD-EPI, MDRD.

The progression of CKD is determined on the basis of the value of GFR (category G; Table 3) and the size of albuminuria (category A; Table 2).

The value of GFR is determined (calculated (c) GFR) based on the concentration of creatinine or cystatin C in serum. The size of albuminuria is determined based on the daily loss of urinary albumin or the albumin / creatinine index.

A complete diagnosis of CKD includes the name of kidney disease (the cause of CKD, if known) along with the assigned appropriate category G and A.

Table 3.

Categories of GFR for CKD according to KDIGO 2012

Categories of GFR	GFR	Interpretations
G1	≥90	normal or elevated GFR
G2	60–89	Mildly decrease in GFR
G3a	45–59	reduction of GFR between mildly and moderate
G3b	30–44	reduction of GFR between moderate and severe
G4	15–29	severe decrease in GFR
G5	<15	terminal renal failure (end stage CKD)

Chronic renal failure (CRF) belongs to categories G3 – G5 CKD; category G5 is called end-stage renal disease (ESRD) or uremia.

2.4. Risk factors for the development and progression of CKD.

There is a proven link between certain clinical conditions and the risk of developing CKD.

Risk factors for CKD:

Cardiovascular diseases:

- hypertension (HT)
- atherosclerosis
- heart failure (HF)

Metabolic disorders:

- diabetes mellitus (DM)
- obesity
- dislipidemia
- disorders of purine metabolism

Lifestyle, diet, habits:

– smoking
– drug use
– alcohol abuse
– abuse of painkillers
– abuse of protein biological supplements
– protein abuse and protein depletion
– professional contacts with organic solvents, salts of heavy metals, toxins
– hypodynamia
– age > 60 years
– male
– ethnicity

Low social level

– Inherited predisposition to kidney disease, heart disease, diabetes
– Disorders of fetal development, malnutrition at birth
– Aplasia, renal hypoplasia
– Low family traditions.

Causes of CKD:

– diabetic nephropathy,
– hypertensive nephropathy,
– glomerulonephritis,
– tubulointerstitial kidney disease,
– multicystic degeneration of the kidneys;
– less often - ischemic nephropathy,
– obstructive nephropathy,
– systemic connective tissue diseases,
– sarcoidosis,
– amyloidosis.

There are 4 groups of RFs that affect the development and course of CKD			
Which have a possible impact on the development of CKD	Which provoke the development of CKD	Progression of CKD	Terminal stage of CKD
– Positive family fnfmnesis by CKD, – Reduction in size and volume of the kidneys, – Low birth weight, prematurity – Low social output and social level	– The presence of DM type 1 and 2, HT, – Autoimmune diseases, – Urinary tract infections, – - Exposure to toxic substances (including drugs)	– High degree of proteinuria, – Insufficient control of hypertension, glycemia, – Smoking, – Excessive alcohol consumption, – Drug addiction	– Untimely start of renal replacement therapy – Low dialysis per dose, – temporary vascular access, – anemia, – hypoalbuminemia

2.5. Pathogenesis of lesions of organs and systems.

Most RFs can cause gradual loss of nephrons, which causes overload of other nephrons, primarily due to hyperfiltration. Initially, the glomeruli undergo hypertrophy, and then sclerotic changes and interstitial fibrosis develop, leading to impaired renal function.

With the progression of CKD, uremic toxins accumulate in the blood, mainly low- and medium-molecular products of protein metabolism.

Reduces the synthesis of erythropoietin in the kidneys, which, along with other factors (iron deficiency, hidden or obvious blood loss, inhibition of bone marrow function by uremic toxins, shortened lifespan of erythrocytes, folic acid deficiency and vitamin B12), leads to anemia.

Decreased α1-hydroxylation of vitamin D in the kidneys is one of the causes of hypocalcemia and secondary hyperparathyroidism.

The kidneys lose the ability to maintain proper volemia, electrolyte composition and blood pH. Due to impaired excretion of sodium and water by the kidneys (hypertensive natriuresis), excessive secretion of vasopressor by the kidneys (angiotensin II, endothelin 1), deficiency of vasodilating factors (NO, prostaglandins), increased activity of the sympathetic system, hormonal disorders,and arterial HT, which occurs in >90% of patients with significant renal excretory dysfunction (this percentage is reduced to 50% after the start of hemodialysis). Erythropoietin, which is used to treat anemia, is also a factor in causing high blood pressure (BP).

RFs that can be modified and associated with faster progression of CRF: proteinuria, hypertension, hyperglycemia, hyperlipidemia, anemia, smoking, metabolic acidosis.

Causes of sudden exacerbation of CKD: dehydration, hypotension, X-ray contrast agents containing iodine, nephrotoxic drugs, obstruction of urine outflow, concomitant acute renal failure, exacerbation of the underlying disease, pyelonephritis with complications, malignant hypertension, exacerbation of heart failure or renal arteries and veins thrombosis.

2.6. See Tables 2 and 3.

2.7. Clinical manifestations and typical course, complications.

The clinical picture depends on the severity of CKD and the underlying disease. At the beginning there may be no clinical symptoms or they are not pathognomonic (eg, hypertension). As GFR decreases, symptoms and complications from various organs and systems appear.

General symptoms: weakness, fatigue, hypothermia, loss of appetite, decreased immunity to infections.

Skin symptoms: paleness, dry skin, earthy brown skin color, prolonged bleeding from wounds and a tendency to bruising (symptom of hemorrhagic diathesis), itching (with severe CRF) - "uremic hoarfrost" (deposition of urea on the skin).

Cardiovascular disorders: hypertension, left ventricular hypertrophy (LVH), heart failure (HF), arrhythmia, accelerated atherosclerosis, vascular calcification, uremic pericarditis.

Respiratory disorders: acidic respiration (Kussmaul), uremic pleurisy, hyperemia and pulmonary edema (so-called uremic lungs with severe CKD).

Digestive disorders: gastritis and enteritis, peptic ulcer of the stomach or duodenum, gastrointestinal bleeding; with severe CKD - uremic bad breath, nausea and vomiting, paralytic intestinal obstruction, acute pancreatitis.

Nervous system and muscle dysfunction: (occurs in severe CKD): impaired concentration and memory, headache, drowsiness or insomnia, behavioral disorders (eg, apathy or irritability), convulsions and coma (symptoms of severe encephalopathy or edema) brain), restless legs syndrome (feeling of discomfort in the legs makes you constantly perform movements of the lower extremities), loss of deep tendon reflexes, muscle weakness, gross wavy tremor, spasms of muscle bundles and muscle groups, chronic hiccups, paralysis of the tibia , peripheral tetraplegia in severe neuropathy.

Reproductive system disorders: menstrual disorders (infrequent menstruation, secondary amenorrhea), infertility, sexual disorders (decreased libido, impotence).

Syndrome of mineral and bone disorders associated with CKD: disorders of calcium metabolism (hypo- or hypercalcemia), phosphorus (hyperphosphatemia), vitamin D deficiency and disorders of parathyroid hormone secretion (secondary or tertiary hyperparathyroidism) lead to disorders of bone metabolism) and calcification of blood vessels and other soft tissues. Renal osteodystrophy is a progressive disorder of bone structure due to too fast (cause -

hyperparathyroidism) or too slow (so-called adynamic bone disease) bone metabolism, or due to deposition of β2-microglobulin or aluminum in the bones; manifests itself in the form of pain in the bones and joints, as well as spontaneous bone fractures.

Disorders of water-electrolyte and acid-base balance: detected in laboratory studies.

G1 (GFR ≥90 ml / min / 1.73 m2): clinical symptoms of the underlying disease (DM, HT, glomerulonephritis, etc.); albuminuria 30 - 300 mg / dL is very common. The first step is to determine the cause and eliminate the risk factors for the progression of kidney disease.

G2 (GFR 60–89 ml / min / 1.73 m2; early CKD): serum creatinine and urea concentration, usually normal. The ability of the renal tubules to concentrate urine decreases, which increases the tendency to dehydration. Phosphorus retention and the onset of secondary hyperparathyroidism may occur. Some patients with diabetic nephropathy and tubulointerstitial kidney disease develop anemia due to decreased erythropoietin synthesis.

G3 (GFR 30–59 ml / min / 1.73 m2, moderate CKD) HT was observed in >50% of patients. Isostenuria, polyuria, polydipsia and nocturia. Creatinineemia is 130–350 mmol/l), increased concentration of phosphates (in some patients) and products of protein metabolism (urea, uric acid) in the blood. Many patients suffer from anemia, some have an unpleasant taste in the mouth, loss of appetite and nausea.

G4 (GFR 15–29 ml / min / 1.73 m2; severe CKD): marked exacerbation of pre-existing symptoms, including loss of appetite, nausea and vomiting. Typically, creatinineemia >442 mmol / L. HT develops in >80% of patients, many of whom develop LVH, and some have symptoms of HF. Most patients have significant anemia, which causes weakness and decreased tolerance to exercise, as well as metabolic acidosis.

G5 (GFR <15 ml / min / 1.73 m2, terminal stage of CKD [uremia]): symptoms from almost all organs and systems. Renal replacement therapy is usually required.

2.8. Diagnosis and principles of differential diagnosis in a patient with CKD.

CKD should be actively detected by screening studies, because for many years the disease can develop without objective or subjective symptoms. Periodic general urinalysis, determination of serum creatinine and urinary microalbuminuria is necessary in patients at increased risk of CKD, especially in patients with DM or HT.

In practice, the best indicator for assessing renal function is the calculation of GFR, rather than determining the concentration of creatinine in the serum, which depends on age and muscle mass. Patients with a burdensome family history of kidney disease (eg, polycystic kidney disease) should be screened by imaging, usually ultrasound.

The cause of CKD can be indicated by: subjective and objective symptoms, comorbidities, incorrect results of past studies and family history of kidney disease.

Investigations:

General examination of urine: albuminuria, proteinuria, micro / macro-hematuria, cylinders, leukocyturia, low relative density of urine.

Blood tests: anemia (usually normocytic and normochromic), increased concentrations of creatinine, urea, uric acid, potassium, phosphates and parathyroid hormone, triglycerides, cholesterol; hypocalcemia; metabolic acidosis.

Imaging studies:

Ultrasound: the kidneys are usually reduced in size (often <10 cm in the long axis); exceptions (large kidneys, despite CKD) in amyloid nephropathy, diabetic nephropathy, polycystic kidney disease and nephropathy in HIV infection.

Contrast-enhanced imaging studies (eg, CT) are performed only when absolutely necessary, given the high risk of contrast-induced nephropathy!

Diagnostic criteria:

The diagnosis of CKD is established if within ≥3 months morphological or functional disorders of the kidneys, or GFR <60 ml / min / 1.73 m2. CRF is diagnosed in patients with CKD and GFR <90 ml / min / 1.73 m2.

The order of formulation of the diagnosis

The International Classification of Diseases of the 10th (ICD-10) revision has been used for statistical coding of diseases since 1999 (WHO, Geneva, 1995). A new version of the classification of diseases of the urinary system, as well as the previous ones, was proposed by a group of employees of the Institute of Nephrology of the National Academy of Medical Sciences of Ukraine under the leadership of Corresponding Member NAMS of Ukraine, prof. M. Kolesnyk. Changes to the previous editions were considered and approved by the IV National Congress of Nephrologists of Ukraine (2013).

According to this classification, the following codes are used to determine chronic renal failure (included in the concept of CKD): N18.0 - terminal stage of kidney damage, N18.8 - other manifestations of chronic renal failure, N18.9 - chronic renal failure unspecified.

In the case of primary chronic kidney disease in the diagnosis indicate the stage of CKD, its nosological basis morphologically (with the date of nephrobiopsy) or clinically (in the absence of morphological verification), indicate the presence of nephrotic syndrome, hypertension and the presence of cardiovascular risk pathology. In the case of secondary chronic kidney disease, the nosological basis of CKD is formulated, then the stage of CKD, the name of kidney disease (with morphological verification, if any), the presence of nephrotic syndrome, the degree of hypertension, anemia, complications and comorbidities.

In cases where it is impossible to determine the nosological basis of primary or secondary chronic kidney disease, a diagnosis of chronic kidney disease is established (see Table 4); then the diagnosis indicates the presence of nephrotic syndrome, the degree of hypertension and the degree of cardiovascular risk, anemia, complications and comorbidities.

Table 4.

Examples of formulation and coding of diagnoses

№	Diagnosis	ICD-10
1.	Diabetes mellitus, type I, severe, decompensation. CKD G4. Diabetic nephropathy. Nephrotic syndrome. Anemia.	N18.0
2.	CKD G4. Glomerulonephritis. Anemia. Hypertension 2 stage (LVH), 1 grade, very high risk.	N18.0
3.	Hypertension, 3 stage, 3 grade, very high risk. CKD G5	N18.0

2.9. Current strategy of managing patients with CKD.

Treatment at different stages of CKD according to evidence-based medicine.

A nephrologist should be consulted when the GFR is below 60 ml / min and is mandatory if the GFR is below 30 ml / min.

If GFR measurement is not available, patients with chronic renal failure should be referred to a nephrologist when in two consecutive measurements, plasma creatinine exceeds 150 μmol / L in men and 120 μmol / L in women, with a GFR ratio of ~ 50 ml / min. These patients should be referred regardless of whether they have other manifestations of renal pathology, such as proteinuria.

The current strategy of management of patients with CKD includes:

- etiotropic treatment of CKD,
- slowing the progression of CKD,
- prevention of complications of CKD and their treatment,
- preparation and treatment with renal replacement therapy.

General recommendations:

- Treat comorbidities.
- Prevention of cardiovascular disease (high risk in patients with CKD), including smoking cessation.

- Avoid nephrotoxic drugs. Remember to adapt the dose of drugs excreted by the kidneys to creatinine clearance.
- Prevention of infection by vaccination: annual vaccination against influenza (all patients with CKD); vaccination with polyvalent pneumococcal vaccine (all patients with an estimated GFR <30 ml / min / 1.73 m2), repeated after 5 years; hepatitis B vaccination (all patients with an estimated GFR <30 ml / min / 1.73 m2 or earlier if there is a gradual decrease in the estimated GFR).

Diet: The main goal: to provide sufficient energy: in adult patients with chronic renal failure and with a normal weight of 35 kcal / kg of body weight per day (30-35 kcal / kg of body weight in people > 60 years) - 50-60% due to carbohydrates, ≤30% of fats (animal ≤1 / 3).

The recommended daily intake of protein depends on GFR (ml / min / 1.73 m2):

> 60 → 0.8–1.0 g / kg of body weight;
25–60 → 0.8 g / kg of body weight;
<25 → 0.6 g / kg of body weight, 2/3 animal protein).

If daily protein intake <0.6 g / kg of body weight → add essential amino acids, preferably in the form of keto-analogues, conduct regular monitoring of nutritional status. Up to 5 days you can use standard diets for enteral nutrition, then - special diets.

In case of hypertension, it is recommended to limit sodium intake to 1.15–2.3 g / day (50–100 mmol / day). Do not recommend commercially available low-sodium salt to patients with renal insufficiency, as sodium is replaced by potassium, and consumption of such products is associated with a high risk of life-threatening hyperkalemia.

Usually, it is not necessary to limit potassium intake in patients with GFR ≥30 ml / min / 1.73 m2, if they do not have hyporenin hypoaldosteronism.

Daily phosphorus intake should be limited to 800–1000 mg if serum inorganic phosphate concentrations exceed the upper limit of normal.

Patients who are not treated with dialysis do not need to add any vitamins.

Pharmacological treatment:

Treatment that reduces proteinuria: the purpose of proteinuria <1 g / day, optimally <0.3 g / day. The main importance is treatment aimed at the cause of proteinuria (primary or secondary glomerulopathy). In any case, if there are no contraindications, prescribe ACE inhibitors or ARBs, also in patients with normal BP. In patients with normal GFR, these drugs should be prescribed in moderate and maximum doses, if these drugs are well tolerated by the patient. Be careful → start with small doses, regularly monitor the concentration of creatinine and potassium in the serum.

We are now at new point in nephrology. We have the RAAS inhibitors, we have the SGLT2 inhibitors, and the nonsteroidal MRAs (ns-MRAs)—specifically finerenone—that has been shown to slow diabetic kidney disease (DKD) independent of the SGLT2 inhibitors, but predicated on good management with maximally tolerated doses of ACE inhibitors and ARBs.

What are these ns-MRAs. This is a new class of drugs [8]. They are a new class of drugs and their chemistries are very different, their interactions are different, the half-lives are different, the blood-pressure responses are different, and they are just very different agents. The half-life of finerenone is 2 to 3 hours. It don't get into the brain; they don't have hormonal side effects; their BP effects are modest [unless you have an elevated BP above 140 mmHg]; and they are highly selective and potent. Because of their chemistry, they block the receptor in a different way than do the steroidal agents [9-11]. There are very large trials. One is the FIDELIO-DKD trial, the other one is the FIGARO-DKD trial, and when we designed these trials, it was done in a way we could combine them to do an individual patient level analysis called FIDELITY. The FIDELITY analysis is each patient from each trial was put together in the database. The FIDELITY analysis is over 13,000 patients studied with finerenone who had T2DM, various levels of kidney function, various levels of cardiac function. The primary endpoint: Major adverse cardiovascular events (MACE) with heart failure hospitalisation (HHF), and the other endpoint, the renal endpoint was a doubling of creatinine, time to dialysis, renal death, or GFR less than 15. The outcomes: there is clear evidence that HHF was dramatically reduced by 22%. Cardiovascular outcomes, cardiovascular death was reduced, which

didn’t quite make statistical significance, but finerenone certainly was effective. The other point is every single component of the renal endpoint, which included kidney failure, dialysis, GFR less than 15, and doubling of serum creatinine, were all significantly reduced. The important point here: dialysis was reduced by 20%. So, clearly showing the benefit on all renal components.

Sodium--glucose co-transporter-2 (SGLT-2) inhibitors. Within the past few years, evidence from cardiovascular outcome trials with SGLT-2 inhibitors clearly suggested that these agents substantially delay CKD progression in patients with diabetes mellitus on top of standard-of-care treatment. The Canagliflozin-and-Renal-Events-in-Diabetes-with-Established-Nephropathy-Clinical-Evaluation(CREDENCE) study, showed that canagliflozin substantially reduced the risk of doubling of serum creatinine (Scr), end-stage kidney disease (ESKD), or death from renal or cardiovascular causes in 4401 patients with diabetic CKD compared with placebo (hazard ratio 0.70; 95% CI 0.59–0.82). Recently, the Study-to-Evaluate-the-Effect-of-Dapagliflozin-on-Renal-Outcomes-and-Cardiovascular-Mortality-in-Patients-With-Chronic-Kidney-Disease (DAPA-CKD), including 2510 patients with diabetic and 1803 with nondiabetic CKD, also showed an impressive reduction in the risk of ≥50% decline in eGFR, ESKD, or death from renal or cardiovascular causes (HR 0.61; 95% CI 0.51–0.72). The benefit was similar for patients with diabetic and nondiabetic CKD, including patients with glomerulonephritides [12].

Thus, SGLT2 inhibitors are associated with a sustained modest reduction in systolic blood pressure (BP) of approximately 3 to 6mm Hg and diastolic BP of approximately 1 to 2 mmHg. BP lowering is mediated through natriuresis and associated plasma volume contraction, reduction in arterial stiffness, and improvement in endothelial function. Reduction in BP is generally observed irrespective of hypertension status and is also achieved in patients with lower eGFR level [13]. Other putative mechanisms through which SGLT2 inhibitors may be beneficial include reduction in inflammatory mediators, including interleukin-6, nuclear factor-kB, and profibrotic factors, such as transforming growth factor-ß. In addition, by conserving energy required to reabsorb the filtered load of glucose and associated sodium, SGLT2 inhibition may attenuate renal hypoxia and is simultaneously associated with a rise in hematocrit level.

Conclusion. SGLT2 inhibitors have emerged as a key therapy to prevent progression of CKD in patients with albuminuria with or without diabetes including patients with IgA nephropathy, FSGS, and heart failure. Although the indications for SGLT2 inhibitors have expanded rapidly, data remain scarce in transplant recipients or patients with ESKD and future studies should evaluate their safety and effectiveness in these populations. Nephrology has entered an exciting era in the development of novel therapeutics for our patients. Although SGLT2 inhibitors were found to have cardiorenal benefit, there remains a large unmet need to reduce remaining risk in patients with CKD.

Treatment of hypertension according to current recommendations[3].

Treatment of hyperlipidemia: the goal is to reduce cardiovascular risk.

1) In all adults after the diagnosis of CKD it is necessary to determine the parameters of the lipid profile (concentration of total cholesterol (cholesterol), X-LDL, X-HDL and triglycerides).

2) In patients aged ≥50 years:

a) with GFR ≥60 ml / min / 1.73 m2 statins should be prescribed according to the principles for the general population

b) with GFR <60 ml / min / 1.73 m2 without renal replacement therapy - prescribe statins in monotherapy (atorvastatin 20 mg / day, rosuvastatin 10 mg / day, simvastatin 40 mg / day) or simvastatin with ezetimibe (20/10 mg / day).

Water-electrolyte balance: intensively treat diseases that lead to dehydration and reduce the effective volume of circulating blood. Beware of diuretic overdose. The patient's diuresis should be ≈2 liters per day. It is recommended to limit sodium intake to <2 g / day (<5 g of sodium chloride) if there is no additional sodium loss.

Control of acidosis: reduction of acidosis is achieved by limiting protein in the diet and the appointment of calcium carbonate between meals (calcium carbonate) per os 3-6 g / day, provided that there is no hypercalcemia. Sodium bicarbonate (sodium bicarbonate) IV 0.5-1.0 mmol / kg / day,

or 0.5-1.0 g / 10 kg / day in 3-5 divided doses is more effective, but may cause sodium and water retention in the body. Maintain blood HCO3 levels> 22 mmol / L.

Treatment of disorders of calcium-phosphorus metabolism and hyperparathyroidism. Monitor disorders of calcium-phosphorus metabolism and parathyroid function every 6-12 months. with G3 category CKD, every 3-6 months. with G4 category CKD and every 1 to 3 months. in G5 category and in patients receiving dialysis treatment, or more often, depending on the type of disorders, their severity and changes in pharmacological treatment. Decide on treatment based on the detected changes in the concentrations of calcium, inorganic phosphates (Pi) in the serum (Increase in the concentration of inorganic phosphates (Pi) in the serum> 1.6 mmol / l) and PTH, taking into account all the parameters together, not on based on one study.

Some G3–5 patients with CKD develop pharmacologically resistant severe hyperparathyroidism with high PTH concentrations, hypercalcemia, hyperphosphatemia, and clinical complications (treatment-resistant anemia, unresponsive itchy skin, tissue calcification). In such cases, consider parathyroidectomy.

Treatment of anemia: target - hemoglobin concentration within 10 - 11.5 g / dl (hematocrit [Ht] 30-36%). *First, restore iron deficiency*. Oral iron intake - usually 200 mg of elemental iron per day in the form of iron sulfate in 3 divided doses may be insufficient due to impaired absorption of iron in the intestine and is often associated with the development of gastrointestinal side effects. In case of ineffective oral treatment or persistent side effects, intravenous iron should be administered.

Erythropoiesis-stimulating agent (ESA):

1) human recombinant α-erythropoietin (epoetin α) and β-erythropoietin (epoetin β) - initially, usually 50 IU / kg iv (erythropoietin β can be administered n / w) 3 × per week;

2) α-darbepoetin - initially 0.45 mg / kg iv or p / w 1 × per week .;

3) methoxy polyethylene glycol epoetin-β: first 0.6 μg / kg every 2 weeks, then 1 × per month.

ESAs are prescribed to patients with a hemoglobin concentration <10 g / dL after the exclusion of causes other than CKD of anemia and the initial recovery of existing iron deficiency or simultaneously with the replenishment of this deficiency. Contraindications: treatment-resistant hypertension, selective erythrocyte aplasia, stroke, active potentially curable tumor disease, hypersensitivity to drugs.

2.10. Renal replacement therapy (RRT): dialysis, kidney transplantation. Indications and contraindications to RRT, complications.

A. Dialysis should be started at a GFR of 15 ml / min and the presence of one or more of the following symptoms: symptoms of uremia, hyperhydration, uncontrollable hypertension, progressive deterioration of nutritional status. In any case, dialysis should be started before the GFR drops to 6 ml / min / 1.73 m², even if optimal pre-dialysis care is performed and there are no listed symptoms.

B. In high-risk patients, such as those with diabetes, an earlier start of dialysis therapy is preferred. (Level of evidence: C)

C. To ensure that dialysis is started before GFR drops to 6 ml / min, the clinical setting should be 8-10 ml / min. (Level of evidence: C).

The dialysis be initiated when one or more of the following are present:

- symptoms or signs attributable to kidney failure (serositis, acidbase or electrolyte abnormalities, pruritus); inability to control volume status or blood pressure;
- a progressive deterioration in nutritional status refractory to dietary intervention;
- or cognitive impairment.

Living donor preemptive renal transplantation in adults should be considered when the GFR is Less 20 ml/min/1.73 m2, and there is evidence of progressive and irreversible CKD over the preceding 6-12 months.

Methods:

Hemodialysis: performed 3 times a week lasts 4-5 hours. In the case of medical care or hospitalization of a patient receiving hemodialysis, the hemodialysis center should always be contacted for important patient information (eg, chronic hepatotropic virus infection) and instructions for further treatment.

Peritoneal dialysis: The most commonly used technique is continuous outpatient peritoneal dialysis. The patient stays at home and independently or with the help of a trained close person several times a day replaces the dialysis fluid in the abdomen. A relatively common complication is peritonitis, the first symptom of which is turbid dialysis fluid flowing from the abdomen, and the clinical symptoms are abdominal pain, nausea and vomiting, and peritoneal symptoms. In each case of hospitalization of a patient with peritoneal dialysis, you need to contact the center that conducts this treatment.

Трансплантація нирки: в усіх відношеннях це найкращий метод замісної ниркової терапії. Протягом усього періоду функціонування трансплантату пацієнт залишається під опікою центру трансплантації, з яким потрібно сконтактуватись при кожному випадку госпіталізації хворого з трансплантованою ниркою.

Kidney transplantation: in all respects it is the best method of renal replacement therapy. Throughout the period of graft operation, the patient remains under the care of the transplant center, which must be contacted in each case of hospitalization of a patient with a transplanted kidney.

Contraindications: common malignancies, severe dementia or other irreversible mental disorders that interfere with compliance with RRT requirements.

2.11. Primary and secondary prevention. Strategy of continuous renoprotection.

Risk factors associated with CKD progression to inform prognosis:

- cause of CKD,
- level of GFR,
- level of albuminuria,
- age, sex, race/ethnicity,
- elevated BP,
- hyperglycemia,
- dyslipidemia,
- smoking,
- obesity,
- history of cardiovascular disease,
- ongoing exposure to nephrotoxic agents, and others.

Early referral to a nephrologist is indicated for: hematuria, high proteinuria, hyperkalemia, rapid decrease in GFR.

The management of progression of CKD is aimed at addressing a multiplicity of factors known to be associated with progression. There are general measures which have been shown to address cardiovascular health and CKD together, or each separately. Addressing CVD risk factors may indirectly and directly impact CKD progression. Strategies include general lifestyle measures which improve cardio-vascular health, BP control, and interruption of the RAAS. In addition, control of other metabolic parameters such as blood sugar, uric acid, acidosis, and dyslipidemia may also be important. This section deals with management of BP, RAAS interruption, glycemic control and dietary/lifestyle manipulations which have been examined in the context of delaying progression of CKD.

2.12. Prognosis in patients with CKD.

In people with CKD, use the estimated risk of existing complications and future consequences to make decisions about screening and treating CKD complications (see Fig. 17 below).

GFR and albuminuria grid to reflect the risk of progression by intensity of coloring (green, yellow, orange, red, deepred). The numbers in the boxes are a guide to the frequency of monitoring (number of times per year). Green reflects stable disease, with follow-up measurements annually if CKD is present; yellow requires caution and measurements at least once per year; orange requires measurements twice per year; red requires measurements at 3 times per year while deep red may

require closest monitoring approximately 4 times or more per year (at least every 1–-3 months). These are general parameters only based on expert opinion and must take intoaccount underlying comorbid conditions and disease state, as well as the likelihood of impacting a change in management for any individual patient.

Rehabilitation of patients with CKD.

Patients with CKD G1-3 require observation by a general practitioner - family medicine, therapist, consultation with a nephrologist.

Patients with CKD G4 are under the supervision of a nephrologist.

Patients with CKD G5 are under the supervision of a doctor of the hemodialysis department (center).

The program of comprehensive medical and social rehabilitation of the disabled due to kidney disease consists of medical, psychological, social and professional activities.

The needs of such patients in different types of rehabilitation are individual: most need restorative outpatient treatment, more than half - rehabilitative treatment in hospital, psychotherapy, rational employment, about a third - spa treatment.

Thus, despite the difficulty of clinical and occupational prognosis of patients with CKD, its complications, correct and timely assessment of employment opportunities and needs of the patient, the use of all available methods of medical and social rehabilitation should improve quality of life, maintaining patients' ability to work.

Resume

3.1. Problems that need to be solved.

The availability of resources for formal multidisciplinary teams, educational materials, and access to specialized counseling for diet, advance directives, access planning, and pre-emptive transplantation varies around the world.

There is a need to focus on regular symptom assessment as part of CKD review in those with lower eGFR values individual assessment and availability of resources will dictate specific timing of therapies.

All countries have people with CKD who withdraw either voluntarily or involuntarily from dialysis services. Best care for those patients will obviously need to respect cultural and religious values, but would necessarily be based on the same philosophical grounds of maintaining dignity of the individual.

Appreciating the need for and articulating conservative care pathways overtly would be internationally applicable.

There is a need to ensure appropriate access to services and education surrounding quality care during terminal stages of a chronic condition. There is increasing attention to this in many societies but not in all. Appreciating the variability in the resources required and their availability to different groups of patients is important for implementation.

There is a need for robust assessment of best practices in CKD and other chronic conditions so that we may provide best care throughout the continuum of life. Researchers around the world are actively pursuing this so that we may have better tools, programs, and ultimately, better outcomes for our patients.

3.2. Questions and tasks to assess the degree of assimilation of lecture material

1. The definition of CKD
2. Markers of kidney damages.
3. Risk factors and causes of CKD development and progression.
4. Methods of clinical, laboratory and instrumental diagnostics of CKD.
5. Classification of CKD (GFR and albuminuria categories).
6. Describe clinical manifestation of CKD depended on stages.
7. The complications of CKD
8. CKD management programs

9. Timing of RRT initiation.

3.3. Tasks

Task 1.

GFR should be monitored at least once a year in patients prescribed drugs with known nephrotoxicity, such as:

A. Nonsteroidal anti-inflammatory drugs
B. Cephalosprorin antibiotics
C. Antibiotics aminoglycosides
D. Diuretics
E. All of the above drugs

Task 2.

Which of the following risk factors for CKD able to be modified?

A. Hypertension
B. Diabetes mellitus
C. Age
D. Heredity of CKD
E. Smoking

Task 3.

Which of the values are included in the classification of CKD?

A. Albuminuria
B. Glomerular filtration rates
C. Serum creatinine
D. Blood urea
E. All of the above

Task 4.

Patients with which conditions should be screened for CKD (GFR calculation, albuminuria assessment)?

A. Hypertension
B. Diabetes mellitus
C. Systemic connective tissue diseases
D. Asymptomatic erythrocyturia
E. All answers are correct

Task 5.

For patients with CKD, the target blood pressure level is as follows:

A. Systolic blood pressure (SBP) <140 and diastolic BP (DBP) <90 mm Hg.
B. SBP <130 and DBP <80 mm Hg.
C. SBP 130-139 and DBP <80 mm Hg.
D. SBP <120 and DBP <70 mm Hg.
E. All answers are correct

Task 6.

What lifestyle recommendations should be given to a patient with CKD?

A. Limit protein intake to 0.8 g / kg body weight per day
B. Exclusion from the diet of salt (sodium chloride)
C. Limiting the amount of fluid
D. Optimization of physical activity
E. Complete cessation of smoking

Clinical task

The 52-year-old patient suffers from diabetes and hypertension. Smoker. The patient's mother suffers from diabetes and is on programmed hemodialysis. The patient receives therapy: Insulin, Metoprolol 100 mg, Fosinopril 40 mg, Atorvastatin 40 mg, Aspirin 75 mg. Objectively: heart rate 72 per minute, regular , BP 165/95 mm Hg, edema of the legs, a weakening of the pulse *on aa. dorsalis pedis*.

Question 1: Is it necessary to screen for CKD?

Patient's laboratory and instrumental data: Hb 120 g / l, fasting glucose 7.9 mmol / l, HbA1c 7.2%, creatinine 106.1 mmol / l, rSKF (SKD-EPI) 59 ml / min / 1.73 m2, albuminuria 300 mg / g, LDL, 2.0 mmol / L.

Question 2: Determine the stage of CKD and the patient's risk.

Question 3: What correction should be made in therapy for optimal nephro- and cardioprotection?

Correct answers:

Task 1: A, C.
Task 2: A, B, E.
Task 3: A, B.
Task 4: E.
Task 5: B.
Task 6: A, D, E.

Clinical task:

Question 1. Yes, because the patient has multiple risk factors development and progression of CKD, namely - diabetes, smoking, positive hereditary history, hypertension, peripheral artery disease.

Question 2. CKD stage 3a, the risk is high.

Question 3. It is necessary to strengthen antihypertensive therapy with the achievement of the target level of blood pressure, glycemic control and lipid profile.

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Lecture # 3

Theme: Chronic obstructive pulmonary disease (COPD). Bronchial asthma (BA).

Goal: prepare specialists who will be able to carry out professional activities, using knowledge of the problems of COPD.

Specific goals of the lecture

– Etiology and pathogenesis of COPD;

– COPD classification;
– Clinical features and differential diagnosis of COPD;
– Modern standards of COPD management.
- evaluate the clinical features of COPD and detail the main complaints;
- compose the plan of investigation for patients with COPD;
- conduct the differential diagnosis of bronchoobstructive syndrome;
- determinate the degree of COPD severity;
- prescribe the standard treatment.
- familiarize students with the contribution of modern pulmonology societies in the study of the BA problem and the development of modern standards of care for patients with COPD (I);
- form an idea of the role of the general practitioner, family physician for the prevention of COPD exacerbation and COPD symptoms control (I).
– Etiology and pathogenesis of BA;
– BA classification;
– Clinical features and differential diagnosis of BA;
– Modern standards of BA management.
- evaluate the clinical features of BA and detail the main complaints;
- compose the plan of investigation for patients with BA;
- conduct the differential diagnosis of bronchoobstructive syndrome;
- determinate the degree of BA severity;
- prescribe the standard treatment.

Basic concepts: COPD, BA, Emphysema, Chronic bronchitis, Spirometry, Tiffeneau-Pinelli index, Broncho-obstructive syndrome, SABA, LABA, SAMA, LAMA.

Plan and organization's structure of the lecture.

№ п/п	Main stages of the lecture and it's content	The objectives in the levels of abstraction	Type lectures, methods and means of enhancing students, equipping	Time distribution
1	2	3	4	5
1.	Preparatory phase: 1. setting learning goals 2. providing positive motivation	 I I	Clinical Lecture: -with elements of a problem, -with application visibility Means of visibility: -codogrammes, - extracts from the case histories of patients with COPD, BA (and / or thematic patient), - GOLD (2022), GINA (2022) - peak flow meter. Material for control: – questions – situation tasks	5
2.	Main part: Plan of the lecture:			75:

	1. Definition 2. Pathogenesis and Pathology 3. Classification of Severity 4. Groups of risk. The CAT and the mMRC scales. 5. Evaluation of clinical features and diagnostic algorithm. 6. Treatment standards. 7. Definition of BA 8. Pathogenesis and Pathology of BA 9. Classification of Severity 10. Evaluation of clinical features 11. Diagnostic algorithm of BA. 12. Treatment standards. 13. Management of the BA exacerbation.			5 10 5 10 25 20
3.	The final stage: 1. Summary and general conclusions, 2. answers to possible questions, 3. checklists and case assignments to identify mastery of the material, 4. tasks for independent work		– References, – Issues, – situational tasks, – tasks for self-study students, – links to sources of new information on the problem of COPD and BA	10

Lecture content.

COPD, a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.

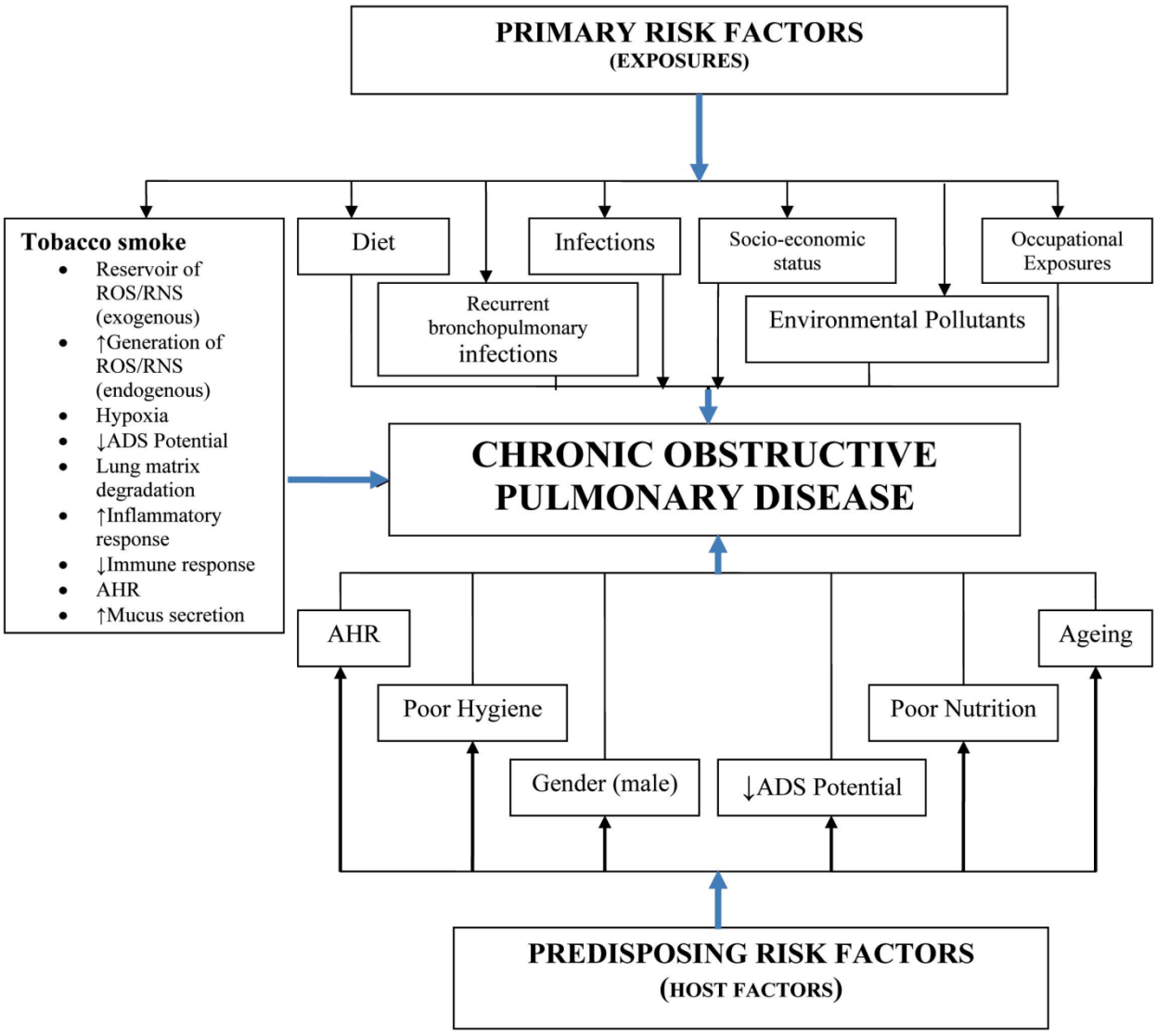
A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and any history of exposure to risk factors for the disease (Table 1).

Table 1

Key indicators for considering a diagnosis of COPD

Consider COPD, and perform spirometry, if any of these indicators are present in an individual over age 40. These indicators are nopt diagnostic themselves, but the presence of multiple key indicators increases the probability of a diagnosis of COPD. Spirometry is required to establish a diagnosis of COPD

Dyspnea that is:	Progressive (worsen over time). Characteristically worse with exercise. Persistant.
Chronic cough:	May be intermittent and may be unproductive
Chronic sputum production:	Any pattern of chronic sputum production may indicate COPD
History of exposure to risk factors:	Tobacco smoke (including popular local preparations). Smoke from home cooking and heating fuels. Occupational dusts and chemicals.
Family history of COPD	



Spirometry is *required* to make the diagnosis of COPD; the presence of a post-bronchodilator FEV1/FVC < 0.70 confirms the presence of persistent airflow limitation and thus of COPD
Diagnosis and Assessment: Key Points

- The goals of COPD assessment are to determine the severity of the disease, including the severity of airflow limitation, the impact on the patient's health status, and the risk of future events.
- Comorbidities occur frequently in COPD patients, and should be actively looked for and treated appropriately if present.

Assessment of COPD

- Assess symptoms
- Assess degree of airflow limitation using spirometry
- Assess risk of exacerbations
- Assess comorbidities

The characteristic symptoms of COPD are chronic and progressive dyspnea, cough, and sputum production that can be variable from day-to-day.

Dyspnea: Progressive, persistent and characteristically worse with exercise.

Chronic cough: May be intermittent and may be unproductive.

Chronic sputum production: COPD patients commonly cough up sputum.

MMRC Dyspnea Scale Grade (Description of Breathlessness)

0 I only get breathless with strenuous exercise.

1 I get short of breath when hurrying on level ground or walking up a slight hill.

2 On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace.

3 I stop for breath after walking about 100 yards or after a few minutes on level ground.

4 I am too breathless to leave the house or I am breathless when dressing.

Assess degree of airflow limitation using spirometry

Use spirometry for grading severity according to spirometry, using four grades split at 80%, 50% and 30% of predicted value

In patients with FEV1/FVC < 0.70:	
GOLD 1: Mild	*FEV1 ≥ 80% predicted*
GOLD 2: Moderate	*50% ≤ FEV1 < 80% predicted*
GOLD 3: Severe	*30% ≤ FEV1 < 50% predicted*
GOLD 4: Very Severe	*FEV1 < 30% predicted*

**Based on Post-Bronchodilator FEV1*

Assess risk of exacerbations

- Two or more exacerbations within the last year *or* an FEV1 < 50 % of predicted value are indicators of high risk.
- One or more hospitalizations for COPD exacerbation should be considered high risk.

Combined Assessment of COPD

Initial pharmacological management

Rescue short-acting bronchodilators should be prescribed to all patients for immediate symptom relief.

Group A

All Group A patients should be offered bronchodilator treatment based on its effect on breathlessness. This can be either a short- or a long-acting bronchodilator.

Group B

Initial therapy should consist of a long acting bronchodilator. Long-acting inhaled bronchodilators are superior to short-acting bronchodilators taken as needed i.e., pro re nata (prn) and are therefore recommended.

There is no evidence to recommend one class of long-acting bronchodilators over another for initial relief of symptoms in this group of patients. In the individual patient, the choice should depend on the patient's perception of symptom relief.

For patients with severe breathlessness initial therapy with two bronchodilators may be considered.

Group C

Initial therapy should consist of a single long acting bronchodilator. In two head-to-head comparisons the tested LAMA was superior to the LABA regarding exacerbation prevention (for details see Chapter) therefore we recommend starting therapy with a LAMA in this group.

Group D

For patients with more severe symptoms (order of magnitude of CAT™ □ 20), especially driven by greater dyspneaand / or exercise limitation, LAMA/LABA may be chosen as initial treatment based on studies with patient reported outcomes as the primary endpoint where LABA/LAMA combinations showed superior results compared to the single substances (see **Chapter 3**). An advantage of LABA/LAMA over LAMA for exacerbation prevention has not been consistently demonstrated, so the decision to use LABA/LAMA as initial treatment should be guided by the level of symptoms.

In some patients, initial therapy with LABA/ICS may be the first choice; this treatment has the greatest likelihood of reducing exacerbations in patients with blood eosinophil counts ≥ 300 cells/µL. LABA/ICS may also be first choice inCOPD patients with a history of asthma.

ICS may cause side effects such as pneumonia,[189,269] so should be used as initial therapy only after the possible clinical benefits versus risks have been considered.

In general, therapy can be started with a LAMA as it has effects on both breathlessness and exacerbations

Patient	Characteristic	Spirometric Classification	Exacerbations per year	CAT	mMRC
A	Low Risk Less Symptoms	GOLD 1-2	≤ 1	< 10	0-1
B	Low Risk More Symptoms	GOLD 1-2	≤ 1	≥ 10	≥ 2
C	High Risk Less Symptoms	GOLD 3-4	≥ 2	< 10	0-1
D	High Risk More Symptoms	GOLD 3-4	≥ 2	≥ 10	≥ 2

Additional Investigations

Chest X-ray: Seldom diagnostic but valuable to exclude alternative diagnoses and establish presence of significant comorbidities.

Lung Volumes and Diffusing Capacity: Help to characterize severity, but not essential to patient management.

Oximetry and Arterial Blood Gases: Pulse oximetry can be used to evaluate a patient's oxygen saturation and need for supplemental oxygen therapy.

Alpha-1 Antitrypsin Deficiency Screening: Perform when COPD develops in patients of Caucasian descent under 45 years or with a strong family history of COPD.

Therapeutic Options: COPD Medications

Beta2-agonists
Short-acting beta2-agonists

Long-acting beta2-agonists
Anticholinergics
Short-acting anticholinergics
Long-acting anticholinergics
Combination short-acting beta2-agonists + anticholinergic in one inhaler **Combination long-acting beta2-agonist + anticholinergic in one inhaler**
Methylxanthines
Inhaled corticosteroids
Combination long-acting beta2-agonists + corticosteroids in one inhaler
Systemic corticosteroids
Phosphodiesterase-4 inhibitors

Other Pharmacologic Treatments

Influenza vaccines can reduce serious illness. Pneumococcal polysaccharide vaccine is recommended for COPD patients 65 years and older and for COPD patients younger than age 65 with an FEV1 < 40% predicted.

The use of *antibiotics*, other than for treating infectious exacerbations of COPD and other bacterial infections, is currently not indicated.

Alpha-1 antitrypsin augmentation therapy: not recommended for patients with COPD that is unrelated to the genetic deficiency.

Mucolytics: Patients with viscous sputum may benefit from mucolytics; overall benefits are very small.

Antitussives: Not recommended.

Vasodilators: Nitric oxide is contraindicated in stable COPD. The use of endothelium-modulating agents for the treatment of pulmonary hypertension associated with COPD is not recommended.

Oxygen Therapy: The long-term administration of oxygen (> 15 hours per day) to patients with chronic respiratory failure has been shown to increase survival in patients with severe, resting hypoxemia.

Ventilatory Support: Combination of noninvasive ventilation (NIV) with long-term oxygen therapy may be of some use in a selected subset of patients, particularly in those with pronounced daytime hypercapnia.

Surgical Treatments

Lung volume reduction surgery (LVRS) is more efficacious than medical therapy among patients with upper-lobe predominant emphysema and low exercise capacity.

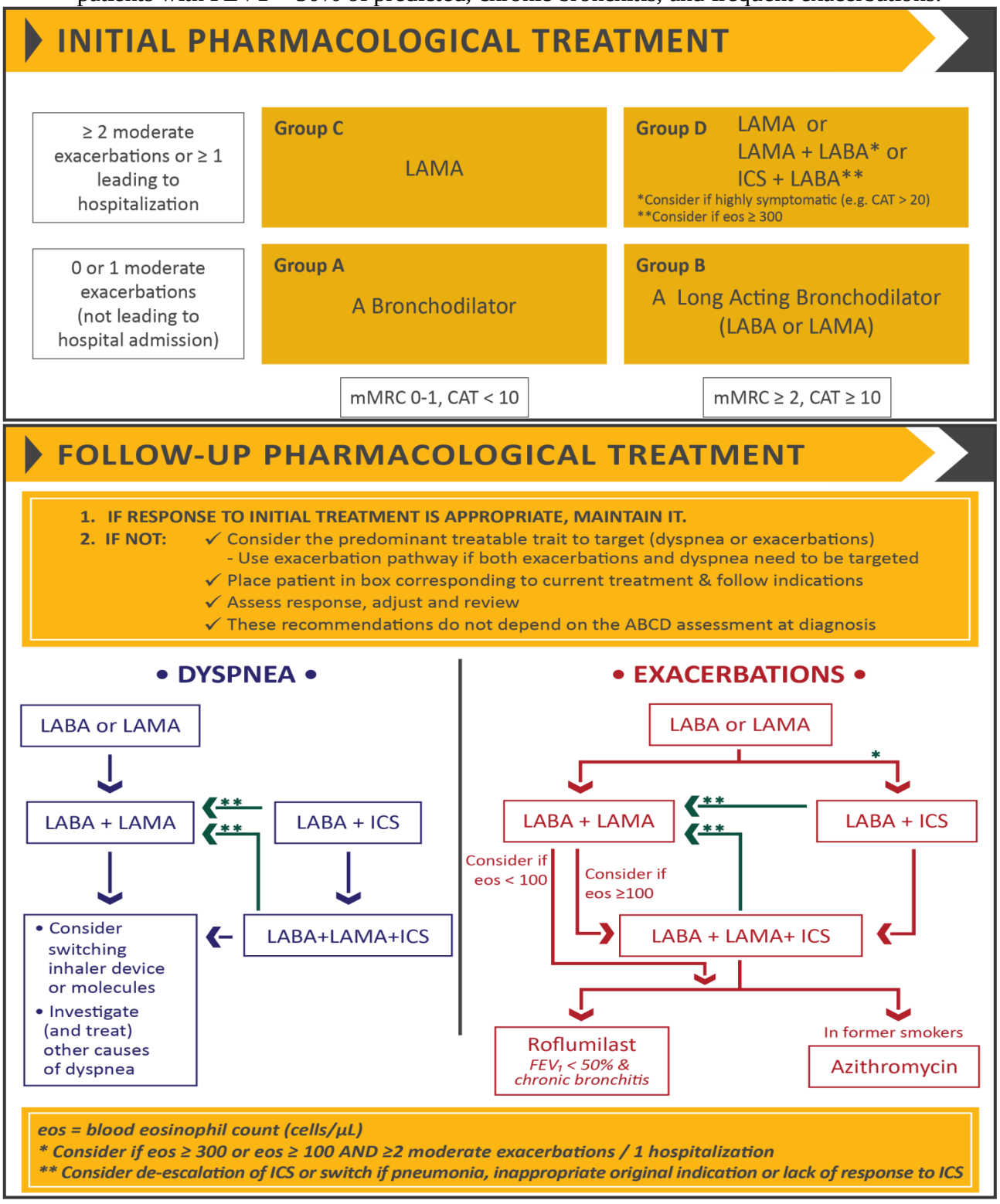
LVRS is costly relative to health-care programs not including surgery.

In appropriately selected patients with very severe COPD, *lung transplantation* has been shown to improve quality of life and functional capacity.

Manage Stable COPD: Key Points

- Long-acting formulations of beta2-agonists and anticholinergics are preferred over short-acting formulations. Based on efficacy and side effects, inhaled bronchodilators are preferred over oral bronchodilators.
- Long-term treatment with inhaled corticosteroids added to long-acting bronchodilators is recommended for patients with high risk of exacerbations.
- Long-term monotherapy with oral or inhaled corticosteroids is not recommended in COPD.

- The phospodiesterase-4 inhibitor roflumilast may be useful to reduce exacerbations for patients with FEV1 < 50% of predicted, chronic bronchitis, and frequent exacerbations.



Manage Exacerbations

An exacerbation of COPD is:

"an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication."

- Short-acting inhaled beta2-agonists with or without short-acting anticholinergics are usually the preferred bronchodilators for treatment of an exacerbation.

- Systemic corticosteroids and antibiotics can shorten recovery time, improve lung function (FEV1) and arterial hypoxemia (PaO2), and reduce the risk of early relapse, treatment failure, and length of hospital stay.

Arterial blood gas measurements (in hospital): PaO2 < 8.0 kPa with or without PaCO2 > 6.7 kPa when breathing room air indicates respiratory failure.
Chest radiographs: useful to exclude alternative diagnoses.
ECG: may aid in the diagnosis of coexisting cardiac problems.
Whole blood count: identify polycythemia, anemia or bleeding.
Purulent sputum during an exacerbation: indication to begin empirical antibiotic treatment.
Biochemical tests: detect electrolyte disturbances, diabetes, and poor nutrition.
Spirometric tests: not recommended during an exacerbation.
Oxygen: titrate to improve the patient's hypoxemia with a target saturation of 88-92%.

Bronchodilators: Short-acting inhaled beta2-agonists with or without short-acting anticholinergics are preferred.
Systemic Corticosteroids: Shorten recovery time, improve lung function (FEV1) and arterial hypoxemia (PaO2), and reduce the risk of early relapse, treatment failure, and length of hospital stay. A dose of 40 mg prednisone per day for 5 days is recommended .
Antibiotics should be given to patients with:

- Three cardinal symptoms: increased dyspnea, increased sputum volume, and increased sputum purulence.
- Who require mechanical ventilation.

Indications for Hospital Admission

- Marked increase in intensity of symptoms
- Severe underlying COPD
- Onset of new physical signs
- Failure of an exacerbation to respond to initial medical management
- Presence of serious comorbidities
- Frequent exacerbations
- Older age
- Insufficient home support

Asthma-COPD overlap syndrome (ACOS) is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. ACOS is therefore identified by the features that it shares with both asthma and COPD.

Syndromic diagnosis of airways disease
The shaded columns list features that, when present, best distinguish between asthma and COPD. For a patient, count the number of check boxes in each column.

- If 3 or more boxes are checked for either asthma or COPD, that diagnosis is suggested.
- If there are similar numbers of checked boxes in each column, the diagnosis of ACOS should be considered.

Stepwise approach to diagnosis and initial treatment
For an adult who presents with respiratory symptoms:

1. Does the patient have chronic airways disease?
2. Syndromic diagnosis of asthma, COPD and ACOS
3. Spirometry

4. Commence initial therapy
5. Referral for specialized investigations (if necessary)

Definition of BA: Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation.
It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

Patophysiology

There are 2 major elements in the pathophysiology: **inflammation and airway hyper-responsiveness (AHR)**. The large and the small airways with diameters <2 micrometres are the sites of inflammation and airway obstruction.
Airway inflammation occurs secondary to a complex interaction of inflammatory cells, mediators, and other cells and tissues in the airway. An initial trigger leads to the release of inflammatory mediators, which leads to the consequent activation and migration of other inflammatory cells. The inflammatory reaction is a T-helper type 2 (Th2) lymphocytic response. Th2 inflammation is characterised by the presence of CD4+ lymphocytes that secrete interleukin (IL)-4, IL-5, and IL-13, the chemokine eotaxin, TNF-alpha, and the leukotriene LTB4, a product of the lipoxygenase pathway, as well as mast cell tryptase. This Th2 response is important in the initiation and prolongation of the inflammatory cascade.

Other WBCs involved are eosinophils, basophils and mast cells, macrophages, invariant NK T cells, and in near-fatal or status asthmaticus, neutrophils are important. These cells move to the airway, causing changes in the epithelium, airway tone, and related autonomic neural control and hyper-secretion of mucus, mucociliary function alteration and increased smooth muscle responsiveness. Pathological studies of fatal asthma show severe hyper-inflation, mucous plugging with the mucus-containing mucins (proteins that are present in the blood). Tissue biopsies show the deposition of eosinophil granular proteins throughout the lung tissue and damage of the epithelium mediated by those proteins. Denudation of the basal layer by epithelial cell sloughing produces clumps of cells in the sputum referred to as Creola bodies. There is also subbasement membrane deposition of collagen often referred to as thickened basement membrane, which is considered another hallmark.

Products of the inflammatory response induce smooth muscle contraction and consequent AHR. There appears to be at least 2 different kinds of AHR, a baseline fixed and an episodic variable element. The underlying fixed AHR is possibly related to airway remodelling, whereas the variable AHR reflects the action of the inflammatory mediators, and are distinguished by direct and indirect bronchial challenges, respectively. Finally, airway smooth muscle in asthmatics is increased in mass, likely as a result of hypertrophy and hyperplasia, which in vitro studies display as having increased contractility.

History & examination/Key factors

- presence of risk factors
- recent upper respiratory tract infection
- dyspnoea
- cough
- expiratory wheezes
- nasal polyposis

Diagnostic tests

1st tests to order

- FEV1/FVC ratio

- FEV1
- peak expiratory flow rate (PEFR)
- CXR
- FBC

Tests to consider

- bronchial challenge test
- serum IgE
- skin prick allergy testing

Emerging tests

- exhaled nitric oxide (eNO)
- sputum eosinophilia

Diagnosis of asthma

– symptoms

Increased probability that symptoms are due to asthma if:

- More than one type of symptom (wheeze, shortness of breath, cough, chest tightness)
- Symptoms often worse at night or in the early morning
- Symptoms vary over time and in intensity
- Symptoms are triggered by viral infections, exercise, allergen exposure, changes in weather, laughter, irritants such as car exhaust fumes, smoke, or strong smells

Decreased probability that symptoms are due to asthma if:

- Isolated cough with no other respiratory symptoms
- Chronic production of sputum
- Shortness of breath associated with dizziness, light-headedness or peripheral tingling
- Chest pain
- Exercise-induced dyspnea with noisy inspiration (stridor)

– variable airflow limitation

Confirm presence of airflow limitation

- Document that FEV_1/FVC is reduced (at least once, when FEV_1 is low)
- FEV_1/ FVC ratio is normally >0.75 – 0.80 in healthy adults, and >0.90 in children

Confirm variation in lung function is greater than in healthy individuals

- The greater the variation, or the more times variation is seen, the greater probability that the diagnosis is asthma
- Excessive bronchodilator reversibility (adults: increase in FEV_1>12% and >200mL; children: increase >12% predicted)
- Excessive diurnal variability from 1-2 weeks' twice-daily PEF monitoring (daily amplitude x 100/daily mean, averaged)
- Significant increase in FEV_1 or PEF after 4 weeks of controller treatment
- If initial testing is negative:
    - Repeat when patient is symptomatic, or after withholding bronchodilators
    - Refer for additional tests (especially children ≤5 years, or the elderly)

– physical examination

Physical examination in people with asthma

- Often normal
- The most frequent finding is wheezing on auscultation, especially on forced expiration

Wheezing is also found in other conditions, for example:

- Respiratory infections
- COPD
- Upper airway dysfunction
- Endobronchial obstruction

- Inhaled foreign body

Wheezing may be absent during severe asthma exacerbations ('silent chest')

Risk factors for exacerbations include:

- Ever intubated for asthma
- Uncontrolled asthma symptoms
- Having ≥1 exacerbation in last 12 months
- Low FEV_1 (measure lung function at start of treatment, at 3-6 months to assess personal best, and periodically thereafter)
- Incorrect inhaler technique and/or poor adherence
- Smoking
- Obesity, pregnancy, blood eosinophilia

Risk factors for fixed airflow limitation include:

- No ICS treatment, smoking, occupational exposure, mucus hypersecretion, blood eosinophilia

Reviewing response and adjusting treatment

How often should asthma be reviewed?

- 1-3 months after treatment started, then every 3-12 months
- During pregnancy, every 4-6 weeks
- After an exacerbation, within 1 week

Stepping up asthma treatment

- *Sustained step-up,* for at least 2-3 months if asthma poorly controlled
  - Important: first check for common causes (symptoms not due to asthma, incorrect inhaler technique, poor adherence)
- *Short-term step-up,* for 1-2 weeks, e.g. with viral infection or allergen
  - May be initiated by patient with written asthma action plan
- *Day-to-day adjustment*
  - For patients prescribed low-dose ICS/formoterol maintenance and reliever regimen (approved only for low dose beclometasone/formoterol and low dose budesonide/formoterol)

Stepping down asthma treatment

- Consider step-down after good control maintained for 3 months
- Find each patient's minimum effective dose, that controls both symptoms and exacerbations

Patients with ***acute severe asthma*** typically have:

- inability to complete a sentence in one breath
- respiratory rate ≥ 25 breaths per minute
- tachycardia ≥ 110 beats/min (pulsus paradoxus, is not useful as it is only present in 45% of cases)
- PEF < 50% of predicted normal or best.

Features of life-threatening attacks are:

- a silent chest, cyanosis or feeble respiratory effort
- exhaustion, confusion or coma
- bradycardia or hypotension
- PEF < 30% of predicted normal or best (approximately 150 L/min in adults).

Treatment: At home

- The patient is assessed. Tachycardia, a high respiratory rate and inability to speak in sentences indicate a severe attack.
- If the PEFR is less than 150 L/min (in adults), an ambulance should be called. (All doctors should carry peak flow meters.)

- Nebulized salbutamol 5 mg or terbutaline 10 mg is administered.
- Hydrocortisone sodium succinate 200 mg i.v. is given.
- Oxygen 40-60% is given if available.
- Prednisolone 60 mg is given orally.

At hospital

- The patient is reassessed.
- Oxygen 40-60% is given.
- The PEFR is measured using a low-reading peak flow meter, as an ordinary meter measures only from 60 L/min upwards.
  Measure O2 saturation with a pulse oximeter.
- Nebulized salbutamol 5 mg or terbutaline 10 mg is repeated and administered 4-hourly.
- Add nebulized ipratropium bromide 0.5 mg to nebulized salbutamol/terbutaline.
- Hydrocortisone 200 mg i.v. is given 4-hourly for 24 hours.
- Prednisolone is continued at 60 mg orally daily for 2 weeks.
- Arterial blood gases are measured; if the Paco2 is greater than 7 kPa, ventilation should be considered.
- A chest X-ray is performed to exclude pneumothorax.
- One of the following intravenous infusions is given if no improvement is seen:
  - salbutamol 3-20 μg/min, or
  - terbutaline 1.5-5.0 μg/min, or
  - magnesium sulphate 1.2-2 g over 20 min.

Conclusions

Overall, Bronchial asthma poses a common, growing, and significant clinical challenge for patients and clinicians alike. Clinicians' expert knowledge regarding diagnosis and management can enhance patients' longevity and quality of life. Results of emerging studies will likely lead to enhancements in current management and new paradigms in managing patients with BA.

Questions for control of received knowledge evaluation:

1. Pathogenesis of bronchoobstructive syndrome.
2. Peculiarity of bronchoobstruction at COPD and bronchial asthma.
3. The main reason and content of updated COPD classification.
4. Clinical feature of COPD and diagnostic algorithm.
5. New standards of management the patients with COPD.
6. Pathogenesis of Bronchial asthma.
7. Clinical feature of bronchial asthma and diagnostic criteria's.
8. The stepwise therapy.
9. Indication to hospitalization patients with Bronchial asthma.
10. Management of life threatening exacerbation of Bronchial asthma.

Used literature during preparing for the lecture

Basic literature:

- Basic literature source:

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD) POCKET GUIDE TO COPD DIAGNOSIS, MANAGEMENT, AND PREVENTION A Guide for Health Care Professionals. 2022
2. Global Initiative for Chronic Obstructive Lung Disease (GOLD). At a Glance Outpatient Management Reference for Chronic Obstructive Pulmonary Disease. 2022
3. BMJ Best Practice. COPD. - BMJ publishing group LTD, 2019. – 92 p.

4. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention (2022 Update). http://www.ginasthma.org/
5. BMJ Best Practice. Asthma in adults. - BMJ publishing group LTD, 2018. – 59 p.

- Additional literature source:

1. Your essential guide to spirometry; Primary Care Respiratory Update, Issue 17, 2019 https://www.pcrs-uk.org/sites/pcrs-uk.org/files/pcru/2019/2019-Spring-Issue-17-Spirometry.pdf

Lecture # 4

Theme: Gastric dyspepsia and chronic gastritis. Peptic ulcers of stomach and duodenum.

Goal: prepare specialists who will be able to carry out professional activities, using knowledge of the problems of gastric dyspepsia and chronic gastritis, peptic ulcers of stomach and duodenum.

Specific goals of the lecture

To study:

- definition of stomach dyspepsia, chronic gastritis, peptic ulcers;
- diagnostic algorithm of stomach dyspepsia;
- etiology, pathogenesis of stomach dyspepsia, chronic gastritis, peptic ulcers, classification, clinic, complications, diagnosis and treatment;
-physiology of hydrochloric acid secretion, the main ways of stimulating, methods of pharmacological blockade of secretion, microbial characteristics of H. Pilory infection, methods of H.Pilory evaluation;
- classification of antisecretory, anti H.Pilory, prokinetic drugs and antacids.
- the difference in patients management in stomach ulcer and duodenum ulcer disease;
- indication to eradication of H.Pilory and schemes of eradication therapy;
- methods of treatment of drug-induced and symptomatic ulcers;
- general and dietary recommendations in ulcer disease and symptomatic ulcers;
- complication of ulcer disease and their management;
- indication to surgery treatment of peptic ulcers.

Basic concepts: stomach dyspepsia, epigastric pain syndrome, postprandial distress syndrome, chronic gastritis, H.Pilory infection, peptic ulcer of stomach, ulcer of duodenum, eradication therapy.

Plan and organization's structure of the lecture.

№ п/п	Main stages of the lecture and it's content	The objectives in the levels of abstraction	Type lectures, methods and means of enhancing students, equipping	Time distribution
1	2	3	4	5
1.	Preparatory phase: 1. setting learning goals 2. providing positive motivation – importance of the stomach dyspepsia, chronic gastritis and stomach and duodenum ulcers problems at clinical practice of general practitioner	 I I	Clinical Lecture: -with elements of a problem, -with application visibility Means of visibility: -codogrammes, - extracts from the case histories of patients with stomach dyspepsia, chronic gastritis and ulcers of stomach and duodenum (and / or thematic patient) Material for control: – questions – situation tasks	5
2.	Main part: Plan of the lecture: 1. Functional dyspepsia: definition, two subgroups,	II-III		75: 25

	clinic, diagnostic procedure and treatment. 2. Chronic gastritis: Definition, etiology, classification, pathogenesis, clinical features and treatment. 3. Ulcers of stomach and duodenum: definition, clinic, diagnostic criteria's, differential diagnosis, complication, surgery treatment, dispanserisation.			25 25
3.	The final stage: 1. Summary and general conclusions, 2. answers to possible questions, 3. checklists and case assignments to identify mastery of the material, 4. tasks for independent work	II III III	– References, – Issues, – situational tasks, – tasks for self-study students, – links to sources of new information on the problem of stomach dyspepsia, chronic gastritis and stomach and duodenum ulcers.	10

Lecture content.

The term dyspepsia (Greek "dys" [bad], "pepsis" [digestion]) is used for a spectrum of symptoms localized by the patient to the epigastric region (between the navel and the xiphoid process) and the flanks. These symptoms include epigastric pain and burning (60 to 70%), feeling bloated after a meal (80%), early satiation (60 to 70%), distension in the epigastric region (80%), Nausea (60%), and vomiting (40%).

Functional dyspepsia (synonym: irritable stomach syndrome) is present whenever routine diagnostic investigations, including endoscopy, do not identify any causal structural or biochemical abnormalities.

According to the recently revised Rome IV criteria, functional dyspepsia is defined by:

- Persistent or recurring dyspepsia for more than 3 months within the past 6 months
- No demonstration of a possible organic cause of the symptoms on endoscopy
- No sign that the dyspepsia is relieved only by defecation or of an association with stool irregularities.

This last criterion was introduced to rule out irritable bowel syndrome (IBS) as a possible cause of the symptoms, although around 30% of patients with functional dyspepsia also have IBS.

The current Rome IV criteria divide functional dyspepsia into two subgroups according to the cardinal symptoms:

- Epigastric pain syndrome (EPS)—predominant epigastric pain or burning
- Postprandial distress syndrome (PDS)—feeling of fullness and early satiation.

The causes of functional dyspepsia are heterogeneous and multifactorial. This includes motility disorders, sensorimotor dysfunction connected with hypersensitivity to mechanical and chemical stimuli, immune activation, elevated mucosal permeability in the proximal small intestine, and disorders of the autonomic and enteric nervous systems.

Confirmation of the diagnosis of functional dyspepsia rests on:

- The typical symptoms and the patient's history
- The exclusion of other diseases of the upper gastrointestinal tract and upper abdominal organs that may present with similar dyspeptic symptoms.

The typical nongastrointestinal accompanying symptoms are general vegetative symptoms such as increased sweating, headache, sleep disorders, muscular tension, functional cardiac symptoms, and irritable bladder. On questioning, the patient typically reports a long history of complaints, variable symptoms with no clear progression, diffuse pain of variable location, absence of unintentional weight loss, and dependence of the symptoms on stress.

The only instrumental diagnostic examinations thought to be sufficiently accurate are esophagogastroduodenoscopy including investigation for *Helicobacter pylori* and abdominal ultrasonography, accompanied in the presence of additional symptoms of IBS by endoscopic inspection of the colon. These investigations are indicated in cases where the medical history and symptoms are typical and the preliminary laboratory tests such as blood count, electrolytes, and hepatic and renal function, as well as erythrocyte sedimentation rate or CRP and, if applicable, peripheral thyroid parameters are in the normal range.

Diagnostic procedure in patients with dyspeptic symptoms:

- Helicobacter pylori,
- Esopagogastroduodenoscopy.

Confirmation of the diagnosis rest on:

- The typical symptoms and the patient's history
- The exclusion of other diseases of the upper gastrointestinal tract and upper abdominal organs that may present with similar dyspeptic symptoms.

When functional dyspepsia has been confirmed, one of the first treatment measures is exhaustive explanation of the diagnosis and its consequences to the patient. It is crucial to the success of treatment to explain the essence of the diagnosis to the patient in simple, comprehensible terms, stressing that functional dyspepsia is a benign but organic disease that may arise from various underlying disorders. At the same time, the patient must be informed about the treatment options. The following nonmedicinal general measures are currently recommended, although their efficacy has not been confirmed in controlled trials:

- Clear explanation of the diagnosis with interpretation of the findings (reassurance that the symptoms are not caused by cancer)
- Explanation of the nature and cause(s) of the symptoms
- Conflict resolution in the psychosocial domain
- Encouraging the patient to take responsibility
- Relaxation exercises
- Treatment alliance for long-term care
- Psychotherapeutic options.

General treatment measures.

It is important to explain the essence of the diagnosis to the patient in simple, comprehensible terms, stressing that functional dyspepsia is a benign but organic disease that may arise from various underlying disorders.

Diet plays only a minor role in functional dyspepsia. The patient should note what foods he/she does not tolerate and avoid them. To this end, it may be useful to keep a symptom diary, particularly in the diagnostic phase. Regular meals, avoidance of excessively large meals, thorough mastication, and not rushing meals are general recommendations that may also be helpful in functional dyspepsia.

Treatment algoritm for dyspepsia:

- Proton pump inhibitors
- *Helicobacter pylori* eradication treatment
- Prokinetics
- Psychotropic drugs.

Chronic gastritis (CG)

Gastric inflammatory disease can be broadly categorized into gastritis and gastropathy based on the presence of associated mucosal inflammation due to gastric injury. Gastritis is predominantly an inflammatory process, while the term gastropathy denotes a gastric mucosal disorder with minimal to no inflammation. Although the term "gastritis" is often used to describe endoscopic or radiologic characteristics of abnormal-appearing gastric mucosa, a diagnosis of gastritis requires histopathologic evidence of inflammation.

Gastropathy — Epithelial cell damage and regeneration with minimal or no associated inflammation is termed "gastropathy."

Gastritis — The term gastritis is used to denote inflammation associated with gastric mucosal injury.

Definition CG– it is disease with a chronic relapsing course, which is based on inflammatory and dystrophic, degenerative lesions of the gastric mucosa, accompanied by disorders of its secretory, motor-evacuation and incretory function.

The causes of gastritis can be summarized as follows:

1. H. pylori-associated gastritis: This is the most common cause of gastritis worldwide.

2. H. pylori-negative gastritis: The patients should fulfill all four of these criteria, a negative triple staining of gastric mucosal biopsies (hematoxylin and eosin, the Alcian blue stain and a modified silver stain), a negative H. pylori culture, A negative IgG H. pylori serology, and No self-reported history of H. pylori treatment. In these patients, the cause of gastritis may relate to tobacco smoking, consumption of alcohol, and/or the use of NSAIDs or steroids.

3. Autoimmune gastritis: This is a chronic inflammatory disease characterized by chronic atrophic gastritis and associated with raised serum anti-parietal and anti-intrinsic factor antibodies. The loss of parietal cells results in a reduction of gastric acid secretion, which is necessary for the absorption of inorganic iron. Therefore, iron deficiency is commonly a finding in patients with autoimmune gastritis. Iron deficiency in these patients usually precedes vitamin B12 deficiency. The disease is common in young women.

4. Gastritis may be the result of infection by organisms other than H. pylori such as Mycobacterium avium-intracellulare, enterococcal infection, Herpes simplex, and cytomegalovirus. Parasitic gastritis may result from cryptosporidium, Strongyloides stercoralis, or anisakiasis infection.

5. Gastritis may result from bile acid reflux.

6. Radiation gastritis.

7. Crohn disease-associated gastritis: This is an uncommon cause of gastritis.

8. Collagenous gastritis: This is a rare cause of gastritis. The disease characteristically presents with marked subepithelial collagen deposition accompanying with mucosal inflammatory infiltrate. The exact etiology and pathogenesis of collagenous gastritis are still unclear.

9. Eosinophilic gastritis: This is another rare cause of gastritis. The disease could be part of the eosinophilic gastrointestinal disorders which is characterized by the absence of known causes of eosinophilia (not secondary to an infection, systematic inflammatory disease, or any other causes to explain the eosinophilia).

10. Sarcoidosis-associated gastritis: Sarcoidosis is a multisystemic disorder characterized by the presence of non-caseating granulomas. Although sarcoidosis can affect any body organ, the gastrointestinal tract, including the stomach, is rarely affected.

11. Lymphocytic gastritis: This is a rare cause of gastritis. The etiology of lymphocytic gastritis remains unestablished, but an association with H. pylori infection or celiac disease has been suggested.

12. Ischemic gastritis: This is rare and associated with high mortality.

13. Vasculitis-associated gastritis: Diseases causing systemic vasculitis can cause granulomatous infiltration of the stomach. An example is Granulomatosis with polyangiitis, formerly known as Wegner granulomatosis.

14. Ménétrier disease: This disease is characterized by- Presence of large gastric mucosal folds in the body and fundus of the stomach, Massive foveolar hyperplasia of surface and glandular mucous cells, Protein-losing gastropathy, hypoalbuminemia, and edema in 20 to 100% of patients, and reduced gastric acid secretion because of loss of parietal cells.

The pathogenesis of autoimmune gastritis focuses on two theories. According to the first theory, an immune response against superimposed H. pylori antigen gets triggered, antigen cross-reacting with antigens within the proton-pump protein or the intrinsic factor, leading to a cascade of cellular changes and causing damages to the parietal cells and stopping hydrochloric acid secretion and thus these cells gradually become atrophic and not functioning. The second theory assumes that the autoimmune disorder develops irrespective of H. pylori infection, and it directs itself against the proteins of the proton-pump. As per both theories, the autoimmune gastritis is the result of a complex interaction between genetic susceptibility and environmental factors resulting in immunological dysregulation involving sensitized T lymphocytes and autoantibodies directed against parietal cells and the intrinsic factor.

H.pylori-associated gastritis transmission is via the fecal-oral route. H. pylori possess several virulence factors which facilitate cell adhesion (e.g., BabA/B, sabA, OipA), cell damage and disruption of tight junctions (e.g., Ure A/B), and evasion from the immune response (e.g. LPS). In particular, the cytotoxin-associated gene a (CagA) is considered a potent inducer of inflammation and correlate with gastric cancer development.

Another factor influencing H. pylori pathogenic effects is host factors. The host susceptible factors such as polymorphism in genes coding for tall receptors or specific cytokines. The infection with H. pylori triggers IL-8, which attracts neutrophils which release oxyradicals leading to cell damages. Lymphocyte infiltration is also present in H. pylori infection.

Chronic gastritis mostly results from H. pylori infection and appears either as non-atrophic or atrophic form. These two forms are phenotypes of gastritis at different stages of the same life-long disease.

The progression from acute to chronic gastritis begins in childhood as a simple chronic superficial mononuclear inflammation of gastric mucosa which progress in years or decades to atrophic gastritis characterized by loss of normal mucosal glands in the antrum, corpus, fundus or all.

Factors that determine progression to atrophic gastritis and sequelae such as a peptic ulcer or gastric cancer are not clearly understood and unpredictable. However, Epstein-Barr virus (EBV) and human cytomegalovirus (HCMV) have been identified in gastric tumors and DNA from H. pylori, EBV, and PCR determined the presence of HCMV in biopsies from patients with gastric cancer complicating chronic gastritis. Some researchers have confirmed the involvement of EBV and H. pylori in the development of gastric cancer in patients with chronic gastritis. They found no role for human papillomavirus (HPV) in gastric tumorigenesis.

NSAIDs cause gastritis through inhibition of prostaglandin synthesis. Prostaglandins are responsible for the maintenance of protective mechanisms of gastric mucosa from injuries caused by hydrochloric acid.

Considering the etiology and pathogenesis of CG to dwell on the role of reactivity, exogenous and endogenous factors that contribute to disease development. In clinical practice, often there are three types of CG (surface - primarily involving the antrum, often with H. pylori - assotiated (gastritis type B), autoimmune fundal gastritis (gastritis type A), the formation of which participate autoimmune mechanisms, chemical, reflux gastritis (gastritis type C), which is characterized by focal lesions of fundus of the stomach due to the cytotoxic effect on the mucosa content of duodenal ulcer by duodenogastric reflux. Then it must be emphasized that there are forms of CG as radiation, lymphocytic, granulomatous, eosinophilic (allergic), other infectious gastritis (non-h.pilori-associated) - the latter are rare. Particular attention should be paid to Menetriye disease - hypertrophic gastropathy. should also pay attention to the morphological changes in CG, such as inflammation,

atrophy, disorders of cell renewal, including including metaplasia and dysplasia. Gastritis is also classified as erosive gastritis or nonerosive gastritis based on the severity of mucosal injury. It is also classified according to the site of involvement (ie, cardia, body, antrum).

Clinical syndromes: pain, dyspeptic syndrome (gastric and intestinal dyspepsia), malabsorption, atsidizm, dumping syndrome, autonomic dysfunction, cardiovascular disorders, asthenic-neurotic.

The most common initial findings for chronic and autoimmune gastritis are hematological disorders such as anemia (iron-deficiency) detected on routine check-up, positive histological examination of gastric biopsies, clinical suspect based on the presence of other autoimmune disorders, neurological symptoms (related to vitamin B12 deficiency) or positive family history. Iron-deficiency anemia (based on blood film showing microscopic hypochromic changes as well as iron studies) commonly presents in the early stages of autoimmune gastritis. Achlorhydria causing impairment of iron absorption in the duodenum and early jejunum is the main cause. Iron-deficiency anemia could also occur in other types of chronic gastritis.

Autoimmune gastritis is associated with other autoimmune disorders (mainly thyroid diseases) including Hashimoto thyroiditis but also with Addison disease, chronic spontaneous urticaria, myasthenia gravis, Diabetes type 1, vitiligo, and perioral cutaneous autoimmune disorders especially erosive oral lichen planus. The association between chronic atrophic autoimmune gastritis and autoimmune thyroid disease earned the name in the early 60s of "thyrogastric syndrome."

Diagnostic: researches of the secretory function of the stomach (gastric sensing and intragastric pH-metry) pepsin forming features motor-evacuation, diagnose of H. Pylori infections, radiological and endoscopic diagnosis, morphological research.

Differential diagnosis of CG: with stomach cancer, peptic ulcer, chronic cholecystitis and pancreatitis, chronic enteritis and colitis, GERD.

Staying on the leading symptoms of the disease, the student lists the disease, in which symptoms may occur east and justifies why should abandon the idea of presence in this patient of each of these diseases.

Peculiarities of CG: disease course exists the phases of exacerbation and remission, sluggish course, course characteristics (stage of compensation, subcompensation and decompensation).

Special forms of CG (hemorrhagic, polypose, antral gastritis, disease of Menetriye).

The complications of CG: bleeding, ferrum-deficiency anemia, B12 - folicdeficitic anemia, gastrogenic colitis, hipopolyvitaminosis, gastric cancer.

The algorithm of CG treatment:

1. Normalization of lifestyle: eliminate stress, if necessary - using sedative drugs.

2. Diet. The principle of mechanical, chemical and thermal sparing. Food must be fractional, 5-6 times a day. Avoid foods that have a stimulating effect on the stomach, stop taking drugs, smoking.

3. Pharmacotherapy - depends on the type of CG.

CG Type B - according to the Maastricht V/ Florence Consensus - should be performed eradication of H. Pylori.

Schemes of antihelicobacter therapy (first line) 1-component 2-component 3-component PPI: omeprazole (OMEP) 20 mg 2 times a day Clarithromycin (Lekoklar) 500 mg 2 times a day Amoxicillin (Ospamoks) 1000 mg 2 times daily or metronidazole 500 mg 2 times a day Schemes of quadruple antihelicobacter therapy (second line) 1-component 2-component 3-component 4-component PPI: omeprazole (OMEP) 20 mg 2 times a day Bismuth subsalicilatis / subcitrate 120 mg 4 times a day Metronidazole 500 mg 3 times a day Tetracycline 500 mg 4 times a day.

If second line is ineffective, therapy based on antibiotic susceptibility testing is recommended.

CG type A - no special treatment. . If megaloblastic anemia - i/m vitamins B12 - 1000 mg during 6 days later for a month 1 time a week, then - continued throughout the life of 1 every 2 months. When concomitant exocrine pancreatic insufficiency (steatorrhea) - pancreatic enzymes

CG Type C - normalization of gastrointestinal tract motility and connection of bile acids. Are effective prokinetic (motilium), cholestyramine (6-10 g per day) in combination with antacids

(Maalox, fosfalugel). When bile reflux gastritis - ursodeoxycholic acid 250-500 mg per night for 6-8 weeks. At NSAID-induced gastritis - cancel NSAID, if you can not - use of selective COX-2 inhibitors. The preparation of choice is mezoprostole (200 mg 3 times a day and at night).

Peptic ulcer.

Definition Peptic ulcer is a clinical-anatomical term, identifying a chronic relapsing disease with a trend to progression, caused by either pathological influences of the aggressive factors on gastroduodenal mucosa (the most important of these are acidic-peptic factors and H.Pylori) or decrease of the defense mechanisms of the mucosa. These factors lead to relapsing formation of the ulcers in gastroduodenal mucosa.

The disease is manifested by pain and dispeptic syndromes of different degree with possible development of life-threatening complications.

Duodenal ulcer and gastric ulcer are often grouped together as peptic ulcers. Although the two diseases have many similarities, they differ in some important aspects such as epidemiology, natural history, outcome, and management. So, they are defined as the manifestation of the peptic ulcer disease with two different localizations: gastric and duodenal. These conditions are managed clinically as separate, although related, diseases.

Etiology

H. pylori and NSAIDs disrupt normal mucosal defense and repair, making the mucosa more susceptible to acid. H. pylori infection is present in 50 to 70% of patients with duodenal ulcers and 30 to 50% of patients with gastric ulcers. If H. pylori is eradicated, only 10% of patients have recurrence of peptic ulcer disease, compared with 70% recurrence in patients treated with acid suppression alone. NSAIDs now account for > 50% of peptic ulcers.

Cigarette smoking is a risk factor for the development of ulcers and their complications. Also, smoking impairs ulcer healing and increases the incidence of recurrence. Risk correlates with the number of cigarettes smoked per day. Although alcohol is a strong promoter of acid secretion, no definitive data link moderate amounts of alcohol to the development or delayed healing of ulcers. Very few patients have hypersecretion of gastrin. A family history exists in 50 to 60% of children with duodenal ulcer.

Clinical manifestation and localization of ulcers.

Objective examination usually non-specific:

- Locally painful palpation
- Mendel's symptom (painful percussion – viscerosensory reflex)
- in 20-30% - Local muscular tension (visceromotoric reflex)
- usually in duodenal ulcers Indeed, severe ulceration to the point of perforation or haemorrhage can be virtually symptomless.

Symptoms and Signs

Symptoms depend on ulcer location and patient age; many patients, particularly elderly patients, have few or no symptoms. Pain is most common, often localized to the epigastrium and relieved by food or antacids. The pain is described as burning or gnawing, or sometimes as a sensation of hunger. The course is usually chronic and recurrent. Only about half of patients present with the characteristic pattern of symptoms.

Gastric ulcer symptoms often do not follow a consistent pattern (eg, eating sometimes exacerbates rather than relieves pain). This is especially true for pyloric channel ulcers, which are often associated with symptoms of obstruction (eg, bloating, nausea, vomiting) caused by edema and scarring.

Duodenal ulcers tend to cause more consistent pain. Pain is absent when the patient awakens but appears in mid-morning, is relieved by food, but recurs 2 to 3 h after a meal. Pain that awakens a patient at night is common and is highly suggestive of duodenal ulcer. In neonates, perforation and hemorrhage may be the first manifestation of duodenal ulcer. Hemorrhage may also be the first recognized sign in later infancy and early childhood, although repeated vomiting or evidence of abdominal pain may be a clue.

Diagnosis

- ✓ Endoscopy
- ✓ Sometimes serum gastrin levels

Diagnosis of peptic ulcer is suggested by patient history and confirmed by endoscopy. Empiric therapy is often begun without definitive diagnosis. However, endoscopy allows for biopsy or cytologic brushing of gastric and esophageal lesions to distinguish between simple ulceration and ulcerating stomach cancer. Stomach cancer may manifest with similar manifestations and must be excluded, especially in patients who are > 45, have lost weight, or report severe or refractory symptoms. The incidence of malignant duodenal ulcer is extremely low, so biopsies of lesions in that area are generally not warranted. Endoscopy can also be used to definitively diagnose H. pylori infection, which should be sought when an ulcer is detected.

Gastrin-secreting cancer and Zollinger-Ellison syndrome should be considered when there are multiple ulcers, when ulcers develop in atypical locations (eg, postbulbar) or are refractory to treatment, or when the patient has prominent diarrhea or weight loss. Serum gastrin levels should be measured in these patients.

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A typic course: dominating dyspepsy syndrome, constipation, loss of body weight or astenicneurotic syndrome.

Differential diagnosis should be performed with:

- Chronic gastritis (In ulcer: acute pain, fasting and nocturnal pain; because of smoothed clinical manifestation in some ulcer cases final diagnose is endoscopic)

- Gastroesophagal reflux (Dominating dyspepsy: recurrent heartburn ascending up to pharynx, acidic belching and nausea. Heartburn increases in lying position and in bendings. Epigastruc pain, which may be present, is not associated with food intake and are aggravated after physical exertion, bending, overeating, especially in the evening. Usually revealed in middle-aged, more often in women with increased body mass, very rare in astenics and in young)

- Cancer (Signs, giving possibility to suspect malignancy: - age over 50 (last years– "cancer becomes younger") - early grey-haired - early old-looking appearance - low or capicious appetite - smoothed pain syndrome - marked body weight loss - decrease of vital tone - decrease of working ability - rapid tiredness appearance during the day - short ulcer anamnesis - prepyloric ulcer localization. Absence of cancer cells in biopsy is not a final confir-mation of benign ulcer; in suspected cases numerous biopsies should be performed. Signs, looking like recovery symptoms, may occur even in malign ulcers due to the cancer infiltration spreading).

Complicaitons of peptic ulcer:

- Bleeding
- Perforation
- Penetration
- Pyloroduodenal stenosis
- Malignisation

Indications to surgical treatment 1. Recurrent bleeding, continuing in spite of active treatment (Omeprosol, H2-blockers, coagulation) 2. Perforation 3. Pyloric stenosis 4. Exacerbation with relapse after the recent complication (including perforation and bleeding), in spite of uninterrupted course of Ranitidin or Famotidin and repeated anti-HP treatment courses.

Hemorrhage.

Mild to severe hemorrhage is the most common complication of peptic ulcer disease. Symptoms include hematemesis (vomiting of fresh blood or "coffee ground" material); passage of bloody stools (hematochezia) or black tarry stools (melena); and weakness, orthostasis, syncope, thirst, and sweating caused by blood loss.

A peptic ulcer may penetrate the wall of the stomach. If adhesions prevent leakage into the peritoneal cavity, free penetration is avoided and confined perforation occurs. Still, the ulcer may penetrate into the duodenum and enter the adjacent confined space (lesser sac) or another organ (eg, pancreas, liver). Pain may be intense, persistent, referred to sites other than the abdomen (usually the back when caused by penetration of a posterior duodenal ulcer into the pancreas), and modified by body position. CT or MRI is usually needed to confirm the diagnosis. When therapy does not result in healing, surgery is required.

Free perforation.

Ulcers that perforate into the peritoneal cavity unchecked by adhesions are usually located in the anterior wall of the duodenum or, less commonly, in the stomach. The patient presents with an acute abdomen. There is sudden, intense, continuous epigastric pain that spreads rapidly throughout the abdomen, often becoming prominent in the right lower quadrant and at times referred to one or both shoulders. The patient usually lies still because even deep breathing worsens the pain. Palpation of the abdomen is painful, rebound tenderness is prominent, abdominal muscles are rigid (boardlike), and bowel sounds are diminished or absent. Shock may ensue, heralded by increased pulse rate and decreased BP and urine output. Symptoms may be less striking in elderly or moribund patients and those receiving corticosteroids or immunosuppressants.

Diagnosis is confirmed if an x-ray or CT shows free air under the diaphragm or in the peritoneal cavity. Upright views of the chest and abdomen are preferred. The most sensitive view is the lateral x-ray of the chest. Severely ill patients may be unable to sit upright and should have a lateral decubitus x-ray of the abdomen. Failure to detect free air does not exclude the diagnosis.

Immediate surgery is required. The longer the delay, the poorer is the prognosis. When surgery is contraindicated, the alternatives are continuous nasogastric suction and broad-spectrum antibiotics.

Gastric outlet obstruction.

Obstruction may be caused by scarring, spasm, or inflammation from an ulcer. Symptoms include recurrent, large-volume vomiting, occurring more frequently at the end of the day and often as late as 6 h after the last meal. Loss of appetite with persistent bloating or fullness after eating also suggests gastric outlet obstruction. Prolonged vomiting may cause weight loss, dehydration, and alkalosis.

If the patient's history suggests obstruction, physical examination, gastric aspiration, or x-rays may provide evidence of retained gastric contents. A succussion splash heard > 6 h after a meal or aspiration of fluid or food residue > 200 mL after an overnight fast suggests gastric retention. If gastric aspiration shows marked retention, the stomach should be emptied and endoscopy done or x-rays taken to determine site, cause, and degree of obstruction.

Edema or spasm caused by an active pyloric channel ulcer is treated with gastric decompression by nasogastric suction and acid suppression (eg, IV H_2 blockers). Dehydration and electrolyte imbalances resulting from protracted vomiting or continued nasogastric suctioning should be vigorously sought and corrected. Prokinetic agents are not indicated. Generally, obstruction resolves within 2 to 5 days of treatment. Prolonged obstruction may result from peptic scarring and may respond to endoscopic pyloric balloon dilation. Surgery is necessary to relieve obstruction in selected cases.

Recurrence.

Factors that affect recurrence of ulcer include failure to eradicate H. pylori, continued NSAID use, and smoking. Less commonly, a gastrinoma (Zollinger-Ellison syndrome) may be the cause. The 3-yr recurrence rate for gastric and duodenal ulcers is < 10% when H. pylori is successfully eradicated but > 50% when it is not. Thus, a patient with recurrent disease should be tested for H. pylori and treated again if the tests are positive.

Although long-term treatment with H_2 blockers, proton pump inhibitors, or misoprostolreduces the risk of recurrence, their routine use for this purpose is not recommended. However, patients who require NSAIDs after having had a peptic ulcer are candidates for long-term therapy, as are those with a marginal ulcer or prior perforation or bleeding.

Stomach cancer.

Patients with H. pylori–associated ulcers have a 3- to 6-fold increased risk of gastric cancer later in life. There is no increased risk of cancer with ulcers of other etiology.

Treatment.

- ✓ Eradication of H. pylori (when present)
- ✓ Acid-suppressive drugs

Treatment of gastric and duodenal ulcers requires eradication of H. pylori when present and a reduction of gastric acidity. For duodenal ulcers, it is particularly important to suppress nocturnal acid secretion.

Methods of decreasing acidity include a number of drugs, all of which are effective but which vary in cost, duration of therapy, and convenience of dosing. In addition, mucosal protective drugs (eg,sucralfate) and acid-reducing surgical procedures may be used. Drug therapy is discussed elsewhere.

Adjuncts.

Smoking should be stopped, and alcohol consumption stopped or limited to small amounts of dilute alcohol. There is no evidence that changing the diet speeds ulcer healing or prevents recurrence. Thus, many physicians recommend eliminating only foods that cause distress.

Indications to surgical treatment 1. Recurrent bleeding, continuing in spite of active treatment (Omeprosol, H2-blockers, coagulation) 2. Perforation 3. Pyloric stenosis 4. Exacerbation with relapse after the recent complication (including perforation and bleeding), in spite of uninterrupted course of Ranitidin or Famotidin and repeated anti-HP treatment courses.

Questions for control of received knowledge evaluation:

1. Diagnostic algorithm of stomach dyspepsia.

2. Definition,etiology, pathogenesis of chronic gastritis.
3. Types of chronic gastritis and differentiated treatment approach.
4. Definition,etiology, pathogenesis of stomach and duodenal ulcer.
5. Features of flow of pH-positive and pH-negative ulcers.
6. Value of laboratory and instrumental methods of researches.
7. Methods of diagnostics of Hp-infection.
8. Differential diagnosis of stomach and duodenal ulcer.
9. Modern tactic of ulcer treatment.
10. Schemes of H.pylori eradication and follow-up control.
11. Medicamental therapy of Hp-negative ulcers.
12. Indications to surgical treatment of stomach and duodenal ulcer.

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Lecture №6

Topic: Chronic hepatitis. Cirrhosis of liver

Objective: to prepare a specialist who is able to perform professional activities, applying the acquired knowledge on the problem of Chronic hepatitis, from the inherent modern laboratory and instrumental research, medical manipulations, tactics and standards of patient management based on evidence medicine, to identify tasks and problems in the field of rheumatology in clinical practice and in further training.

Prepare specialists who will be able to carry out professional activities, using knowledge of the problems of liver cirrhosis.

Specific objectives of the lecture:

- Discuss the prevalence of Chronic hepatitis and its impact on public health in the world and in Ukraine
- Define Chronic hepatitis.
- Explain the etiology, pathogenesis of risk factors for the development and progression of Chronic hepatitis.
- Discuss the clinical manifestations of the typical course of Chronic hepatitis and complications of Chronic hepatitis.
- Explain the current classification of Chronic hepatitis.
- To substantiate the use of the main methods of diagnosis of Chronic hepatitis, to discuss their informativeness, to determine the indications and contraindications for their use.
- Explain the basic principles of differential diagnosis in a patient with suspected Chronic hepatitis using the analysis of clinical manifestations, laboratory data and instrumental examination, to substantiate the clinical diagnosis of Chronic hepatitis. Give examples of diagnosis in patients with different variants of Chronic hepatitis.
- Explain the basic principles of modern strategy of continuous organoprotection of patients with Chronic hepatitis, as components of primary and secondary prevention of Chronic hepatitis, treatment of patients with different stages of Chronic hepatitis according to evidence-based medicine.
- Discuss modern approaches and methods of antiviral, hepatoprotective drugs, indications and contraindications to it, complications.
- To present modern methods of assessment of the prognosis in patients with Chronic hepatitis.
- Demonstrate moral and deontological principles of a medical specialist and the principles of professional subordination when working with patients with Chronic hepatitis.
- pathogenesis of LC;
- classification of LC;
- clinical features and differential diagnosis of LC;
- modern standards of LC management.
- estimate the data of external inspection and palpation- percussion picture of the liver, spleen, and confront it with ultrasound examination of abdominal cavity data to assess the severity of the disease;
- make a program of differential diagnosis with syndrome-like diseases, primarily with primary biliary cirrhosis, primary sclerosing cholangitis, overlap-syndromes;
- assign standard treatment of LC.
- familiarize students with the contribution of modern gastroenterology societies in the study of the CH problem and the development of modern standards of care for patients with LC (I);
- form an idea of the role of the general practitioner, family physician for the primary and secondary prevention and symptoms control (I) of LC.

Basic concepts: Chronic hepatitis, LC, risk factors (RFs), criteria for diagnosis of Chronic hepatitis and LC, stages of Chronic hepatitis, LC, immune system and immune response, inflammation, antiviral therapy, support therapy.

Lecture plan and organizational structure

N IO	The main stages of the lecture and their content	Goals in levels of abstraction	Type of lecture, methods and means of activating students, equipment	Time distributio n, min
1	*2*	*3*	*4*	*5*
1.	Preparatory stage: 1. setting educational goals	I	Clinical lecture: – with elements of problem, – with the use of clearness,	5

	2. providing positive motivation - the importance of the problem of Chronic hepatitis for the clinical practice of a family doctor - general practice.	I	– with the use of interactive communication–	
2.	The main stage: presentation of lecture material according to the plan: 2.1.Epidemiology of Chronic hepatitis 2.2. The role of the general practitioner in the management of patients with Chronic hepatitis Lecture content: 2.3. Definition of Chronic hepatitis and LC. 2.4. Risk factors for the development and progression of Chronic hepatitis and LC 2.5. Pathogenesis of lesions of organs and systems. 2.6. Classification of Chronic hepatitis, LC. Changes in laboratory parameters depending on the stage. 2.7. Clinical manifestations and typical course, complications. 2.8. Diagnosis and principles of differential diagnosis in a patient with Chronic hepatitis, LC. 2.9. Current strategy of managing patients with Chronic hepatitis, LC Treatment at different stages of Chronic hepatitis and LC according to evidence-based medicine. 2.10. Primary and secondary prevention. Strategy of continuous renoprotection. 2.11. Prognosis in patients with Chronic hepatitis and LC	I II III III III III III II II II II II II	Visual tools: – multimedia presentation of the lecture in Power Point format, incl. using the Microsoft Teams platform, – extracts from medical records of patients with Chronic hepatitis and LC (or thematic patient), – adapted clinical guidelines for the management of patients with Chronic hepatitis and LC	75
3.	Final stage:		Materials to control: - questions	10

	3.1. Problems that need to be solved. 3.2. Questions and tasks to assess the degree of assimilation of lecture material The lecturer's answer to possible questions. 3.3. Tasks for self-preparation.	II III III III	- situational tasks	

Contents of the topic

Chronic hepatitis is hepatitis that lasts > 6 months. Common causes include hepatitis B and C viruses, nonalcoholic steatohepatitis (NASH), alcohol-related liver disease, and autoimmune liver disease (autoimmune hepatitis). Many patients have no history of acute hepatitis, and the first indication is discovery of asymptomatic aminotransferase elevations. Some patients present with cirrhosis or its complications (eg, portal hypertension). Biopsy is sometimes necessary to confirm the diagnosis and to grade and stage the disease. Treatment is directed toward complications and the underlying condition (eg, corticosteroids for autoimmune hepatitis, antiviral therapy for viral hepatitis). Liver transplantation is often indicated for decompensated cirrhosis.

Hepatitis lasting > 6 months is generally defined as chronic, although this duration is arbitrary.
Etiology of Chronic Hepatitis
Common causes
The most common causes of chronic hepatitis are

- Hepatitis B virus
- Hepatitis C virus
- Nonalcoholic steatohepatitis (NASH)
- Alcohol-related liver disease

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are frequent causes of chronic hepatitis; 5 to 10% of cases of HBV infection, with or without hepatitis D virus (HDV) coinfection, and about 75% of cases of HCV infection become chronic. Rates are higher for developing chronic HBV infection in children (eg, up to 90% of infected neonates and 25 to 50% of young children). Although the mechanism of chronicity is uncertain, liver injury is mostly determined by the patient’s immune reaction to the infection.

Rarely, hepatitis E virus genotype 3 has been implicated in chronic hepatitis.
Hepatitis A virus does not cause chronic hepatitis.
NAFLD develops most often in patients with at least one of the following risk factors:

- Obesity
- Dyslipidemia
- Insulin resistance

NASH is the progressive form of NAFLD that causes chronic hepatitis.

Alcohol-related liver disease (a combination of fatty liver, diffuse liver inflammation, and liver necrosis) results from excess alcohol consumption.

Less common causes

Autoimmune hepatitis (immune-mediated hepatocellular injury) accounts for a high proportion of hepatitis not caused by viruses or steatohepatitis; features of autoimmune hepatitis include the following:

- The presence of serologic immune markers (eg, antinuclear antibodies, anti–smooth muscle antibodies, liver-kidney microsomal antibodies)
- An association with histocompatibility haplotypes common in autoimmune disorders (eg, HLA-B1, HLA-B8, HLA-DR3, HLA-DR4)
- A predominance of T cells and plasma cells in histologic liver lesions
- Complex in vitro defects in cellular immunity and immunoregulatory functions
- An association with other autoimmune disorders (eg, rheumatoid arthritis, autoimmune hemolytic anemia, proliferative glomerulonephritis)
- A response to therapy with corticosteroids or immunosuppressants

Primary biliary cholangitis (formerly, primary biliary cirrhosis) is an immune-mediated process resulting in bile duct injury. Patients usually present with a positive antimitochondrial antibody (AMA) test and elevated alkaline phosphatase. Most patients with primary biliary cholangitis are women. Symptoms include fatigue, joint pain, and pruritus.

Sometimes chronic hepatitis has features of both autoimmune hepatitis and another immune-mediated chronic liver disorder (eg, primary biliary cholangitis, primary sclerosing cholangitis). These conditions are called overlap syndromes.

Many drugs, including isoniazid, methotrexate, methyldopa, nitrofurantoin, tamoxifen, amiodarone, and rarely acetaminophen, can cause chronic hepatitis. The mechanism varies with the drug and may involve altered immune responses, development of steatohepatitis, cytotoxic intermediate metabolites, or genetically determined metabolic defects.

Less often, chronic hepatitis results from alpha-1 antitrypsin deficiency, celiac disease, a thyroid disorder, hereditary hemochromatosis, or Wilson disease.

Classification of Chronic Hepatitis

Cases of chronic hepatitis were once classified histologically as chronic persistent, chronic lobular, or chronic active hepatitis. Current classification specifies the following:

- Etiology
- Intensity of histologic inflammation and necrosis (grade)
- Degree of histologic fibrosis (stage)

Inflammation and necrosis are potentially reversible; fibrosis usually is not.

Symptoms and Signs of Chronic Hepatitis

Clinical features of chronic hepatitis vary widely. About one third of cases develop after acute hepatitis, but most develop insidiously de novo.

Many patients are asymptomatic, regardless of the etiology. However, malaise, anorexia, and fatigue are common, sometimes with low-grade fever and nonspecific upper abdominal discomfort. Jaundice is usually absent.

Often, the first findings are

- Signs of cirrhosis (eg, splenomegaly, spider nevi, palmar erythema)
- Complications of cirrhosis (eg, portal hypertension, ascites, encephalopathy)

A few patients with chronic hepatitis develop manifestations of cholestasis (eg, jaundice, pruritus, pale stools, steatorrhea).

In autoimmune hepatitis, especially in young women, manifestations may involve virtually any body system and can include acne, amenorrhea, arthralgia, ulcerative colitis, pulmonary fibrosis, thyroiditis, nephritis, and hemolytic anemia.

Chronic hepatitis C is occasionally associated with lichen planus, mucocutaneous vasculitis, glomerulonephritis, porphyria cutanea tarda, mixed cryoglobulinemia, and, perhaps, non-

Hodgkin B-cell lymphoma. Symptoms of cryoglobulinemia include fatigue, myalgias, arthralgias, neuropathy, glomerulonephritis, and rashes (urticaria, purpura, leukocytoclastic vasculitis); asymptomatic cryoglobulinemia is more common.

Diagnosis of Chronic Hepatitis

- Liver test results compatible with hepatitis
- Viral serologic tests
- Possibly autoantibodies, immunoglobulins, alpha-1 antitrypsin level, and other tests
- Occasionally biopsy
- Serum albumin, platelet count, and prothrombin time/international normalized ratio (PT/INR)

Chronic hepatitis is suspected in patients with any of the following:

- Suggestive symptoms and signs
- Incidentally noted elevations in aminotransferase levels
- Previously diagnosed acute hepatitis

In addition, to identify asymptomatic patients, the CDC recommends testing of all adults ≥ 18 years at least once.

Liver tests

Liver tests are needed if not previously done and include serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and bilirubin.

Aminotransferase elevations are the most characteristic laboratory abnormalities (ALT normal values: 29 to 33 IU/L [0.48 to 55 microkat/L] for males and 19 to 25 IU/L [0.32 to 0.42 microkat/L] for females [1]). ALT is usually higher than AST. Aminotransferase levels can be normal during chronic hepatitis if the disease is quiescent, particularly with HCV infection and nonalcoholic fatty liver disease (NAFLD).

Alkaline phosphatase is usually normal or only slightly elevated but is occasionally markedly high, particularly in primary biliary cholangitis.

Bilirubin is usually normal unless the disease is severe or advanced.

Other laboratory tests

If laboratory results are compatible with hepatitis, viral serologic tests are done to exclude HBV and HCV (see tables Hepatitis B Serology and Hepatitis C Serology). Unless these tests indicate viral etiology, further testing is required.

The next tests done include

- Autoantibodies (antinuclear antibody, anti–smooth muscle antibody, antimitochondrial antibody, liver-kidney microsomal antibody)
- Immunoglobulins
- Serum transferrin saturation and ferritin
- Thyroid tests (thyroid-stimulating hormone)
- Tests for celiac disease (tissue transglutaminase antibody)
- Alpha-1 antitrypsin level
- Ceruloplasmin

Children and young adults are screened for Wilson disease by measuring the ceruloplasmin level.

Autoimmune hepatitis is normally diagnosed based on the presence of antinuclear (ANA), anti–smooth muscle (ASMA), or anti-liver/kidney microsomal type 1 (anti-LKM1) antibodies at titers of 1:80 (in adults) or 1:20 (in children) and usually elevations in serum immunoglobulins. Antimitochondrial antibodies most often present in primary biliary cholangitis. (See also the American Association for the Study of Liver Disease's practice guideline Diagnosis and management of autoimmune hepatitis in adults and children.)

Serum transferrin saturation > 45% and elevated ferritin suggests hereditary hemochromatosis and should be followed by genetic testing for the hemochromatosis gene (HFE).

Serum albumin, platelet count, and PT should be measured to assess liver function and disease severity; low serum albumin, a low platelet count, or prolonged PT may suggest cirrhosis and even portal hypertension.

If the cause of hepatitis is identified, noninvasive tests (eg, ultrasound elastography, serum markers) can be done to assess the degree of liver fibrosis.

Autoimmune Hepatitis

Diagnostic Criteria

Biopsy

Unlike in acute hepatitis, biopsy may be necessary to confirm the diagnosis or etiology of chronic hepatitis.

Mild cases may have only minor hepatocellular necrosis and inflammatory cell infiltration, usually in portal regions, with normal acinar architecture and little or no fibrosis. Such cases rarely develop into clinically important liver disease or cirrhosis.

In more severe cases, biopsy typically shows periportal necrosis with mononuclear cell infiltrates (piecemeal necrosis) accompanied by variable periportal fibrosis and bile duct proliferation. The acinar architecture may be distorted by zones of collapse and fibrosis, and frank cirrhosis sometimes coexists with signs of ongoing hepatitis.

Biopsy is also used to grade and stage the disease.

Screening for complications

If symptoms or signs of cryoglobulinemia develop during chronic hepatitis, particularly with HCV, cryoglobulin levels and rheumatoid factor should be measured; high levels of rheumatoid factor and low levels of complement suggest cryoglobulinemia.

Patients with chronic HBV infection or cirrhosis due to any underlying liver disorder should be screened every 6 months for hepatocellular carcinoma with ultrasonography and sometimes serum alpha-fetoprotein measurement, although the cost-effectiveness of this practice, particularly alpha-fetoprotein measurement, is debated. (See also the Cochrane review abstract on Alpha-foetoprotein and/or liver ultrasonography for liver cancer screening in patients with chronic hepatitis B.)

Prognosis for Chronic Hepatitis

Prognosis for patients with chronic hepatitis is highly variable and often depends on the cause and availability of treatment.

Chronic hepatitis caused by a drug often regresses completely when the causative drug is withdrawn.

Without treatment, cases caused by HBV can resolve (uncommon), progress rapidly, or progress slowly to cirrhosis over decades. Resolution often begins with a transient increase in disease severity and results in seroconversion from hepatitis B e antigen (HBeAg) to antibody to hepatitis B e antigen (anti-HBe). Coinfection with HDV causes the most severe form of chronic HBV infection; without treatment, cirrhosis develops in up to 70% of patients with coinfection.

Untreated chronic hepatitis due to HCV causes cirrhosis in 20 to 30% of patients, although development may take decades and varies because it is often related to a patient's other risk factors for chronic liver disease, including alcohol use and obesity.

Chronic autoimmune hepatitis usually responds to therapy but sometimes causes progressive fibrosis and eventual cirrhosis.

Chronic HBV infection increases the risk of hepatocellular carcinoma. The risk is also increased in other liver disorders (eg, HCV infection, NAFLD), but usually when cirrhosis or advanced fibrosis has developed.

Treatment of Chronic Hepatitis

- Supportive care
- Treatment of cause (eg, corticosteroids for autoimmune hepatitis, antivirals for HBV and HCV infection)

General treatment

Treatment goals for chronic hepatitis include treating the cause and, if cirrhosis and portal hypertension have developed, managing complications (eg, ascites, encephalopathy).

Drugs that cause hepatitis should be stopped. Acetaminophen is contraindicated in patients with severe hepatic impairment or severe active liver disease. NSAIDs should also be avoided in patients with severe hepatic impairment.

Underlying disorders should be treated. Lifestyle changes should be recommended for patients with NAFLD or alcohol-related liver disease.

Liver transplantation may be required for decompensated cirrhosis.

Chronic hepatitis B and C

There are specific antiviral treatments for chronic hepatitis B (eg, entecavir and tenofovir as first-line therapies) and antiviral treatments for chronic hepatitis C (eg, interferon-free regimens of direct-acting antivirals).

In chronic hepatitis due to HBV, prophylaxis (including immunoprophylaxis) for contacts of patients may be helpful. No vaccination is available for contacts of patients with HCV infection.

Corticosteroids and immunosuppressants should be avoided in chronic hepatitis B and C because these drugs enhance viral replication. If patients with chronic hepatitis B have other disorders that require treatment with corticosteroids, immunosuppressive therapies, or cytotoxic chemotherapy, they should be treated with antiviral drugs at the same time to prevent a flare or reactivation of hepatitis B or acute liver failure due to hepatitis B. A similar situation with hepatitis C being activated or causing acute liver failure has not been described.

Nonalcoholic steatohepatitis (NASH)

Treatment of NASH aims to

- Reduce weight
- Control risk factors and comorbidities

It may involve

- Recommending weight loss of 7 to 10% of body weight via dietary changes and exercise
- Treating concomitant metabolic risk factors such as hyperlipidemias and insulin resistance
- Stopping drugs associated with NASH (eg, amiodarone, tamoxifen, methotrexate, corticosteroids such as prednisone or hydrocortisone, synthetic estrogens)
- Avoiding exposure to toxins (eg, pesticides)

Autoimmune hepatitis

Corticosteroids, with or without azathioprine, prolong survival. Prednisone is usually started at 30 to 60 mg orally once a day, then tapered to the lowest dose that maintains aminotransferases at normal or near-normal levels. To prevent long-term need for corticosteroid treatment, clinicians can transition to azathioprine 1 to 1.5 mg/kg orally once a day or mycophenolate mofetil 1000 mg twice a day after corticosteroid induction is complete and then gradually taper the corticosteroid. Most patients require long-term, low-dose, corticosteroid-free maintenance treatment.

Hereditary hemochromatosis

Hereditary hemochromatosis is treated with phlebotomy.

Key Points

- Chronic hepatitis is usually not preceded by acute hepatitis and is often asymptomatic.
- If liver test results (eg, unexplained elevations in aminotransferase levels) are compatible with chronic hepatitis, do serologic tests for hepatitis B and C.
- If serologic results are negative, do tests (eg, autoantibodies, immunoglobulins, alpha-1 antitrypsin level) for other forms of hepatitis.
- Consider a liver biopsy to confirm the diagnosis and assess the severity of chronic hepatitis if noninvasive testing is nondiagnostic.
- Noninvasive tests (eg, elastography, serum markers) can be used to assess the degree of liver fibrosis.

- Consider entecavir or tenofovir as first-line therapies for chronic hepatitis B.
- Treat chronic hepatitis C of all genotypes with interferon-free regimens of direct-acting antivirals.
- Treat autoimmune hepatitis with corticosteroids and transition to maintenance treatment with azathioprine or mycophenolate mofetil.
- Encourage diet and exercise for weight loss in patients with nonalcoholic fatty liver disease.
- Treat hereditary hemochromatosis with phlebotomy.

Cirrhosis is characterized by regenerative nodules surrounded by dense fibrotic tissue.
Hepatocellular carcinoma frequently complicates cirrhosis, particularly cirrhosis resulting from chronic hepatitis B or C, hemochromatosis, alcohol-related liver disease, alpha-1 antitrypsin deficiency, or glycogen storage disease.

Histopathology

Cirrhosis is characterized by regenerating nodules and fibrosis. Incompletely formed liver nodules, nodules without fibrosis (nodular regenerative hyperplasia), and congenital hepatic fibrosis (ie, widespread fibrosis without regenerating nodules) are not true cirrhosis.
Cirrhosis can be micronodular or macronodular. Micronodular cirrhosis is characterized by uniformly small nodules (< 3 mm in diameter) and thick regular bands of connective tissue. Typically, nodules lack lobular organization; terminal (central) hepatic venules and portal triads are distorted. With time, macronodular cirrhosis often develops. The nodules vary in size (3 mm to 5 cm in diameter) and have some relatively normal lobular organization of portal triads and terminal hepatic venules. Broad fibrous bands of varying thickness surround the large nodules. Collapse of the normal hepatic architecture is suggested by the concentration of portal triads within the fibrous scars. Mixed cirrhosis (incomplete septal cirrhosis) combines elements of micronodular and macronodular cirrhosis. Differentiation between these morphologic types of cirrhosis has limited clinical value.

Symptoms and signs

Cirrhosis may be asymptomatic for years. One third of patients never develop symptoms. Often, the first symptoms are nonspecific; they include generalized fatigue (due to cytokine release), anorexia, malaise, and weight loss. The liver is typically palpable and firm, with a blunt edge, but is sometimes small and difficult to palpate. Nodules usually are not palpable.
Clinical signs that suggest a chronic liver disorder or chronic alcohol use but are not specific for cirrhosis include muscle wasting, palmar erythema, parotid gland enlargement, white nails, clubbing, Dupuytren contracture, spider angiomas (< 10 may be normal), gynecomastia, axillary hair loss, testicular atrophy, and peripheral neuropathy.
Once complications of cirrhosis develop, decompensation inexorably ensues.

Common Symptoms and Signs Due to Complications of Cirrhosis

Symptom or Sign	Possible Cause
Abdominal distention	Ascites
Abdominal discomfort with fever or hepatic encephalopathy (infrequently with peritoneal signs)	Spontaneous bacterial peritonitis
Calf pain or swelling, symptoms of pulmonary embolism	Thromboembolism
Clubbing	Hepatopulmonary syndrome
Confusion, lethargy	Hepatic encephalopathy
Dyspnea, hypoxia	Hepatopulmonary syndrome Portopulmonary hypertension

Fatigue, pallor	Anemia due to bleeding, hypersplenism, undernutrition with deficiency of folate (or iron or vitamin B_{12}), chronic disease, or effects of alcohol (eg, bone marrow suppression)
Fluid overload, oliguria, symptoms of renal failure	Hepatorenal syndrome
Fragility fracture (due to a fall from standing height or less)	Osteoporosis
Symptoms of infection	Leukopenia
Jaundice	Cholestasis
Petechiae, purpura, bleeding	Thrombocytopenia caused by splenomegaly due to portal hypertension or the direct effects of alcohol on bone marrow Coagulopathy due to impaired liver synthetic function, vitamin K deficiency, or both
Pruritus, xanthelasmas	Cholestasis
Rectal bleeding	Rectal varices
Splenomegaly	Portal hypertension
Steatorrhea	Fat malabsorption
Upper GI bleeding	Esophageal varices Portal hypertensive gastropathy

Diagnosis

- Liver function tests, coagulation tests, CBC, and serologic tests for viral causes
- Sometimes biopsy (eg, when clinical and noninvasive tests are inconclusive or when biopsy results may change management)
- Sometimes ultrasound elastography or MRI elastography
- Identification of cause based on clinical evaluation, routine testing for common causes, and selective testing for less common causes

General approach

Cirrhosis is suspected in patients with manifestations of any of its complications, particularly portal hypertension or ascites. Early cirrhosis should be considered in patients with nonspecific symptoms or characteristic laboratory abnormalities detected incidentally during laboratory testing, particularly in patients who have a disorder or take a drug that might cause fibrosis.

Testing seeks to detect cirrhosis and any complications and to determine its cause.

Laboratory tests

Diagnostic testing begins with liver function tests, coagulation tests, CBC, and serologic tests for viral causes (eg, hepatitis B and C). Laboratory tests alone may increase suspicion for cirrhosis but cannot confirm or exclude it. Liver biopsy becomes necessary if a clear diagnosis would lead to better management and outcome.

Test results may be normal or may indicate nonspecific abnormalities due to complications of cirrhosis or alcoholism. ALT and AST levels are often modestly elevated. Alkaline phosphatase and γ-glutamyl transpeptidase (GGT) are often normal; elevated levels indicate cholestasis or biliary obstruction. Bilirubin is usually normal but increases when cirrhosis progresses, particularly in primary biliary cirrhosis. Decreased serum albumin and a prolonged PT directly reflect impaired hepatic synthesis—usually an end-stage event. Albumin can also be low when nutrition is poor. Serum globulin increases in cirrhosis and in most liver disorders with an inflammatory component. Anemia is common and usually normocytic with a high RBC distribution width. Anemia is often multifactorial; contributing factors may include chronic GI bleeding (usually causing microcytic anemia), folate nutritional deficiency (causing macrocytic anemia, especially in alcohol abuse), hemolysis, and hypersplenism. CBC may also detect leukopenia, thrombocytopenia, or pancytopenia.

Diagnostic imaging

Conventional imaging tests are not highly sensitive or specific for the diagnosis of cirrhosis by themselves, but they can often detect its complications. Ultrasound elastography and MRI elastography are useful in detection of early cirrhosis when conventional imaging findings are equivocal and portal hypertension is not evident.

In advanced cirrhosis, ultrasonography shows a small, nodular liver. Ultrasonography also detects portal hypertension and ascites.

CT can detect a nodular texture, but it has no advantage over ultrasonography. Radionuclide liver scans using technetium-99m sulfur colloid may show irregular liver uptake and increased spleen and bone marrow uptake. MRI is more expensive than other imaging tests and has little advantage.

Identification of the cause

Determining the specific cause of cirrhosis requires key clinical information from the history and examination, as well as selective testing.

Alcohol is the likely cause in patients with a documented history of alcoholism and clinical findings such as gynecomastia, spider angiomas (telangiectasia), and testicular atrophy plus laboratory confirmation of liver damage (AST elevated more than ALT) and liver enzyme induction (a greatly increased GGT). Fever, tender hepatomegaly, and jaundice suggest the presence of alcoholic hepatitis.

Detecting hepatitis B surface antigen (HBsAg) and IgG antibodies to hepatitis B (IgG anti-HBc) confirms chronic hepatitis B. Identifying serum antibody to hepatitis C (anti-HCV) and HCV-RNA points to hepatitis C. Most clinicians also routinely test for the following:

- Autoimmune hepatitis: Suggested by a high antinuclear antibody titer (a low titer is nonspecific and does not always mandate further evaluation) and confirmed by hypergammaglobulinemia and the presence of other autoantibodies (eg, anti–smooth muscle or anti-liver/kidney microsomal type 1 antibodies)
- Hemochromatosis: Confirmed by increased serum Fe and transferrin saturation and possibly results of genetic testing
- Alpha-1 antitrypsin deficiency: Confirmed by a low serum alpha-1 antitrypsin level and genotyping

If these causes are not confirmed, other causes are sought:

- Presence of antimitochondrial antibodies (in 95%) suggests primary biliary cirrhosis.
- Strictures and dilations of the intrahepatic and extrahepatic bile ducts, seen on magnetic resonance cholangiopancreatography (MRCP), suggest primary sclerosing cholangitis.
- Decreased serum ceruloplasmin and characteristic copper test results suggest Wilson disease.
- The presence of obesity and a history of diabetes suggest nonalcoholic steatohepatitis (NASH).

Liver biopsy

If clinical criteria and noninvasive testing are inconclusive, liver biopsy is usually done. For example, if well-compensated cirrhosis is suspected clinically and imaging findings are inconclusive, biopsy should be done to confirm the diagnosis. Sensitivity of liver biopsy approaches 100%. Nonalcoholic fatty liver disease (NAFLD) may be evident on ultrasound scans. However, NASH, often associated with obesity, diabetes, or the metabolic syndrome, requires liver biopsy for confirmation.

In obvious cases of cirrhosis with marked coagulopathy, portal hypertension, ascites, and liver failure, biopsy is not required unless results would change management. In patients with coagulopathy and thrombocytopenia, the transjugular approach to biopsy is safest. When this approach is used, pressures can be measured and thus the transsinusoidal pressure gradient can be calculated.

Monitoring

All patients with cirrhosis, regardless of cause, should be screened regularly for hepatocellular carcinoma. Currently, abdominal ultrasonography is recommended every 6 mo, and if abnormalities

compatible with hepatocellular carcinoma are detected, contrast-enhanced MRI or triple-phase CT of the abdomen (contrast-enhanced CT with separate arterial and venous phase images) should be done. Contrast-enhanced ultrasonography appears promising as an alternative to CT or MRI but is still under study in the US.

Upper endoscopy to check for gastroesophageal varices should be done when the diagnosis is made and then every 2 to 3 yr. Positive findings may mandate treatment or more frequent endoscopic monitoring.

Prognosis

Prognosis is often unpredictable. It depends on factors such as etiology, severity, presence of complications, comorbid conditions, host factors, and effectiveness of therapy. Patients who continue to drink alcohol, even small amounts, have a very poor prognosis. The Child-Turcotte-Pugh scoring system uses clinical and laboratory information to stratify disease severity, surgical risk, and overall prognosis (see Appendix 1: Child-Turcotte-Pugh Scoring System and Interpretation of the Child-Turcotte-Pugh Scoring System).

However, the Child-Turcotte-Pugh scoring system has limitations; for example, assessments of the severity of ascites and encephalopathy are subjective; interrater reliability of results is thus decreased. In contrast, the Model for End-Stage Liver Disease (MELD) score estimates the severity of end-stage liver disease, regardless of cause, based solely on objective results of laboratory tests: serum creatinine, serum total bilirubin, and INR. The MELD score is used to determine allocation of available organs to liver transplant candidates. Variations of the MELD score are sometimes used for other purposes (eg, to estimate risk of 90-day mortality in patients with alcoholic hepatitis, to predict risk of postoperative mortality in patients with cirrhosis). A variation that incorporates serum sodium (MELDNa) has been extensively studied but is not yet widely used clinically in the US.

MELD Score for End-Stage Liver Disease (NOT appropriate for patients under the age of 12)

$$MELDScore = 10 * ((0.957 * \ln(Creatinine)) + (0.378 * \ln(Bilirubin)) + (1.12 * \ln(INR))) + 6.43$$

The MELD score should be calculated differently for patients who have hepatocellular carcinoma. For patients who are 12 to 17 yr old and who have a urea cycle disorder, organic acidemia, or hepatoblastoma, the MELD score is set at 30. Higher MELD scores predict higher risk.

For patients < 12 yr, the corresponding Pediatric End-Stage Liver Disease (PELD) score is calculated. Higher PELD scores predict higher risk.

Treatment

- Supportive care

In general, treatment is supportive and includes stopping injurious drugs, providing nutrition (including supplemental vitamins), and treating the underlying disorders and complications. Doses of drugs metabolized in the liver should be reduced. All alcohol and hepatotoxic substances must be avoided. Withdrawal symptoms during hospitalization should be anticipated in patients who have cirrhosis and have continued to abuse alcohol. Patients should be vaccinated against viral hepatitis A and B unless they are already immune.

Patients with varices need therapy to prevent bleeding. No evidence supports treating small esophageal varices. Medium and large esophageal varices should be treated prophylactically with nonselective beta-blockers or endoscopic banding (ligation). If gastric varices are not amenable to

endoscopic banding and do not respond to nonselective beta-blockers, balloon-occluded retrograde transvenous obliteration or endoscopic cyanoacrylate injection may be used.

Transjugular intrahepatic portosystemic shunting (TIPS) should be considered if patients have complications of portal hypertension that are refractory to standard treatments, including ascites and recurrent variceal bleeding.

Liver transplantation is indicated for patients with end-stage liver disease or hepatocellular carcinoma. Risk of death without liver transplantation begins to exceed risks of transplantation (eg, perioperative complications, chronic immunosuppression) when the MELD score is more than about 15. Thus, if the score is ≥ 15 or if cirrhosis has decompensated clinically, patients should be referred to a transplantation center.

Key points

- Morbidity and mortality in cirrhosis usually result from its complications (eg, complications of portal hypertension, liver failure, hematologic problems).
- Do liver biopsy if a clear diagnosis would lead to better management and outcome.
- Evaluate all patients with cirrhosis for autoimmune hepatitis, hereditary hemochromatosis, and alpha-1 antitrypsin deficiency, as well as for the more common causes, alcoholic and viral hepatitis.
- Evaluate all patients periodically for gastroesophageal varices and hepatocellular carcinoma.
- Predict prognosis using the Child-Turcotte-Pugh and MELD scoring systems, and refer patients with a MELD score ≥ 15 to be evaluated for a liver transplant.
- Treat cirrhosis supportively, including using therapies to prevent bleeding.

Appendix 1

Child-Turcotte-Pugh Scoring System

Clinical or Laboratory Factor	Degree of Abnormality	Points Assigned*
Encephalopathy (grade†)	None	1
	1–2	2
	3–4	3
Ascites	None	1
	Mild (or controlled by diuretics)	2
	At least moderate despite diuretic treatment	3
Albumin (g/dL)	> 3.5	1

	2.8–3.5	2
	< 2.8	3
Bilirubin (mg/dL)	< 2	1
	2–3	2
	> 3	3
PT (seconds prolonged)	< 4	1
	4–6	2
	> 6	3
or, instead of PT		
INR	<1.7	1
	1.7–2.3	2
	> 2.3	3

*Risk (grade) is based on the total number of points:

- Low (A): 5–6
- Moderate (B): 7–9
- High (C): 10–15

†Encephalopathy is graded based on symptoms:

1: Sleep disturbances; impaired concentration; depression, anxiety, or irritability
2: Drowsiness, disorientation, poor short-term memory, uninhibited behavior
3: Somnolence; confusion; amnesia; anger, paranoia, or other bizarre behavior
4: Coma

Interpretation of the Child-Turcotte-Pugh Scoring System

Points	Risk (Grade)	Survival Rate (%)	
		1-yr	2-yr
5–6	Low (A)	100	85
7–9	Moderate (B)	80	60
10–15	High (C)	45	35

3.2. Questions and tasks to assess the degree of assimilation of lecture material

1. The definition of Chronic hepatitis
2. Markers of desease activity.
3. Risk factors and causes of Chronic hepatitis development and progression.
4. Methods of clinical, laboratory and instrumental diagnostics of Chronic hepatitis.
5. Classification of Chronic hepatitis.
6. Describe clinical manifestation of Chronic hepatitis depended on etiology.
7. The complications of Chronic hepatitis
8. Chronic hepatitis management programs

3.3. Tasks

1. A 40 y.o. patient was admitted to the gasteroenterology with skin itching, jaundice, discomfort in the right subcostal area, generalized weakness. On examination: skin is jaundice, traces of scratches, liver is +5 cm, splin is 6x8 cm. In blood: alkaline phosphatase - 2,0 mmol/(hour*L),

general bilirubin - 60 mcmol/L, cholesterol - 8,0 mmol/L. What is the leading syndrome in the patient?

A Cholestatic
B Cytolytic
C Mesenchymal inflammatory
D Asthenic
E Liver-cells insufficiency

2. A 40-year-old man is ill with autoimmune hepatitis. Blood test:A/G ratio 0,8, bilirubin - 42mcmol/l, transaminase : ALT- 4,3 u/l, AST – 2.8 U/l. What is the most effective means in treatment from the given below?

A Glucocorticoids, cytostatics
B Antibacterial medication
C Hepatoprotectors
D Antiviral medications
E Hemosorbtion, vitamin therapy

3. A patient has been in a hospital. The beginning of the disease was gradual: nausea, vomiting, dark urine, acholic stools, yellowness of the skin and scleras. The liver is protruded by 3 cm. Jaundice progressed on the 14th day of the disease. The liver diminished in size. What complication of viral hepatitis caused deterioration of the patient's condition?

A Hepatic encephlopathy
B Meningitis
C Relapse of viral hepatitis
D Cholangitis
E Infectious-toxic shock

4. A 22 year old woman complained of right subcostal aching pain, nausea, and decreased appetite. She fell ill 2 months after appendectomy when jaundice appeared. She was treated in an infectious hospital. 1 year later above mentioned symptoms developed. On exam: the subicteric sclerae, enlarged firm liver. Your preliminary diagnosis:

A Chronic viral hepatitis
B Calculous cholecystitis
C Gilbert's disease
D Acute viral hepatitis
E Chronic cholangitis

5. A 32 year old patient suffering from chronic viral hepatitis complains about dull pain in the right subcostal area, nausea, dry mouth. Objectively: liver dimensions are 13-21-11 cm (according to Kurlov), spleen is by 2 cm enlarged, aspartate aminotransferase is 3,2 micromole/l*h, alanine aminotransferase - 4,8 millimole/l*h. Serological study revealed HBeAg, high concentration of DNA HBV. What drug should be chosen for treatment of this patient?

A α-interferon
B Acyclovir
C Remantadinum
D Arabinoside monophosphate
E Essentiale-forte

6. A 48-year-old patient complains of heaviness in the right hypochondrium, itching of the skin.He had been treated in infectious diseases hospital repeatedly due to icterus and itch. On physical exam: meteorism, ascitis, dilation of abdominal wall veins, protruded umbilicus, spleen enlargement. What can be diagnosed in this case?

A Liver cirrhosis
B Cancer of the liver
C Cancer of the head of pancreas
D Gallstones

E Viral hepatitis B

7. A 60-year-old patient has been admitted to a hospital with complaints of dyspnea, tightness in the right subcostal area, abdomen enlargement. These presentations have been progressing for a year. Heart auscultation reveals presystolic gallop rhythm. Objectively: swelling of the neck veins, ascites, palpable liver and spleen. What disease requires differential diagnostics?

A Constrictive pericarditis
B Hepatocirrhosis
C Lung cancer with invasion to the pleura
D Chronic pulmonary heart
E Pulmonary embolism

8. A 42-year-old female patient suffers from micronodular cryptogenic cirrhosis. Over the last week her condition has deteriorated: she developed convulsions, mental confusion, progressing jaundice. What study may give reasons for such aggravation?

A Determination of serum ammonia
B Determination of cholesterol ethers
C Determination of alpha-phetoprotein
D Determination of ALAT and ASAT
E Determination of alkaline phosphatase

9. 47 y.o. patient complains of intensive skin itching, jaundice, bone pain. The skin is hyperpigmentated. There are multiple xanthelasma palpebrae. The liver is +6 cm enlarged, solid with acute edge. The blood analysis revealed total bilirubin -160 mcmol/L, direct - 110 mkmol/L, AST- 2,1 mmol/L, ALT- 1,8 mmol/L, alkaline phosphotase - 4,6 mmol/L, cholesterol- 9,2 mmol/L, antimitochondrial antibodies M2 in a high titer. What is the probable diagnosis?

A Primary biliary liver cirrhosis
B Primary liver cancer
C Chronic viral hepatitis B
D Acute viral hepatitis B
E Alcoholic liver cirrhosis

10. A patient with hepatic cirrhosis drank some spirits that resulted in headache, vomiting, aversion to food, insomnia, jaundice, fetor hepaticus, abdominal swelling. What complication of hepatic cirrhosis is meant?

A Hepatocellular insufficiency
B Hemorrhage from varicosely dilatated veins of esophagus
C Portal hypertension
D Acute stomach ulcer
E Thrombosis of mesenteric vessels

Questions for control of received knowledge evaluation:

1. LC: definition, classification.
2. Chemistry tests for evaluation compensation of LC.
3. Features of clinical implications and diagnostics of different LC variants.
4. Complications of LC.
5. Standarts of management the patient with LC.

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-Basic

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